8.01
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: No Extra Heteroatom

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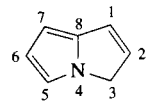
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8.01.1 INTRODUCTION

The trivial name 3H-pyrrolizine has been proposed for the parent compound (**1**) and is widely used instead of the systematic name 3H-pyrrolo(1,2-a)pyrrole. Numbering is shown in (**1**).



(**1**)

Bicyclic 5–5 systems with one ring junction nitrogen atom and no extra heteroatoms were not covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). Pyrrolizines ⟨84AHC(37)1, 87S10⟩, pyrrolizidines ⟨88H(27)1465⟩ and the asymmetric synthesis of pyrrolizidines ⟨90H(30)1231⟩ have been reviewed.

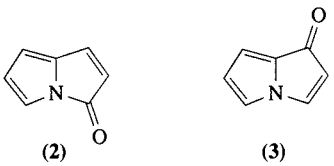
Pyrrolizines and hydrogenated derivatives (pyrrolizidines) are covered here, however, the chemistry of natural pyrrolizidines (see Section 8.01.11) is beyond the scope of this Chapter.

8.01.2 THEORETICAL METHODS

Resonance stabilization energies of tautomeric pyrrolizines (see Section 8.01.4.2) and benzo derivatives have been obtained from HMO calculations ⟨84AHC(37)1⟩. Attempts to explain the acidity of 3H-pyrrolizine using HMO theory showed only limited success ⟨67T2941⟩. The electronic structure of the pyrrolizine anion has been investigated by HMO ⟨84AHC(37)1⟩. ASMO–SCF (ASMO, antisymmetrized MO) ⟨68MI 801-01⟩ and CNDO/2–SCF methods ⟨69G1078⟩. The CNDO/2 calculations show that the σ-core polarization plays a fundamental role in determining the overall charge distribution and is relatively less important for interpreting electronic spectra.

According to HMO as well as SCF calculations, electrophilic attack should occur at the 3-position of the pyrrolizine anion, a conclusion that fits experimental findings (see Section 8.01.4.2).

A calculation using Hess and Schaad parameters on pyrrolizinones, yields resonance energies REPE = 0.0155β for (**2**) and 0.0110β for (**3**) thus explaining the remarkable stability of these compounds ⟨84ACH(37)1⟩.



(**2**) (**3**)

8.01.3 EXPERIMENTAL STRUCTURAL METHODS

8.01.3.1 X-ray

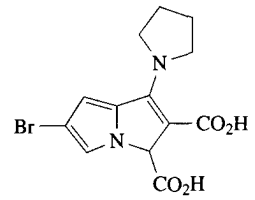
An x-ray structure is available for 6-bromo-1-(*N*-pyrrolinyl)pyrrolizine-2,3-carboxylic acid (**4**). Bond lengths and angles of the rings are shown in Table 1.

Noteworthy is the small bond angle at N—C_5—C_6 and the greater bond alternation in the partially hydrogenated ring, indicating a limited conjugation of the C_1=C_2 double bond with the pyrrole ring ⟨74CSC623⟩.

8.01.3.2 NMR Spectra

Proton NMR spectra of 3H-pyrrolizines, 1H-pyrrolizin-1-ones and 3H-pyrrolizin-3-ones have been compiled from the literature ⟨84AHC(37)1⟩. Chemical shifts and coupling constants of 3H-pyrrolizine (**1**) ⟨68TL1181⟩, the pyrrolizine anion and the pyrrolizinones (**2**) ⟨71CB2170⟩ and (**3**) ⟨82CB706⟩ are grouped in Table 2. The ^{1}H-NMR spectra of the pyrrolizine anion with various

Table 1 Bond lengths and bond angles of 6-bromo-1-(*N*-pyrrolidinyl) pyrrolizine-2,3-dicarboxylic acid (**4**).



(**4**)

Bond length: (Å)	1,2	2,3	3,4	4, 5	5,6	6,7	7,8	8,1	8,4	
	1.33	1.51	1.50	1.36	1.41	1.39	1.38	1.49	1.37	
Bond angles:	8–1–2	1–2–3	2–3–4	3–4–8	8–4–5	4–5–6	5–6–7	6–7–8	7–8–4	4–8–1
	105.5	111.5	102.7	113.1	112.5	99.8	112.3	108.6	106.5	107.2

cations was reported and attempts were made to correlate HMO charge densities with those deduced from the chemical shifts ⟨67T2941⟩.

The ^{13}C spectrum of 3H-pyrrolizin-3-one (**2**) was reported albeit without assignment ⟨81JOC2809⟩.

Table 2 Proton NMR spectra of pyrrolizines.

		Chemical shifts						
Compound	*Coupling constants (Hz)*	*H-1*	*H-2*	*H-3*	*H-5*	*H-6*	*H-7*	*Solvent*
(**1**)	1,2 = 6.2; 2,3 = 2.2; 5,6 = 2.7	6.2	5.63	3.75	6.54	6.08	5.77	neat
($\mathbf{1}^-$)	1,2 = 2.1; 2,3 = 3.2; 1,3 = 1	4.75	6.03	6.43	6.43	6.03	4.75	THF
(**2**)	1,2 = 6.0	7.1	5.61		6.83	5.97	5.97	CS_2
(**3**)	2,3 = 4.11; 5,6 = 2.64; 6,7 = 3.52; 2,6 = 5,7 = 3,7 = 0.9		5.47	7.55	6.75	6.25	6.62	CD_2Cl_2

8.01.3.3 UV and IR Spectroscopy

The parent compound (**1**) and simple alkyl derivatives, show two major bands at 210–220 nm and 285–295 nm, of approximately equal intensity. Substituents extending conjugation produce a considerable shift in the long wavelength band ⟨84AHC(37)1⟩.

There is surprizingly little difference in the electronic absorption in 3H-pyrrolizine (**1**) and its anion ⟨67T2941⟩.

3H-pyrrolizin-3-ones are highly colored with bands at 220–240 nm, 290–300 nm, and 410–440 nm ⟨84AHC(37)1⟩. Strong acids cause a spectacular bathochromic shift of the long wavelength band up to 544 nm which has been attributed to O-protonation ⟨82CB706⟩.

IR spectra of pyrrolizines are not very characteristic. The carbonyl band of 3H-pyrrolizin-3-ones is at 1730–1745 cm^{-1}. A compilation is given in ⟨84AHC(37)1⟩.

8.01.4 THERMODYNAMIC ASPECTS

8.01.4.1 Aromaticity

Okamura and Katz have determined the pK_a of 3H-pyrrolizine (**1**) measuring the rate of exchange of the protons with 5 M D_2O in DMF containing 1 M triethylamine ⟨67T2941⟩. The value of $pK_a = 29$, which was attributed to the aromaticity of the pyrrolizine anion, however, seems surprisingly high compared with those of indene ($pK_a = 18.2$), cyclopentadiene ($pK_a = 15$) and fluorene ($pK_a = 22.8$).

8.01.4.2 Tautomerism

From the four possible tautomers of pyrrolizines, of particular interest are the tautomeric equilibria (**1b**)⇌(**1c**) and (**1a**)⇌(**1d**), the former being more widespread.



(**1a**) (**1b**) (**1c**) (**1d**)

In the absence of strong substituent influences, 3H-pyrrolizines ((**1b**) and (**1c**)) are more stable than their 1H-tautomers (**1a**) and (**1d**). A very detailed study of the ^{1}H-NMR spectrum of 3H-pyrrolizine (**1b**) (R = H) proved the structure ⟨68TL1181⟩. No 1H-tautomer could be detected.

One 1H-pyrrolizine has been observed, however, in equilibrium with the 3H-isomers. An attempt to prepare 5-methyl-3H-pyrrolizine (**1c**) (R = 5-Me) from 2-formyl-5-methylpyrrole and vinyl phosphonium salts (see Section 8.01.7.6) gave a mixture of three isomeric methylpyrrolizines (**1a**), (**1c**), and (**1d**) in the ratio of 44 : 46 : 10 ⟨72JCS(P1)2517⟩.

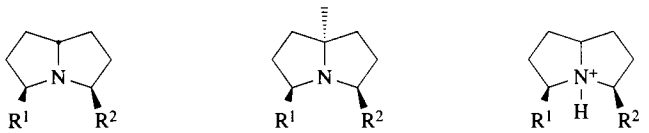
In pyrrolizines with substituents in position 2(6), the equilibrium (**1b**)⇌(**1c**) appears to depend on the electron-withdrawing or electron-donating character of the substituents: (**1b**), R = Me ⟨72JCS(P1)840⟩, Ph ⟨82TL1947⟩; (**1c**), R = CoPh and CO_2Et ⟨68CB3843⟩, COMe, SR and CHO ⟨71ACS2447⟩.

In 3(5)-substituted 3H-pyrrolizines the tautomer (**1c**) predominates if the substituent is conjugative. Tautomerism of mono- and polysubstituted pyrrolizines has been reviewed ⟨84AHC(37)1⟩.

8.01.4.3 Miscellaneous

The acidity of pyrrolizidines was studied in H_2O and MeCN–H_2O. For monosubstituted pyrrolizines, the pK_a values were greater for (**5**) than for (**6**). Proton and ^{13}C-NMR spectra indicated that 3,5-dimethylpyrrolizine exists mainly in the *trans*-fused form. In going from cyclopentane to a polar solvent, conformers with *cis*-fused rings predominate ⟨82KGS39⟩.

The stereochemistry of pyrrolizidinium salts (**7**) was studied using ^{13}C-NMR spectroscopy ⟨85KGS1638⟩.



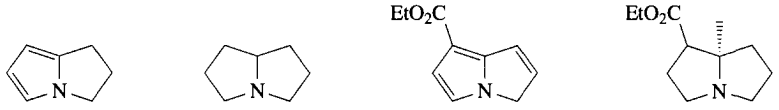
(**5**) (**6**) (**7**)

8.01.5 REACTIVITY OF FULLY CONJUGATED RINGS

8.01.5.1 Reduction

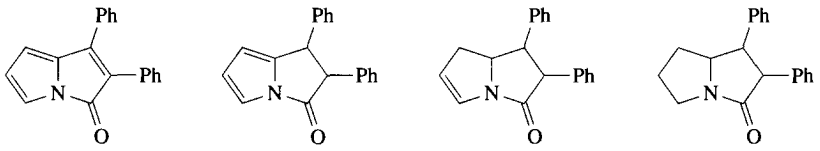
The (1,2- or 2,3-)double bond of pyrrolizines (**1**) and pyrrolizinones (**2**) and (**3**) is much more readily reduced than the pyrrole ring. 3H-pyrrolizine can be reduced to the dihydro derivative (**8**) using rhodium on carbon in ether. In ethanol, however, the same catalyst yields the pyrrolizidine (**9**) ⟨64JA2963⟩. Selective reduction of substituted pyrrolizines has been used to determine the proportion of mixtures of isomeric pyrrolizines ⟨66JOC2912, 72JCS(P1)2517⟩.

The stereoselective formation of a single isomer is particularly noteworthy. Ethyl ester (**10**) gives on reduction, predominantly the diastereomeric pyrrolizidine ester (**11**) ⟨71ACS2447⟩.



(8) (9) (10) (11)

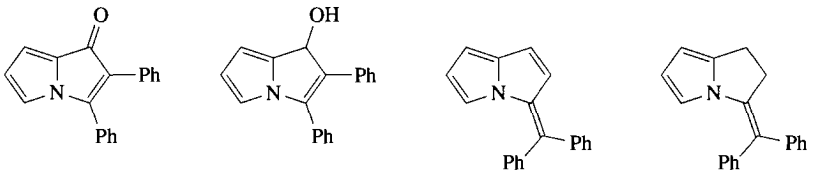
The double bond of 3H-pyrrolizin-3-one (**2**) is easily hydrogenated in the presence of palladium on charcoal yielding the dihydro derivative (**2a**) ⟨71CB2170⟩. From (**12**), a mixture of hydrogenated products (**13a**) and (**13b**) was obtained using Adams catalyst in ethanol. Reduction with the same catalyst in acetic acid, however, gave only the pyrrolizidine (**13c**) ⟨61AC(R)604⟩.



(12) (13a) (13b) (13c)

Reduction of 1H-pyrrolizin-1-one (**14**) with LAH gave the alcohol (**15**) ⟨61AC(R)595⟩.

A selective hydrogenation of the fulvenoid (**16**) to (**17**) took place with palladium/charcoal as a catalyst ⟨68CB3843⟩.



(14) (15) (16) (17)

8.01.5.2 Electrophilic Attack

Since 3H-pyrrolizines are vinylpyrroles, a high reactivity towards electrophiles is to be expected. Because of the instability of pyrrolizines, electrophilic reactions have only rarely been translated into synthetically useful processes.

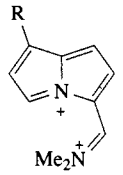
In dilute acids, pyrrolizines are generally unstable. Protonation of 3H-pyrrolizine (**1**) in concentrated sulfuric acid however, could be achieved yielding a mixture of 45% (**18a**) and 55% (**18b**) ⟨68CB3843⟩.



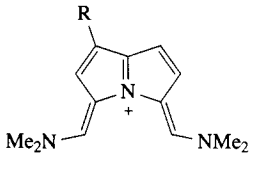
(18a) (18b)

The Vilsmeier reaction has attracted some attention as a route to cyclazines. 3H-pyrrolizine (**1**) gave the Vilsmeier salt (**19a**) on treatment with dimethylformamide and phosphoryl chloride at −60 °C. A second formylation to (**20a**) was achieved by treatment of (**19a**) with dimethylthioformamide and acetic anhydride ⟨80JCS(P1)1319⟩. Similar products were obtained from a chloroformylation of the ketone (**3a**): the Vilsmeier reaction at −50 °C gave the salt (**19b**) in 65% yield. From a reaction at 0 °C, 91% of the trisubstituted derivative (**21**) was obtained, which was hydrolysed

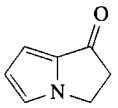
subsequently to give the dialdehyde (**22**). From (**19b**) the disubstituted product (**20b**) was obtained with dimethylthioformamide and acetic acid ⟨79CB2465⟩.



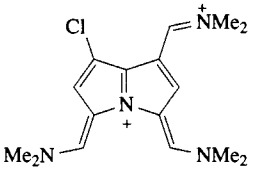
(**19**) (**a**) R = H
(**b**) R = Cl



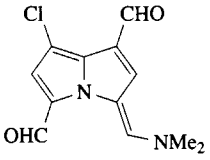
(**20**) (**a**) R = H
(**b**) R = Cl



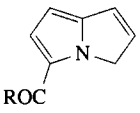
(**3a**)



(**21**)



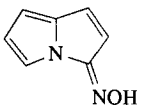
(**22**)



(**23**) (**a**) R = Me
(**b**) R = $CHCl_2$
(**c**) R = CCl_3

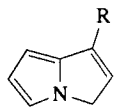
Acyl derivatives are formed in a reaction of 3H-pyrrolizine (**1**) with dichloroketene; ketones (**23**) were formed depending on the conditions used. Ketones (**23b**) and (**23c**) could be obtained in good yields from (**1**) and the appropriate acid chloride in ether in the presence of anhydrous potassium carbonate, but the 2-acetyl derivative (**23a**) could not be obtained in this way ⟨82JCR(S)54⟩.

The oxime (**24**) produced from 3H-pyrrolizine (**1**) with amyl nitrite is probably formed by electrophilic attack ⟨68CB3843⟩.

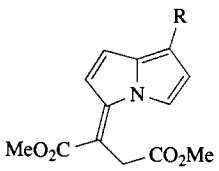


(**24**)

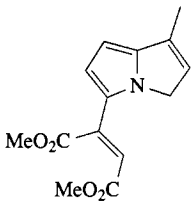
Electrophilic attack of acetylenedicarboxylates on 3H-pyrrolizines (**25**) are followed by a hydrogen shift to azafulvenes (**26**). A possible intermediate (**27**) has been obtained from (**25**; R = Me) and transformed into (**26**) (R = Me) at elevated temperature ⟨73JOC1583⟩. The cyclazine derivative (**28**) is a side product of the reaction ⟨72JCS(P1)844⟩.



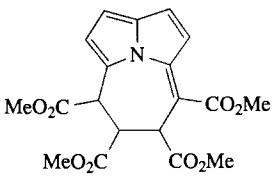
(**25**) R = H, Me



(**26**) R = H, Me

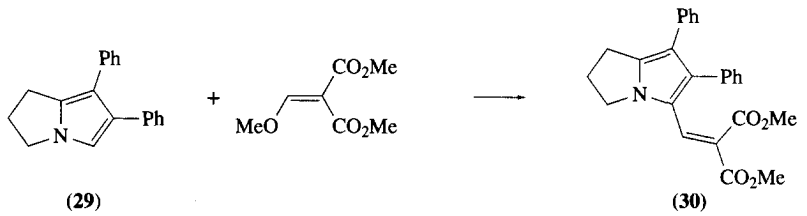


(**27**)



(**28**)

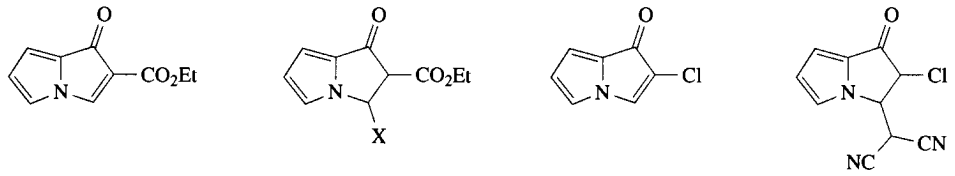
From a reaction of methoxymethylene malonate with the dihydropyrrolizine (**29**) the 2-substituted derivative (**30**) was obtained (Equation (1)) ⟨86AP(319)234⟩.



(29) (30) (1)

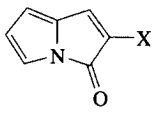
8.01.5.3 Nucleophilic Attack

Nucleophilic additions occur at 1H-pyrrolizin-1-ones that contain electron-withdrawing substituents at position 2. Pyrrolizinone (**31**) adds alcohol and dimethylamine, respectively, to give adducts (**32**). The chloro compound (**33**) is reported to react with malononitrile giving (**34**) although the chemical shift of H-3 (6.22 ppm) seems hard to justify ⟨82CB706⟩.



(31) (32) X = OH, NMe_2 (33) (34)

No Michael additions have been reported for pyrrolizin-3-ones. The chloro derivative (**35a**) experienced a nucleophilic substitution yielding derivatives (**35b**) ⟨80JCR(S)233⟩.

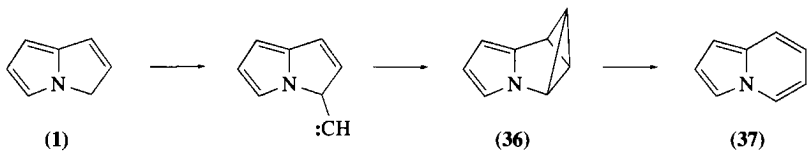


(35) (**a**) X = Cl
(**b**) X = OH, OEt, NEt_2

8.01.5.4 Cycloaddition and Cyclization

Cycloaddition reactions of 3H-pyrrolizines involve only the 1,2-double bond; azafulvenes and pyrrolizinimines can act as 8π-electron donors in the formation of a new ring linking C-3 to C-5.

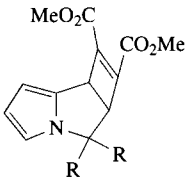
The reaction of 3H-pyrrolizine (**1**) with dichloromethane and *n*-butyllithium yielded the tetracyclic pyrrolizine derivative (**36**) and indolizine (**37**). The route in Scheme 1 has been proposed ⟨79HCA540⟩.



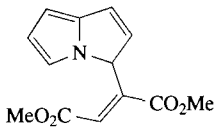
(1) (36) (37)

Scheme 1

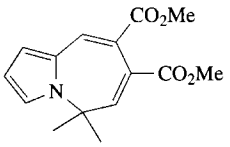
Photochemical $[\pi_2 + \pi_2]$ additions have been investigated by Johnson and Jones ⟨72JCS(P1)2517⟩. The parent 3H-pyrrolizine (**1**) reacted very rapidly with acetylenedicarboxylates in a thermal reaction. Only 5% of adduct (**38a**) was obtained from a photochemical reaction together with addition products (**39**). From 3,3-dimethyl-3-H-pyrrolizine, in which the thermal addition is slow because of steric hindrance, 26% of the adduct (**38b**) was obtained, which on heating gave the pyrroloazepine (**40**). This transformation throws some light on a reaction of the azafulvene (**41**) which resulted in the formation of pyrrolizine (**42**) and pyrroloazepine (**43**) ⟨74JHC811, 74CSC623⟩.



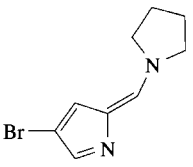
(38) (a) R = H
(b) R = Me



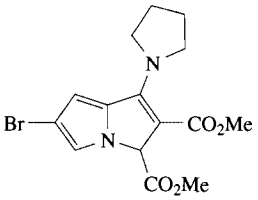
(39) *cis* = 17%
trans = 3%



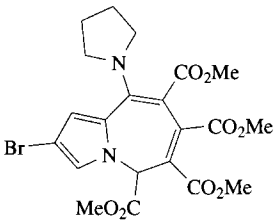
(40)



(41)

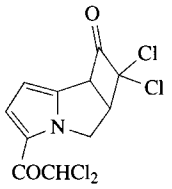


(42)

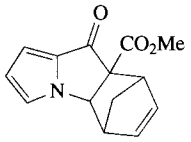


(43)

Dichloroketene generated from trichloroacetyl chloride and activated zinc in ether reacted with 3H-pyrrolizine (**1**) to give the adduct ((**44**) or its regioisomer) ⟨71ACS2447⟩. The double bond in methyl-1H-pyrrolizin-1-one-2-carboxylate reacts with cyclopentadiene forming (**45**) ⟨82CB706⟩.

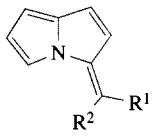


(44)

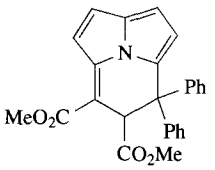


(45)

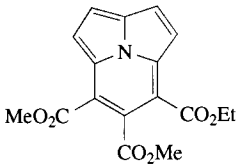
Azafulvenes can react with acetylenes to give cyclazines, in a $[\pi_8 + \pi_2]$-cycloaddition. Some activation of the exocyclic double bond seems to be necessary. The diphenyl derivative (**46a**) reacted rapidly with dimethyl acetylene dicarboxylate to give the (2.2.3)-cyclazine (**47**) after a hydrogen shift ⟨73JOC1583⟩. Ester (**46b**) reacted more slowly to give the cyclazine (**48**) dehydrogenation taking place in the reaction mixture ⟨72JCS(P1)2517⟩.



(46) (a) $R^1 = R^2 = Ph$
(b) $R^1 = CO_2Et$, $R^2 = H$

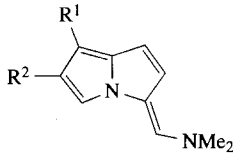


(47)

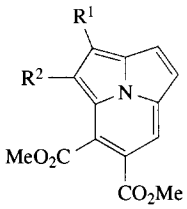


(48)

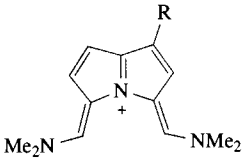
The dimethylamino derivatives (**49**) reacted with dimethyl acetylene dicarboxylate to give the cyclazines (**50**), elimination of dimethylamine provided the final unsaturation. Pyrrolizinium salts (**51**) have been cyclized by aqueous ammonia or by nitromethane and potassium *t*-butoxide to give cyclazines (**52**) ⟨79CB2465, 80JCS(P1)1319, 84CB1649⟩.



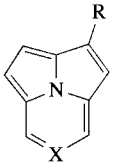
(49) $R^1 = R^2 = H$
R^1 = Cl, R^2 = H
R^1 = H, R^2 = COPh



(50)

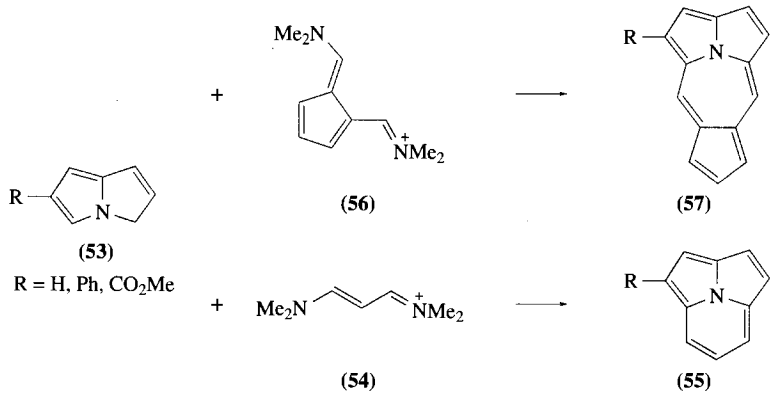


(51) R = H, Cl



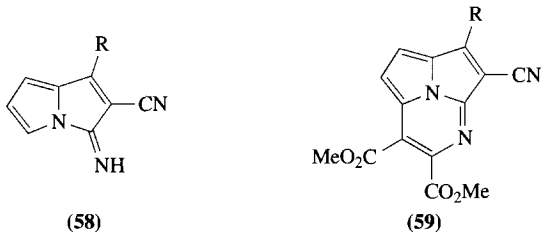
(52) R = H, Cl
X = CNO_2, N

(2.2.3)Cyclazines (**55**) can be made from 3H-pyrrolizines (**53**) and vinamidinium salts (**54**), or malondialdehyde diacetal. The cyclopentano(2.2.4)cyclazines (**57**) are formed by a similar route ⟨80JCS(P1)1324, 82TL1947, 84CB1649⟩.



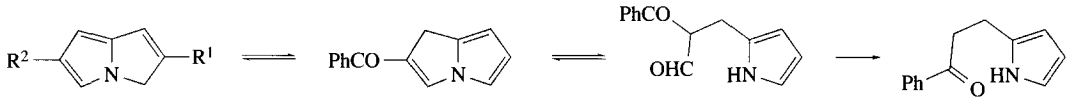
Scheme 2

5-Azacyclazines (**59**) have been obtained by [8π + 2π]cycloaddition of imino-3H-pyrrolizines (**58**) with DMAD ⟨88H(27)1465⟩.



8.01.5.5 Ring-opening Reactions

The benzoylpyrrolizines (**60**) are converted by dilute aqueous sodium hydroxide to 1-phenyl-3-(2-pyrryl)propan-1-one (**62**) (Scheme 3). Both pyrrolizines isomerize to the 1H-isomer (**60a**), which is an enamine of a β-diketone. A twofold hydrolysis gives the propanone (**62**) via (**61**) ⟨68CB3843⟩.

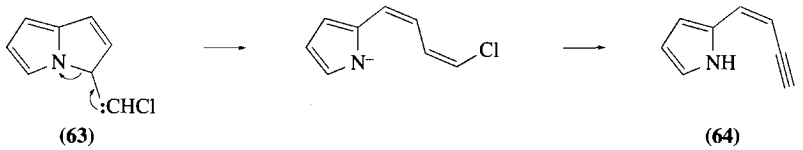


(**60**) R^1 = COPh, R^2 = H
R^1 = H, R^2 = COPh

(**60a**) (**61**) (**62**)

Scheme 3

In a reaction of 3H-pyrrolizine (**1**) with a lithium dicarbenoid species described in Section 8.01.5.4, anion (**63**) was assumed to be an intermediate which formed the butenyne (**64**) by ring opening ⟨79HCA540⟩. A similar ring-opening reaction has been described ⟨82JCR(S)54⟩:



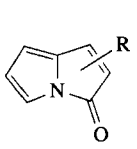
(**63**) (**64**)

Scheme 4

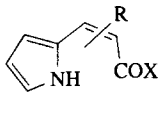
Pyrrolizinones can react with nucleophiles with opening of the carbonyl-containing ring. Pyrrolizin-3-ones (**65**) react with alcoholates in alcohol to give ester (**66**), hydrolysis by dilute sodium

hydroxide gives acrylic acids (**66**). A compilation of the reactions described is given in a 1984 review ⟨84AHC(37)1⟩.

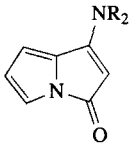
Dialkylaminopyrrolizin-3-ones (**67**) were reported to be stable to sodium ethoxide but hydrolyzed by aqueous acid or alkali to give 2-acetylpyrrole presumably via β-ketoacids which decarboxylate ⟨60JOC(25)2049, 65JOC(30)339⟩.



(**65**)

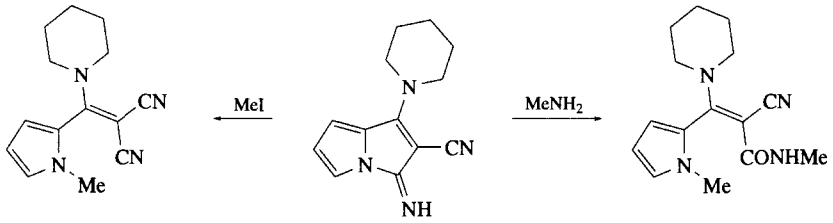


(**66**) R = OH, OR



(**67**) R = Me, Et

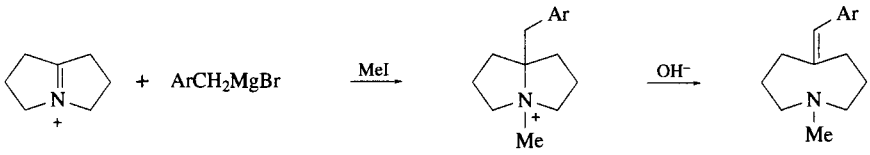
The pyrrolizinimine (**68**), reacted with methyl iodide or with methylamine in water to give pyrroles (**69**) and (**70**) ⟨74LA2110⟩.



(**69**) (**68**) (**70**)

Scheme 5

Ring opening of the 4,8-dehydropyrrolizinium ion was realized by the route in Scheme 6 ⟨85JCS(P1)2611⟩.



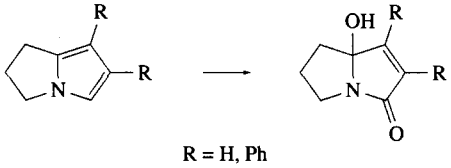
(**71**) (**72**) (**73**)

Scheme 6

A nucleophilic attack at one carbonyl group of 3,5-dioxopyrrolizidine results in ring opening. The keto derivative thus formed may cyclize again or react with a second molecule of a nucleophile yielding tertiary alcohol. Using special nucleophiles, both carbonyl groups of 3,5-dioxopyrrolizidine may react subsequently ⟨53LA225, 61CB1749, 64CB1542, 64CB1548, 71CB2852⟩. These reactions are summarized in Scheme 7.

8.01.5.6 Miscellaneous

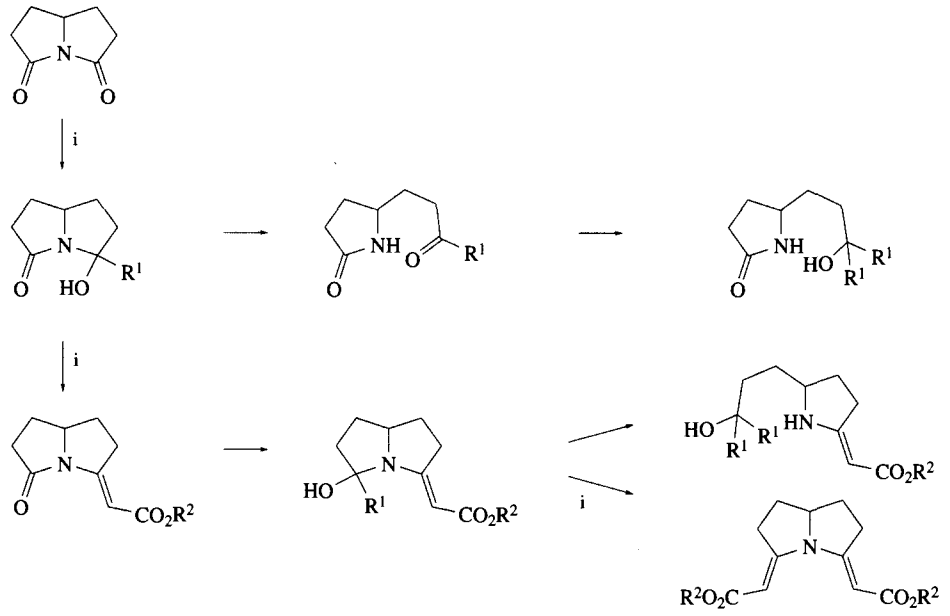
The reaction of 1,2-dihydropyrrolizines with singlet oxygen proceeds as expected for pyrroles ⟨85AP(318)663⟩, as shown in Equation (2).



R = H, Ph (2)

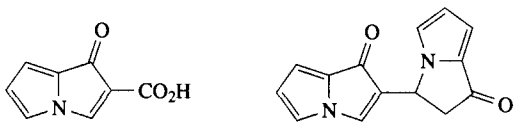
8.01.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Decarboxylation of the carboxylic acid (**74**) gives very little of the parent compound (**3**); instead (**75**) is produced when the anionic intermediate, formed on decarboxylation, adds in a Michael manner to the pyrrolizinone ⟨82CB706⟩.



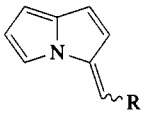
i, $BrZnCH_2CO_2R^1$; $R^1 = CH_2CO_2R^2$

Scheme 7



(74) **(75)**

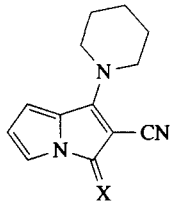
A number of transformations of the carbonyl group of pyrrolizin-3-ones have been reported. Wittig alkenation of 3H-pyrrolizin-3-one (**2**) gave the azafulvenes (**76**) ⟨71CB2170, 73CB1993⟩.



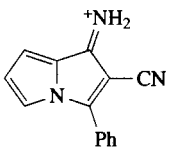
(76) R = CN, CO_2Et

The dimethyliminopyrrolizinium salt (**77a**) has been hydrolyzed to (**77b**) and converted into a mixture of *E*- and *Z*-imines (**77c**) by primary amines ⟨74LA2110⟩. On the other hand, the immonium salt (**78**) was reported to give the adduct (**79**) on hydrolysis ⟨82CB714⟩.

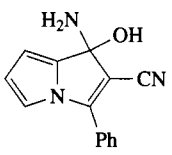
The diketopyrrolizine (**80a**) can be converted into a number of derivatives of the C-2 carbonyl group (i.e. (**80b**)).



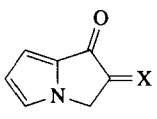
(77) **(a)** X = $^+NMe_2$
(b) X = O
(c) X = NPr^i, NC_6H_{11}



(78)



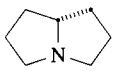
(79)



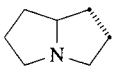
(80) **(a)** X = O
(b) X = NOH, NTs, NOAc

8.01.7 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

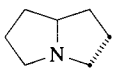
Synthetic routes can be classified according to the number and positions of new bonds formed. Because the sequence of bond formation is not always known, this representation is sometimes arbitrary. The classification used is shown in Figures 1 and 2.



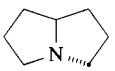
8.01.7.1
1,8-bond formation



8.01.7.2
1,2-bond formation

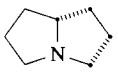


8.01.7.3
2,3-bond formation

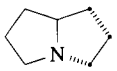


8.01.7.4
3,4-bond formation

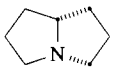
Figure 1 Modes of bond formation: formation of one bond.



8.01.7.5
1,8:2,3-bond formation



8.01.7.6
1,2:3,4-bond formation

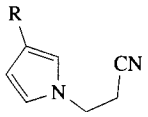


8.01.7.7
1,8:3,4-bond formation

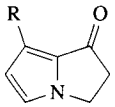
Figure 2 Modes of bond formation: formation of two bonds.

8.01.7.1 1,8-Bond Formation

Intramolecular acylation has been used frequently ⟨84AHC(37)1⟩. Houben–Hoesch cyclization of 1-β-cyanoethylpyrrole (**81a**) to 1-oxo-2,3-dihydropyrrolizine (**82a**) has been described repeatedly. A reproducible procedure gave 22% of (**82a**) ⟨79CB2465⟩. Purification of (**82a**) should be carried out in an efficient fume hood because it appears to induce analgesia ⟨67JHC627⟩. The methyl group in (**81b**) selectively activates C-2 for intramolecular substitution so that only the isomer (**82b**) is formed ⟨66JA1305⟩.

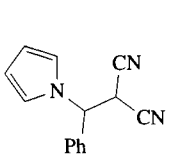


(**81**) (**a**) R = H
(**b**) R = Me

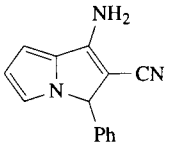


(**82**)

A reaction of the dinitrile (**83**) with hydrogen chloride in ether yielded the enaminonitrile (**84**). From the unsaturated (**85**), a dark blue immonium salt (**86**) was obtained ⟨80JCR(S)233⟩. A new metabolite from *Streptomyces olivaceus* has been shown to be (2*S*)-1-oxo-2,3-dihydropyrrolizin-3-carboxylic acid (**88b**) by total synthesis. Compound (**87**) was cyclized stereoselectively with phosphorus pentoxide in toluene. Partial racemization occurred during the hydrolysis of (**88a**) ⟨81TL3293⟩.



(**83**)

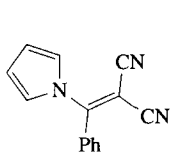


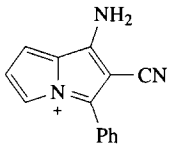
(**84**)

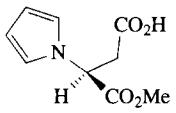
Further reactions have been used for cyclization. Phenylindole and diketene gave the acetoacetyl derivative (**89**), which on treatment with PPA gave the benzopyrrolizinone (**90**) ⟨76AP(309)131, 76AP(309)185⟩. An efficient synthesis of the aminopyrrolizine (**92a**) was achieved by Mannich reaction of aldehyde (**91**). Treatment with sodium cyanide gave nitrile (**92b**) ⟨71JOC3992⟩.

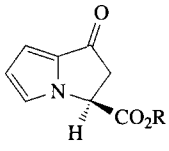
Intramolecular condensation of pyrrolidone (**93**) gave the hydroxypyrrolizidine (**94**) ⟨70HCA351⟩. Oxidative coupling of N-benzoylpyrroles gave benzopyrrolizinones (**95**) ⟨81CC254⟩.

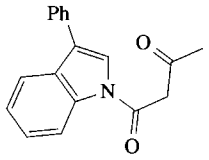
Benzopyrrolizinones were obtained from phthalimides (**96**) by photochemical routes. A mixture

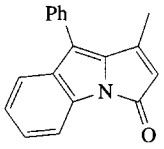

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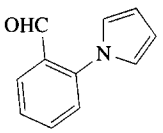

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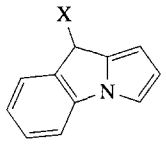

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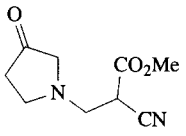

(88) (a) R = Me
(b) R = H

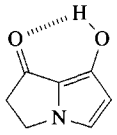

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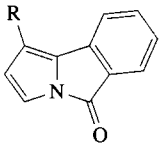

(90)


(91)

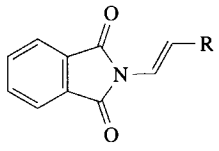

(92) (a) X = NMe_2
(b) X = CN

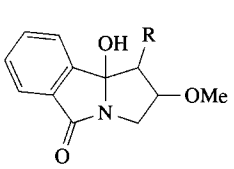

(93)

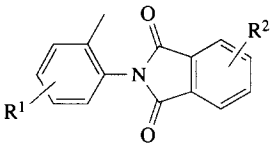

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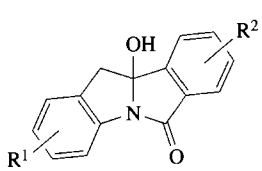

(95)

of isomers (**97**) whose configuration was carefully investigated was formed in methanol, ⟨81JOC3612⟩. Formation of dibenzopyrrolizinone (**99**) from (**98**) was also reported, phthalimides with electron withdrawing groups resisting cyclization ⟨75H(3)553⟩.

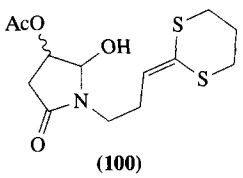

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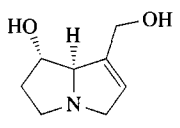

(97)


(98)


(99)

A practical synthesis of the unsaturated pyrrolizidine (+)-heliotridane (**101**) was achieved via stereoselective acyliminium cyclization of (**100**). The ketene dithioketal substituent served both as an efficient cationic cyclization terminator and as a means of controlling double-bond migration regioselectively into the correct position ⟨93JA3653⟩.

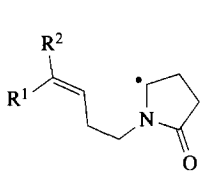

(100)


(101)

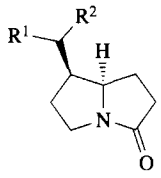
Acylaminoradicals (**102**), which can be generated by butyltin radical-mediated cleavage of a C—S bond, cyclize with good regio- and stereoselectivity to afford pyrrolizidinones (**103**) ⟨84JA8209⟩.

The cyclization of (**104**) to the pyrrolizidine derivative (**105**) involves addition of a tributylstannyl radical to the thiocarbonyl group and intramolecular addition of the radical formed to the double bond ⟨92JOC6803⟩.

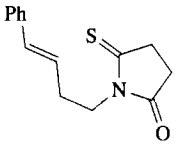
Intramolecular nucleophilic aromatic substitution of (**106**) was useful for a synthesis of dihydropyrrolizines (**107**) ⟨85TL2831⟩.



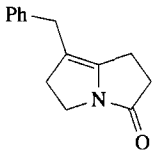
(102)



(103)

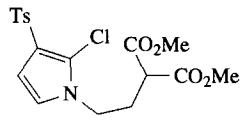


(104)

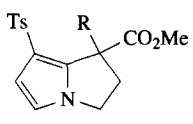


(105)

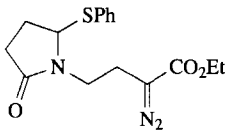
A synthesis of pyrrolizidine (**109**) from (**108**) by intramolecular carbene displacement has been described ⟨88JCS(P1)833⟩.



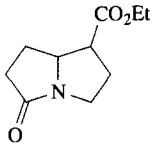
(106)



(107) R = H, CO_2Me

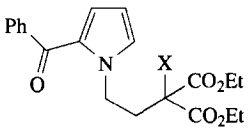


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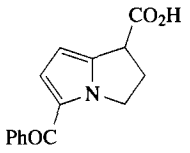


(109)

Compound (**111**) was obtained either from (**110a**) by intramolecular oxidative addition or from (**110b**) by bromine abstraction mediated by aerial oxidation of triethylborane ⟨92CJC1838⟩.



(110) (a) X = H
(b) X = Br



(111)

8.01.7.2 1,2-Bond Formation

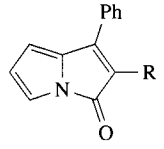
From reaction of 2-formylpyrrole and 2-benzoylpyrrole with phenacyl bromide pyrrolizinones (**112**) were obtained via N-acylpyrroles ⟨71CB2170⟩. Similarly, 5-alkoxy-2-formylindoles (**113**) were converted to benzopyrrolizines (**114**) by treatment with methyl vinyl ketone in the presence of trimethylbenzylammonium hydroxide in dioxane ⟨74ABC381⟩. From diketone (**115**) a mixture of pyrrolizines (**116**) was obtained ⟨78CB2407⟩. A base catalyzed cyclization of compound (**117**) gave a mixture of isomeric esters or ketones (**118**) ⟨68CB3843⟩.

Intramolecular Claisen condensation of triester (**119**) gave the ketopyrrolizine (**120**), which, following saponification and decarboxylation was reduced to (**121**) or (**122**). Dihydropyrrolizines such as (**121**) are metabolites of highly toxic pyrrolizidine alkaloids ⟨71HCA449⟩.

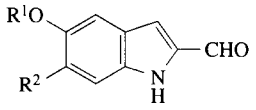
Friedel–Crafts reaction has found application to form the 1,2-bond in pyrrolizines. The anhydride (**123**) was treated with aluminum chloride to give a 93% yield of (**124a**) which on heating with copper gave a 91% yield of (**124b**) ⟨60CB81⟩.

The fully conjugated pyrrolizine (**126**) was obtained from indole (**125**) on treatment with PPA ⟨76M663, 69JHC514⟩.

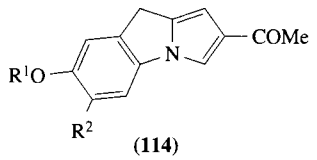
Enantioselective synthesis of (−)trachelanthamidine (**127**) took place from allylic iodoacetamide (**128**) by atom-transfer annulation ⟨88JA7536⟩ and functional group transformation.



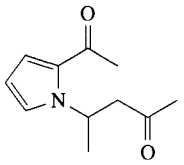
(112) R = H, Ph



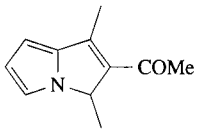
(113) R^1 = Me, CH_2Ph
R^2 = H, Me

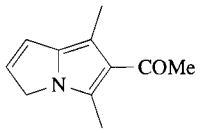


(114)

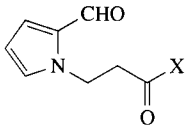


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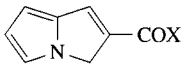




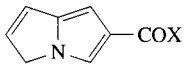
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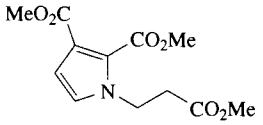
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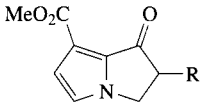
X = OR, Ph



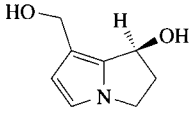
(118)



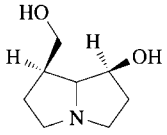
(119)



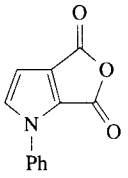
(120) R = CO_2H, H



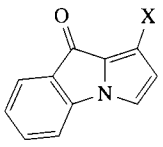
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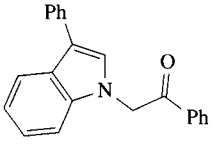
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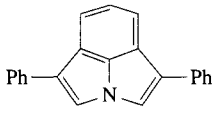
(123)



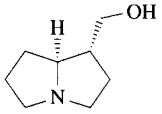
(124) (a) X = CO_2H
(b) X = H



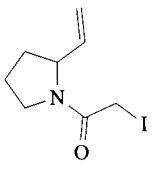
(125)



(126)



(127)



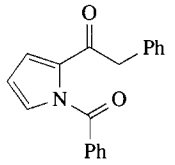
(128)

8.01.7.3 2,3-Bond Formation

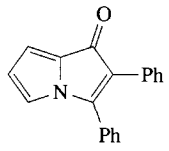
2,3-Diphenylpyrrolizin-1-one (**130**) was prepared by cyclization of the ketoamide (**129**) ⟨61AC(R)595⟩.

The 2-aza-Cope N-acyliminium ring closure of hydroxy lactone (**131**) proceeds in a stereoselective fashion via primary N-acyliminium intermediates (**132**), which may also be obtained from hydroxymethyl lactam (**133**). From a reaction of (**131**) in HCO_2H at room temperature for 18 h 77% of diastereomeric pyrrolizidines (**134**) were obtained ⟨83TL2109⟩.

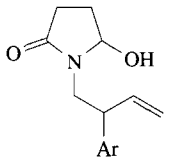
(**135**) was transformed into (**136**) by the same route ⟨85T1999⟩.



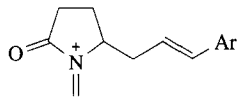
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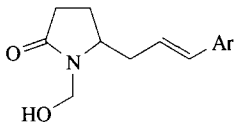
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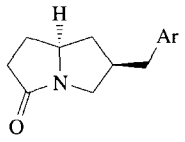
(131)



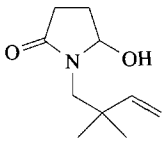
(132)



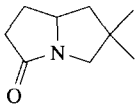
(133)



(134)



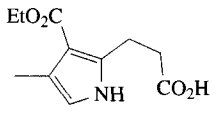
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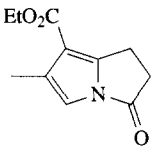
(136)

8.01.7.4 3,4-Bond Formation

An early example from the 1930s, of an intramolecular *N*-acylation of a pyrrole was provided by Fischer ⟨32LA1⟩ who obtained the pyrrolizinone (**138**) from acid (**137**) using acetic anhydride. Similar cyclizations have been reported to proceed in moderate yields only ⟨80JCS(P1)97⟩.

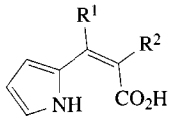


(137)

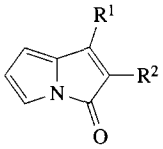


(138)

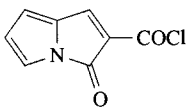
Several pyrrolizinones (**140**) have been prepared from pyrrolyl acrylic acids (**139**) with acetic anhydride; (**140a**) could be obtained from (**139a**) or (**139b**) ⟨77H(6)1125, 79TL3699⟩. A reaction of (**139b**) with phosphorus pentachloride gave the acid chloride (**141**) ⟨80JCR(S)233⟩.



(139) (**a**) $R^1 = R^2 = H$
(**b**) $R^1 = H$, $R^2 = CO_2H$
(**c**) $R^1 = Me$, $R^2 = H$
(**d**) $R^1 = CH_2{-}O{-}CH_2{-}Ph$, $R^2 = CO_2H$



(140a,c,d)



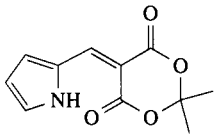
(141)

Compound (**140a**) is formed in 98% yield by flash thermolysis of (**142**) which was obtained from 2-formylpyrrole and Meldrum's acid. A possible ketene intermediate may react in an intramolecular cyclization ⟨81JOC2809⟩.

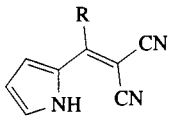
Dinitriles (**143**) on treatment with bases gave iminopyrrolizines (**144**) or aminopyrrolizines (**145**) depending on the substituent R ⟨74LA2110, 74AJC2635⟩.

Intramolecular alkylation of suitably substituted pyrroles and indoles gives pyrrolizines in excellent yields. The transformation of (**146**) into (**147**) may serve as an example ⟨80JCS(P1)97⟩.

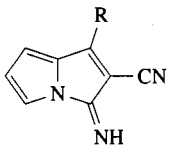
2-Acylpyrroles react with allylphosphoranes to give pyrrolizines (**149**). One butadiene (**148**) has been isolated and cyclized subsequently ⟨66JOC2912⟩. This example may, however, not generally be



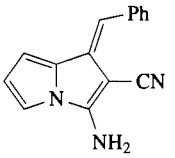
(142)



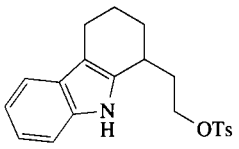
(143)



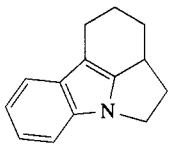
(144)



(145)

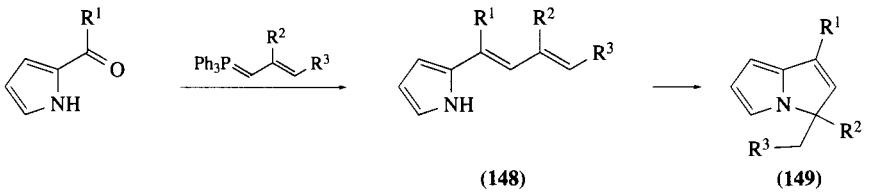


(146)



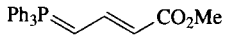
(147)

the case since (**151**) which was obtained from 2-formylpyrrole and (**150**) could be cyclized only to 3*a*-azaazulenone (**152**) ⟨73CB1993⟩.

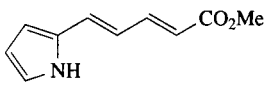


(148) (149)

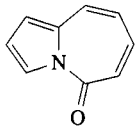
Scheme 8



(150)



(151)



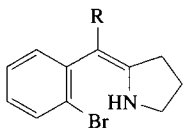
(152)

The formation of (**154**) from (**153**) occurred in a nuclear aromatic substitution ⟨76JCS(P1)389⟩. The formally similar transformation of (**155**) to (**156**), however, used potassium ferricyanide to form a quinone in the first place, cyclization being effected subsequently by reductive addition ⟨71CPB977⟩.

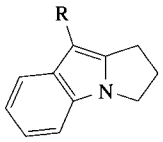
The synthesis of 3,5-dioxopyrrolizidine (**158**) from (**157**) was carried out by a route which has been described repeatedly ⟨53LA225, 55CB509, 88SC37⟩.

8.01.7.5 1,8 : 2,3-Bond Formation

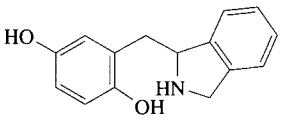
A synthesis of 1-oxo-1H-2,3-benzopyrrolizines (**161**), using a 1,3-dipolar cycloaddition, has been reported ⟨77JOC559⟩. Isatins (**159**) on treatment with acetic anhydride formed mesoionic intermediates (**160**), which underwent 1,3-dipolar cycloaddition *in situ* with dimethyl acetylenedicarboxylate to give benzopyrrolizines (**161a**). Ethyl propiolate gave only (**161b**) with no evidence of a second possible isomer.



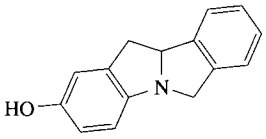
(153)



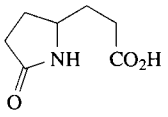
(154)



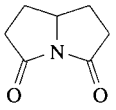
(155)



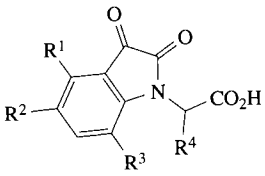
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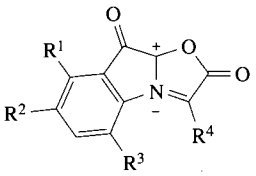
(157)



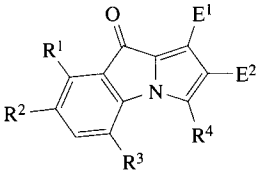
(158)



(159)

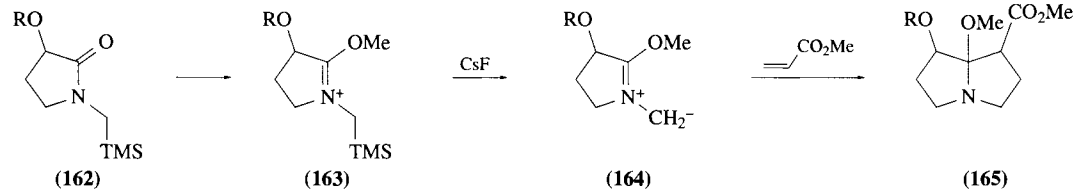


(160)



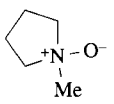
(161) (a) $E^1 = E^2 = CO_2Me$
(b) $E^1 = CO_2Me$, $E^2 = H$

Pyrrolidone (**162**) was treated with methyl triflate to generate the imidate salt (**163**) which was desilylated in the presence of methyl acrylate to give the pyrrolizidine (**165**) presumably via (**164**) ⟨85JOC2170⟩. Ylide intermediates of type (**164**) are accessible also from *N*-methylpyrrolidine *N*-oxides (**166**) with LDA ⟨85H(23)653⟩.



(162) (163) (164) (165)

Scheme 9

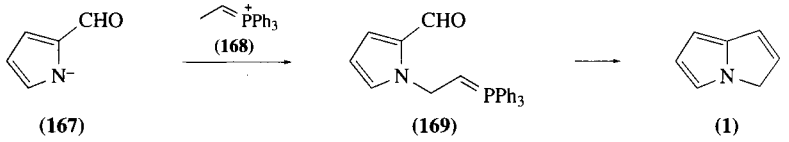


(166)

8.01.7.6 1,2:3,4-Bond Formation

A widely applicable cyclization method discovered by Schweizer is based on a nucleophilic addition to vinylphosphonium salts followed by an intramolecular Wittig reaction ⟨64JA2744⟩. The

reaction of the 2-formyl pyrrole anion (**167**) with vinyltriphenylphosphonium bromide (**168**) is among the first to have been investigated (Scheme 10) ⟨66JOC870⟩.

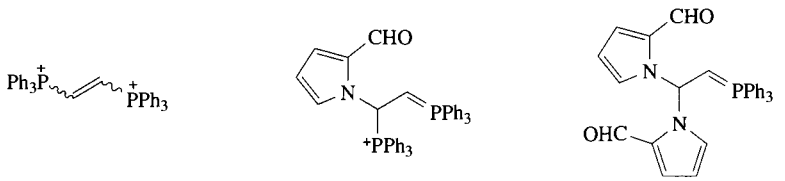


(**167**) (**169**) (**1**)

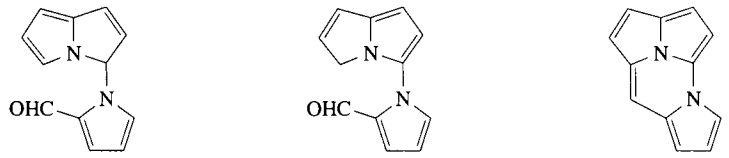
Scheme 10

Numerous substituted pyrrolizines have been obtained by this route from 2-acylated pyrroles and indoles respectively with substituted vinylphosphonium salts ⟨84AHC(37)1⟩.

A reaction of the anion of 2-formylpyrrole (**167**) with the bisphosphonium salt (**170**) gave the cyclazine derivative (**174**). From a transformation of isolated intermediates (**173**) and additional experiments a multistep reaction via (**171**)–(**173**) was deduced ⟨80CB614⟩.



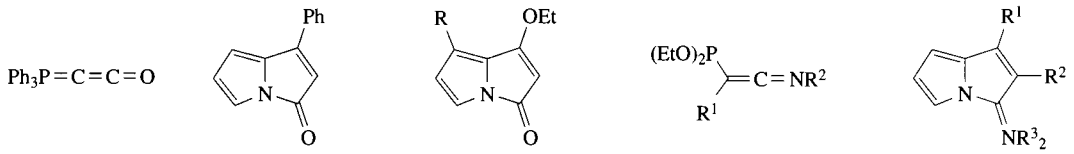
(**170**) (**171**) (**172**)



(**173a**) (**173b**) (**174**)

3H-Pyrrolizin-3-one (**176**) was obtained from 2-benzoylpyrrole and the ylide (**175**) ⟨76AG92, 81TL3839⟩. No analogous reaction could be achieved with 2-formylpyrrole. Pyrrolizinones (**177**) however, were obtained from the corresponding esters ⟨80CB2694, 80CB3086⟩.

From 2-acylpyrroles and keteniminophosphonates (**178**) 3H-pyrrolizin-3-imines (**179**) were obtained ⟨76AG92⟩.

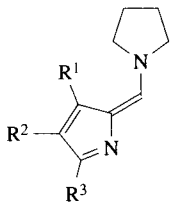


(**175**) (**176**) (**177**) (**178**) (**179**) R^1 = H, Ph; R^2 = H, Me; R^3 = Ph, Et

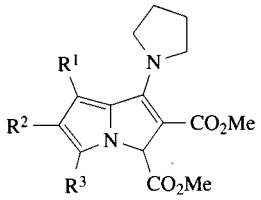
Cycloaddition reactions have been carried out with Vilsmeier bases of pyrroles. Thus reaction of (**180**) with dimethylacetylene dicarboxylate gave pyrrolizines (**181**) and 3*a*-azaazulenes (**182**) in a non-concerted reaction ⟨74JHC811⟩. In a closely related reaction, (**183**) was obtained from the Vilsmeier base with phenyl isocyanate ⟨76H(4)1281⟩.

Reactions of pyrrole carboxaldehyde with various hetero-substituted ethenes (**184**) yielded 3H-pyrrolizines (**185**) which, in the case of vinylsulfones, react further to give a cyclazine (**186**) and a disubstituted pyrrolizine (**187**) ⟨84CB1424⟩.

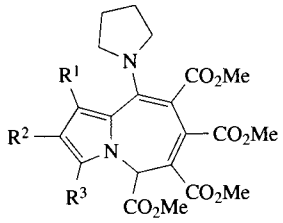
The chiral auxiliary (**188**) was obtained from the anion of pyrrol-2-aldehyde and phosphonate (**189**) and used in asymmetric synthesis ⟨92TA1515⟩.



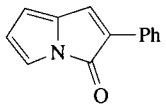
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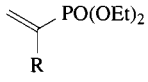
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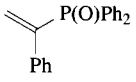
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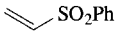
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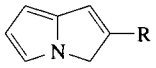
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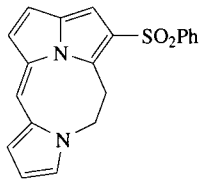
(184b)



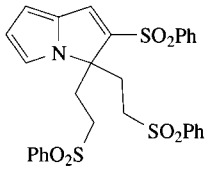
(184c)



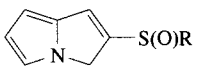
(185) R = CO_2Et, SO_2Ph, Ph



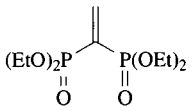
(186)



(187)



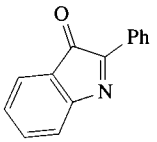
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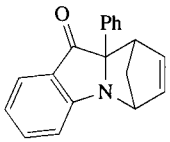
(189)

8.01.7.7 1,8:3,4-Bond Formation

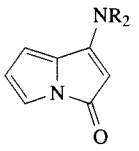
Diels–Alder reaction of indolone (**190**) with cyclopentadiene in the presence of aluminum chloride gave (**191**) ⟨69TL1527⟩. Under the influence of phosphoryl chloride, pyrrole reacts with malonic acid derivatives to give 1-aminopyrrolizin-3-ones (**192**) ⟨60JOC2049, 65JOC339⟩. Condensation of 3-substituted indoles with acetone in the presence of aluminum chloride gave both possible benzopyrrolizines (**193**) and (**194**) ⟨72AP(305)96, 72AP(305)117⟩.



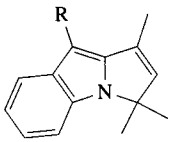
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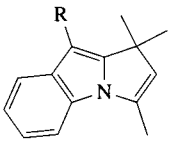
(191)



(192)



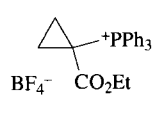
(193)



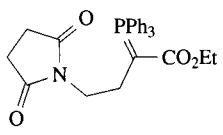
(194)

Partially hydrogenated pyrrolizines are easily obtained in high yield from a reaction of imides with cyclopropylphosphonium salt (**195**). Pyrrolizine ester (**197**) was obtained from succinimide, in a reaction via (**196**); phthalimide gave the benzopyrrolizinone (**198**) ⟨80TL4585, 81TL719⟩. Compound (**199**) was obtained from succinimide with triphenylcyclopropylphosphonium tetrafluoroborate ⟨88LA387⟩.

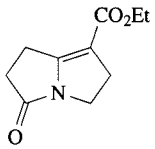
Pyrrolidine formamidine (**200**) transformed into the metalloderivative (**201**) was alkylated with



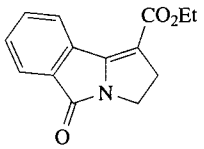
(195)



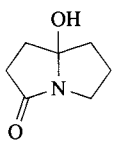
(196)



(197)

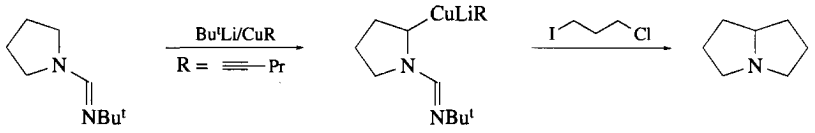


(198)



(199)

bifunctional electrophiles and cyclized, on formamidine removal, to pyrrolizidine (**202**) (Scheme 11) ⟨84TL939⟩.

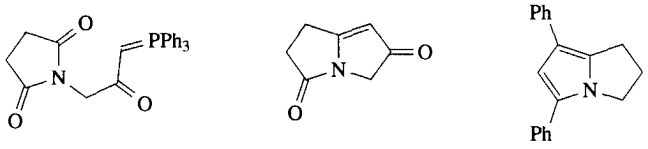


(200) (201) (202)

Scheme 11

Pyrrolizinedione (**204**) was obtained from succinimide with 1-bromoacetyl-triphenylphosphonium bromide via (**203**) ⟨88LA387⟩.

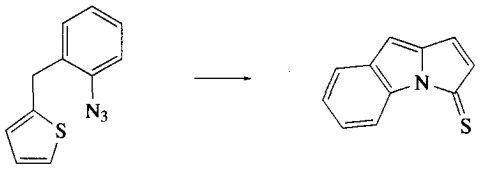
Compound (**205**) was synthesized in 60% yield by heating dibenzoylmethane with pyrrolidine in a limited amount of benzene in the presence of molecular sieves ⟨92SC2737⟩.



(203) (204) (205)

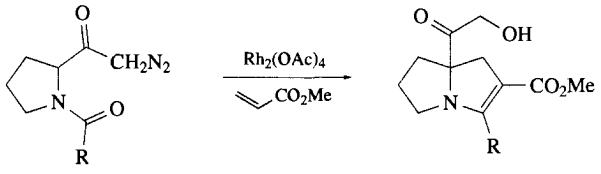
8.01.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

An intramolecular insertion of an intermediate nitrene occurs when azide (**206**) is heated in trichlorobenzene at 180 °C to give the benzopyrrolizinehione (**207**), albeit in poor yield ⟨74JCS(P1)2072⟩.



(206) (207) (3)

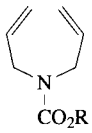
A tandem cyclization–cycloaddition reaction was developed as a method for synthesizing polycyclic ring systems which involved a rhodium(II) acetate-induced diazoketone cyclization onto a neighboring carbonyl group to generate an ylide followed by 1,3-dipolar cycloaddition. Thus (**208**) has been transformed into the 8-substituted pyrrolizidone (**209**) ⟨89JA6451⟩.



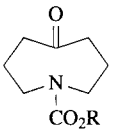
(208) (209) (4)

8.01.9 MISCELLANEOUS SYNTHETIC METHODS

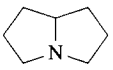
Hydroboration–carbon monoxide insertion of bisalkenic amino derivatives (**210**) provided facile preparations of 5-azacyclooctanes (**211**). Reductive ring closure afforded pyrrolizidines (**212**) ⟨82JOC1494⟩.



(210)

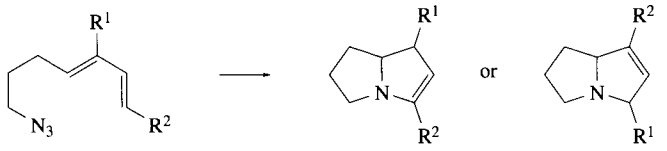


(211)



(212)

Intramolecular cycloaddition of azidodienes (**213**) gave pyrrolizidines (**214**) ⟨86JA3755, 90JOC5719, 90SL433⟩.

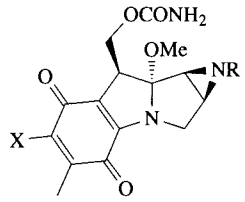


(213) (214a) (214b) (5)

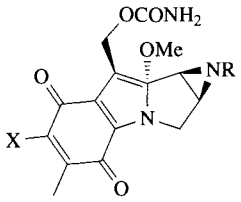
$R^1 = CO_2Et$, $R^2 = H$
$R^1 = H$, $R^2 = CO_2Et$
$R^1 = SPh$, $R^2 = H$

8.01.10 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

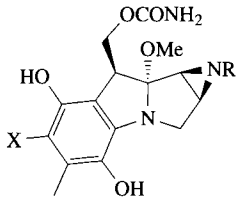
Mitomycin C (**215a**) shows a potent activity against a wide spectrum of tumors and bacteria. In spite of its high toxicity it is extensively used in chemotherapy especially in treating gastrointestinal cancers ⟨B-80MI 801-01⟩.



(215) (**a**) R = H, X = NH_2
(**b**) R = H, X = OMe



(216)

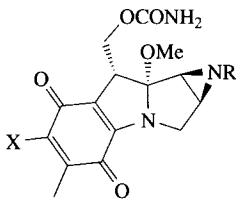


(217)

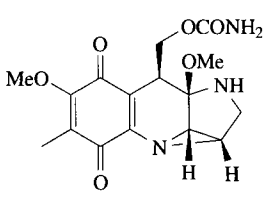
For synthetic chemists the structure of mitomycins presents a formidable challenge. This is mainly because these pyrrolizine derivatives undergo facile elimination of methanol to give unstable aziridino mitosenes (**216**) which easily react to give solvolyzed products. Reduction of the quinone group gives even more unstable hydroquinones (**217**).

The instability of mitomycin (**215a**) under reductive and acidic conditions is the basis for its biological activity ⟨88MI 801-01⟩.

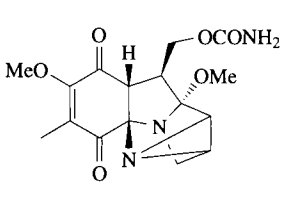
Taking into consideration the properties of mitomycins, two total syntheses have been achieved. The synthesis of mitomycin B (**217a**), reported by Kishi ⟨79MI 801-01⟩, comprises many steps, two of which are not stereoselective. The total yield of 0.2% demonstrates the enormous difficulties in the synthesis of such a highly functionalized molecule.



(217a)



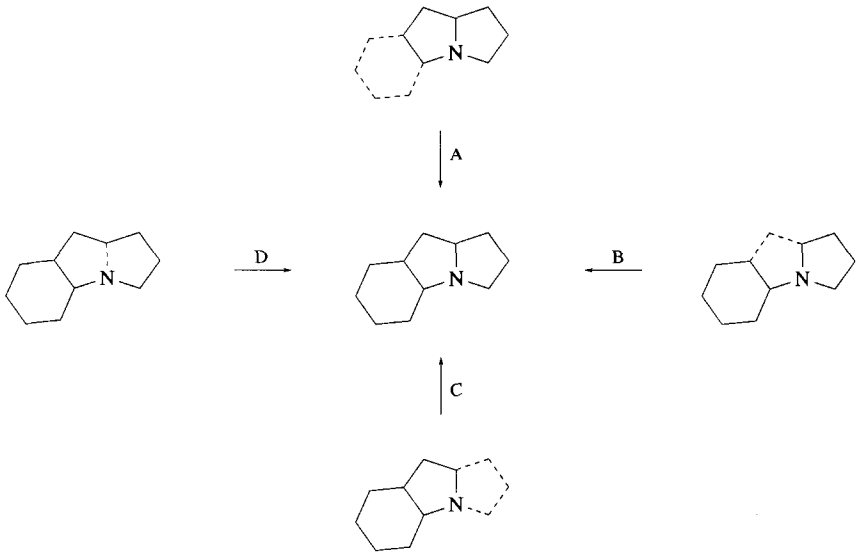
(218)



(219)

The second synthesis was based on results from screening studies of minor constituents from the fermentation broth of mitomycins, which led to isomers (**218**) and (**219**) of mitomycin equilibrating with mitomycin A (**215b**). Isomitomycin A (**218**) could be synthesized in reasonable yields and transformed subsequently into mitomycin A and mitomycin C in optically active forms. A detailed review of this work has appeared ⟨93MI 801-01⟩. Because of its low versatility, this very elegant and successful synthesis however, is not very suitable for syntheses of mitomycin derivatives which attact interest of medicinal chemists looking for analogues with higher activity and lower toxicity.

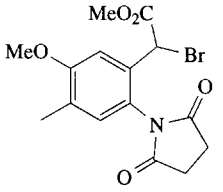
Synthetic studies in the mitomycin field have been reviewed several times ⟨79FOR1, 85LA1398, 92MI 801-01, 93MI 801-01⟩. This work is summarized in Scheme 12 ⟨85LA1398⟩.



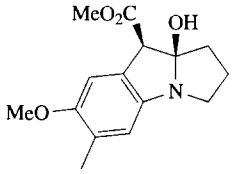
Scheme 12

The Kishi ⟨88MI 801-02⟩ synthesis follows route D. Here only some recent developments concerning routes A and B will be discussed.

Intramolecular Reformatski reaction yields suitably substituted benzopyrrolizidines. Thus from (**220**), the mitosane (**221**) was obtained ⟨85LA1398⟩.

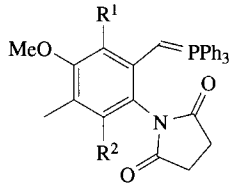


(**220**)

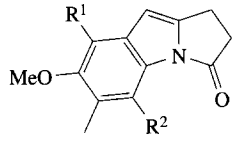


(**221**)

Cyclization by intramolecular Wittig reaction is a more versatile synthesis for substituted mitosenes as in the conversion of (**222**) to (**223**).



(**222**)

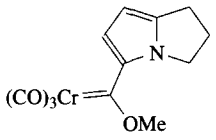


(**223**)

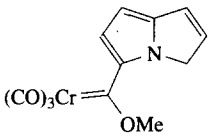
$R^1 = R^2 = H$; $R^1 = R^2 = OMe$; $R^1 = OBn$, $R^2 = OMe$

Functionalization of mitosenes has been studied thoroughly ⟨85LA1413, 85LA1422, 88LA381, 89LA239, 90MI 801-01⟩. The Dötz reaction ⟨84AG(E)587⟩ offers a simple and versatile route to mitosanes.

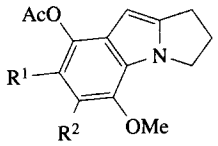
Benzopyrrolizines (**226**) and (**227**) were obtained from chromium(0) carbene complexes (**224**) and (**225**) with acetylenes. The regioselectivity of the cycloaddition of alkoxypropynes could be reversed leading for the first time to a trimethylsilyl benzopyrrolizine (**226d**) with a substitution pattern necessary for subsequent synthesis of mitomycins ⟨89TL1633, 89MI 801-01⟩.



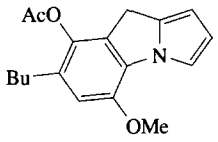
(**224**)



(**225**)



(**226**)



(**227**)

(**a**) R^1 = Me, R^2 = OMe; (**b**) R^1 = Me, R^2 = OEt
(**c**) R^1 = Bu^n, R^2 = H; (**d**) R^1 = TMS, R^2 = Me
(**e**) R^1 = Me, R^2 = TMS

8.01.11 IMPORTANT COMPOUNDS AND APPLICATIONS

Pyrrolizidine alkaloids are widespread in nature. New results in this field are reported annually ⟨93MI 801-02⟩. General reviews ⟨B-85MI 801-01, B-90MI 801-01, 87MI 801-01⟩ as well as reviews on the toxicology ⟨93MI 801-03⟩ and the synthesis ⟨88MI 801-02⟩ of pyrrolizidine alkaloids have appeared.

2,3-Dihydro-1H-pyrrolizines are as proline specific Maillard products ⟨85MI 801-01⟩.

Some pyrrolizidine derivatives are medically useful. 3,5-Dioxopyrrolizidine (**158**) (Rolziacetam, CI-911) is a cognition activator of the nootropic class. ⟨87JMC498⟩. Compounds of this type have the potential in treating disorders of learning and memory, for example Alzheimer's disease, age-associated memory impairment and other forms of senile cognitive decline. Background information is given by Moos *et al.* ⟨88MI 801-01⟩.

The antitumor activity of pyrrolizidine derivatives is noteworthy. A proof has been given that these antitumor compounds act by interstrand cross-linking ⟨93JA3407⟩. Most important are mitomycins, which are treated in Section 8.01.10.

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8.02
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: One Extra Heteroatom 1 : 0

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8.02.1 INTRODUCTION

This chapter covers those bicyclic 5-5 systems with one ring junction nitrogen atom and one extra heteroatom. There is no related chapter in the first edition of *Comprehensive Heterocyclic*

Chemistry (CHEC-I), but there is information about some of these types of compound in the two chapters dedicated to "Two Fused Five-membered Heterocyclic Rings" in CHEC-I ⟨84CHEC-I(6)973, 84CHEC-I(6)1027⟩. No general review of the topic exists, nor are there any systematic studies. The aim of this chapter is to present in a methodical way the work done primarily from 1982.

There are nine possible parent structures (labelled (A) to (I) below), in which the double bonds can be arranged in different ways to give 22 basic structures (Structures (**1**)–(**22**) in Figure 1):

(i) pyrrolo[1,2-*b*]pyrazole (A). The different arrangement of the double bonds give four tautomeric systems: 1*H*-(A) (**1**), 3*H*-(A) (**2**), 4*H*-(A) (**3**), 6*H*-(A) (**4**).

(ii) pyrrolo[1,2-*a*]imidazole (B) and pyrrolo[1,2-c]imidazole (C), which each exist as four tautomeric systems: 1*H*-(B) (**5**), 3*H*-(B) (**6**), 5*H*-(B) (**7**), 7*H*-(B) (**8**), 1*H*-(C) (**9**), 3*H*-(C) (**10**), 5*H*-(C) (**11**), 7*H*-(C) (**12**).

(iii) pyrrolo[1,2-*b*]isoxazole (D) (**13**).

(iv) pyrrolo[2,1-*b*]oxazole (E) (**14**).

(v) pyrrolo[1,2-*c*]oxazole (F). This parent structure must be partially saturated. There are three possible isomeric systems: 1*H*,3*H*-(F) (**15**), 3*H*,5*H*-(F) (**16**), 3*H*,7*H*-(F) (**17**).

(vi) pyrrolo[1,2-*b*]isothiazole (G) (**18**).

(vii) pyrrolo[2,1-*b*]thiazole (H) (**19**).

(viii) pyrrolo[1,2-*c*]thiazole (I). This system, like (F), must be partially saturated, and again three isomers are possible: 1*H*,3*H*-(I) (**20**), 3*H*,5*H*-(I) (**21**), 3*H*,7*H*-(I) (**22**).

Reduced derivatives of all these parent structures that is, dihydro, tetrahydro, and fully

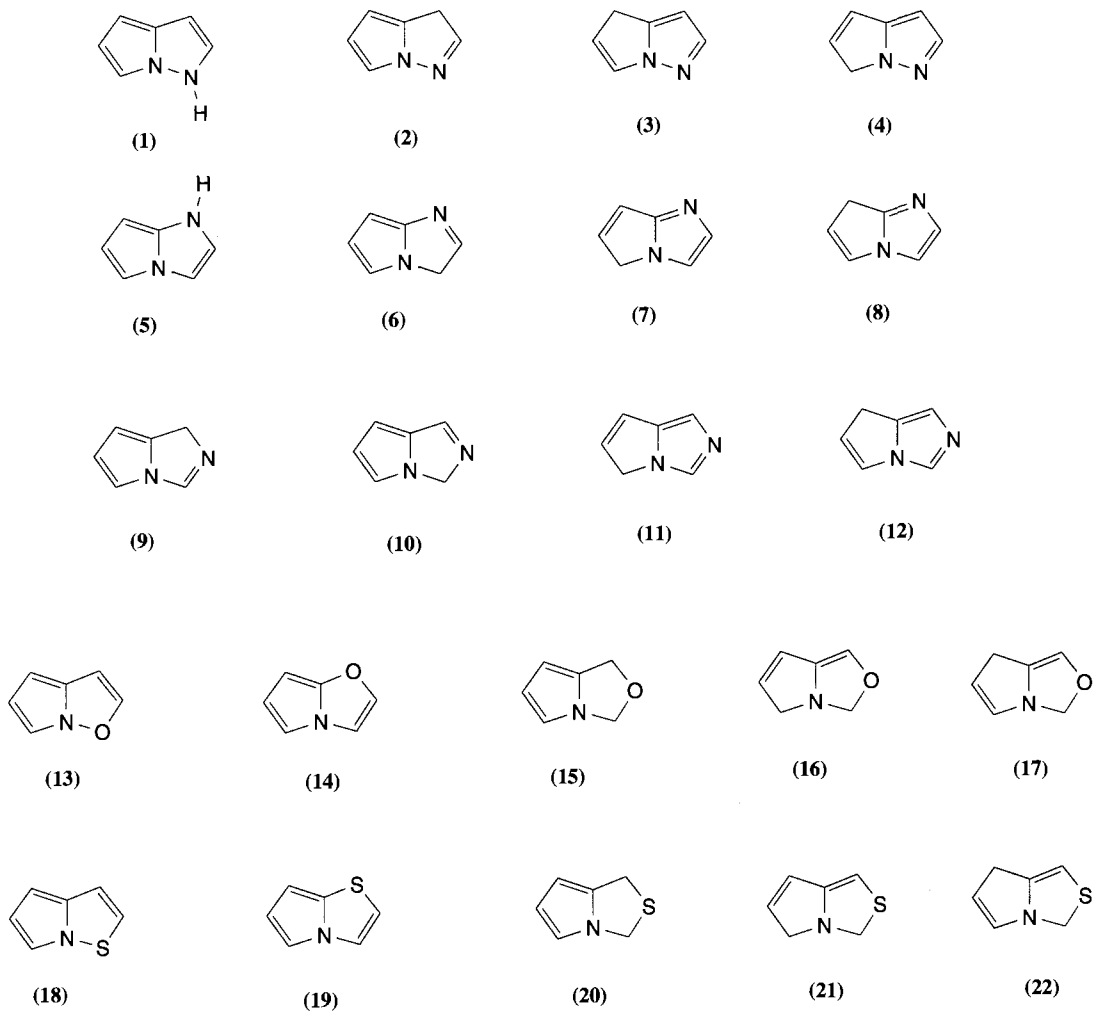


Figure 1 The 22 basic structures.

saturated systems increase greatly the number of possible compounds. Oxo compounds are also possible, and each of the nine parent structures has five different positions where the carbonyl group could be.

In spite of this wide variety of possibilities, very few structures are known, and the majority are found in the context of other fields of research, reported as casual examples.

Only eight of the 22 basic structures are in the literature: 6*H*-pyrrolo[1,2-*b*]pyrazole ⟨85T811⟩, 1*H*-pyrrolo[1,2-*a*]imidazole ⟨90H(31)977, 92JHC1473⟩, 7*H*-pyrrolo[1,2-*a*]imidazole ⟨90JCS(P1)1821, 92CB1939⟩, 1*H*-pyrrolo[1,2-*c*]imidazole ⟨89H(29)1137⟩, 3*H*-pyrrolo[1,2-*c*]imidazole ⟨83CL763⟩, 5*H*-pyrrolo[1,2-*c*]imidazole ⟨89JCS(PI)957⟩, pyrrolo[2,1-*b*]thiazole ⟨84AJC1473, 86JCS(P1)1255, 87JCS(P2)591, 88ZC214, 92JHC1473⟩, and 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole ⟨87JMC2109⟩.

Below are listed all other types of compound found, grouped as derivatives of the parent structures.

Four examples of the pyrrolo[1,2-*b*]pyrazole nucleus are described: 5,6-dihydro-4*H*- ⟨83TL1067, 85SC259⟩, 1,2,5,6-tetrahydro-4*H*-, 3a,4,5,6-tetrahydro-3*H*-⟨83TL1067⟩, and 6-oxo- ⟨87JCS(P1)653, 87JCS(P1)657⟩.

The pyrrolo[1,2-*a*]imidazole nucleus is known as dihydro or tetrahydro derivatives—2,3-dihydro-1*H*- ⟨84TL3901, 92JOC2347⟩, 6,7-dihydro-5*H*- ⟨83JCS(P1)3027, 86TL323, 87JHC561⟩, 2,3,6,7-tetrahydro-5*H*- ⟨83AX1426, 83CL93, 84MI 802-01, 85JOC2220, 85MI 802-01, 86JCS(P1)205⟩, 5,6,7,7a-1*H*- ⟨89TL6599⟩—and as oxo compounds: 5-oxo-5*H*- ⟨87JCS(P1)653, 87JCS(P1)657⟩, 2-oxo-2,3-dihydro-1*H*- ⟨86JHC393⟩, 7-oxo-5,6-dihydro-1*H*- ⟨89TL6599⟩, 2-oxo-2,3-dihydro-1*H*,5*H*- ⟨86JOC1537⟩, 5-oxo-2,3,5,6-tetrahydro-1*H*- ⟨89CB95⟩, 6-oxo-2,3,5,6-tetrahydro-1*H*- ⟨85H(23)1073⟩, 5-oxoperhydro- ⟨92SL219⟩, 2,5-dioxoperhydro- ⟨93JMC4214⟩, and 2,7-dioxoperhydro- ⟨84JOC113⟩. There is also one example of a zwitterionic compound with this basic structure ⟨84JOC3672, 86LS1085⟩.

Perhydropyrrolo[1,2-*c*]imidazoles are also known ⟨82TL4953, 83JOM(250)C9, 84BSF(2)77, 85JOM(296)173⟩. Ten different oxo derivatives have been reported: 1-oxoperhydro- ⟨90JOC2254⟩, 3-oxoperhydro- ⟨85JMC434⟩, 5-oxo-5*H*- ⟨87JCS(P1)653, 87JCS(P1)657⟩, 1,3-dioxo-2,3,5,6-tetrahydro-1*H*- ⟨82JPP752, 83JOC2337, 83LA1623, 83OMR(21)328⟩, 1-oxo-3-thioxo-2,3,5,6-tetrahydro-1*H*- ⟨83LA1468⟩, 1-oxo-3-thioxo-2,3,7,7a-tetrahydro-1*H*- ⟨82S502⟩, 3-oxo-1-thioxo-2,3-dihydro-1*H*- ⟨83IJC(A)24, 83IJC(A)1050, 84CJC1845, 84IJC(A)122, 84IJC(A)204, 84ZN(B)586, 86MI 802-01, 86PIA73⟩, 3,5-dioxo-2,3-dihydro-5*H*- ⟨91JOC858, 92JMC1267⟩, 1,3-dioxoperhydro- ⟨85BSB187⟩, 3,5-dioxoperhydro- ⟨92H(33)619⟩, and one 1-oxo-3-ammonio-2,3,5,6-tetrahydro-1*H*- ⟨83LA1623⟩, as well as two mesoionic compounds ⟨84MI 802-02, 90JOC910, 91JOC110⟩.

Only three types of pyrrolo[1,2-*b*]isoxazoles are reported—3a,4,5,6-tetrahydro-, perhydro-, and 2-oxoperhydro-—but there are many references that describe their synthesis ⟨82JOC5171, 82T2627, 83CC250, 83CC271, 83CL1195, 83JCS(P1)1275, 83TL1049, 84JA7979, 84JOC2412, 84JOC3127, 84T4513, 85CL957, 85CL1049, 85CPB351, 85HCA2299, 85JCS(P1)261, 85JOC3076, 85T3447, 85TL6249, 86JOC549, 86TL1489, 86TL1727, 89JCS(P1)2415, 89JOC1748, 90JOC1762, 91JOC4252, 91MRC645⟩.

Perhydropyrrolo[2,1-*b*]oxazoles are reported ⟨85AJC1591, 85G569, 86JOC3140⟩ as well as 3-oxoperhydro ⟨89AP(322)93⟩ and 5-oxoperhydro derivatives ⟨84JA1146, 85TL2047, 86JA306, 86JOC1541, 87T5663, 88JA7245, 89TL1745, 89TL4019, 90JOC791, 90T4951, 91JCS(P1)2299, 91JOC2294, 91SL863, 92SL219, 92T3945⟩.

Two derivatives of the perhydropyrrolo[1,2-*c*]oxazole are known ⟨84JA5360, 85TL5303⟩ and several oxoperhydro derivatives: 1-oxo- ⟨83JA5390, 85HCA155, 85T603⟩, 3-oxo- ⟨82TL4887, 83JA654, 83JCS(P1)395, 84JA4192, 85CPB5042, 85JMC482, 85JOC3669, 86CL735, 88JOC5491, 89CL1449, 92T9373, 94CC1383⟩, 1,3-dioxo-⟨83JPS(A)1699, 83MI 802-01, 86JMC89⟩, 1,5-dioxo-⟨84JHC1393⟩, and 3,5-dioxo- ⟨92H(33)619⟩. A mesoionic compound is also known ⟨85TL1295⟩.

No pyrrolo[1,2-*b*]isothiazoles are reported in the literature.

Pyrrolo[2,1-*b*]thiazoles are reported as 2,3-dihydro- ⟨83BJ(211)447, 88JMC1427⟩, 5,6,7,7a-tetrahydro-⟨82H(19)2259, 85BCJ3137, 85BCJ3320, 85T3537⟩, or perhydro- ⟨83CC250, 83H(20)1907, 83TL3419, 84T4513⟩ derivatives. Also described are some oxo derivatives: the 3-oxo-2,3-dihydro- ⟨83JHC591, 83JOC3365⟩, 5-oxo-5*H*,7a*H*-⟨84H(22)2341⟩, 5-oxo-2,3,5,6-tetrahydro- ⟨88S284⟩, 5-oxo-2,3-dihydro-5*H*,7a*H*-⟨86JCS(P1)2195⟩, 5-oxo-6,7-dihydro-5*H*,7a*H*- ⟨86TL3453⟩, 6-oxo-2,3,5,6-tetrahydro- ⟨85H(23)1073⟩, 3-oxoperhydro- ⟨87AP(320)799, 87AP(320)1278⟩, 5-oxoperhydro- ⟨86CC409, 86TL3453, 89T4537⟩, 3,5-dioxoperhydro- ⟨87JMC498⟩, and mesoionic compounds ⟨86JOC117⟩.

3-Oxoperhydropyrrolo[1,2-*c*]thiazole derivatives are also reported in the literature ⟨82TL3807, 82TL3811, 85T1999, 85T2861⟩.

Due to the diversity of compounds, the information in this chapter is organized in sections, each of which covers one parent structure and its derivatives. The last section is concerned with the biological activity and applications of these bicyclic 5-5 systems.

8.02.2 PYRROLO[1,2-*b*]PYRAZOLES

8.02.2.1 Introduction

Relatively little has been reported on the chemistry of this system. In CHEC-I ⟨84CHEC-I(6)973⟩ there are only five examples ⟨72TL1707, 73JOC4259, 81JA239, 81T2595, 82JOC4256⟩. Only a few references can be found from 1983, all of them related to the synthesis of individual derivatives.

8.02.2.2 Theoretical and Experimental Structural Methods

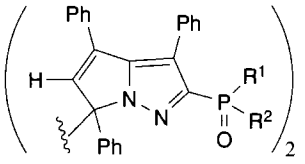
8.02.2.2.1 Theoretical methods

Theoretical calculations on this type of compound have not been described. No thermodynamic aspects are reported.

8.02.2.2.2 Experimental methods

(i) X-ray

The structure of a bis(6*H*-pyrrolo[1,2-*b*]pyrazole) (**23**) has been determined by x-ray crystallography ⟨85T811⟩.

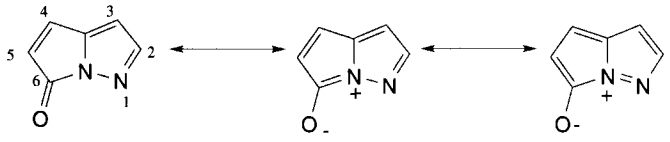


$R^1 = R^2 = OMe$

(23)

(ii) NMR spectroscopy

The ^1H and ^{13}C NMR spectra of 6-oxopyrrolo[1,2-*b*]pyrazole (**24**) (Scheme 1) were studied, and the parameters were assigned unambiguously (Table 1) ⟨87JCS(P1)657⟩.



(24)

Scheme 1

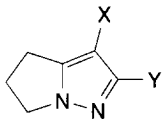
Table 1 Proton and carbon-13 NMR chemical shifts of compound (**24**) in $CDCl_3$.

	H-2(C-2)	*H-3(C-3)*	*(C-3a)*	*H-4(C-4)*	*H-5(C-5)*	*(C-6)*
$^1H^a$	7.61	6.12		7.19	5.97	
$^{13}C^b$	148.54	105.51	146.51	133.88	125.44	161.49
	(189.5)	(181.9)		(180.4)	(184.4)	

[a] ^1H NMR J(Hz) $J_{2,3} = 1.3$; $J_{2,5} = 6.9$; $J_{4,5} = 6,2$. [b] ^{13}C NMR Long range $^nJ_{CH}$ (Hz); $^2J_{2\text{-}3} = 6.4$; $^2J_{3\text{-}2} = 11.1$; $^2J_{4\text{-}5} = 2.6$; $^2J_{6\text{-}5} = 7.6$; $^3J_{6\text{-}4} = 11.0$ ($^1J_{CH}$ in parentheses).

Analysis of this data reveals that the parameters are very similar to those of the monocyclic model compound *N*-carboxamidopyrazole, but there is a small shielding effect due to contribution of the resonance structures (see Scheme 1), which may be indicative of a small magnetic ring current. The ^{1}H coupling constants are of similar magnitude to those of simple pyrazoles. The chemical shift of the carbonyl carbon appears in the amide rather than in the ketone region.

Proton NMR data of a series of 5,6-dihydro-4*H*-pyrrolo[1,2-b]pyrazoles (**25**) have been described in a paper related to synthesis of the alkaloid withasomnine (R^1 = Ph, R^2 = H) ⟨83TL1067⟩, and are collected in Table 2.



(**25**)

Table 2 Proton NMR chemical shifts (in $CDCl_3$) of some 2,3-disubstituted 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazoles (**25**).

Structure	R^1	R^2	*H-2*	*H-3*	*2H-4*	*2H-5*	*2H-6*	*Other*
25a	Ph	Ph			2.85	2.58	4.12	7.2–7.8
25b	CO_2Me	CO_2Me			3.00	2.60	4.08	3.83;3.70
25c	COPh	COPh			2.85	2.55	4.12	
25d	H	CO_2Et		7.56	3.00	2.65	4.20	1.3;4.2
25e	CO_2Et	H	6.35		2.70	2.70	4.20	1.3;4.2
25f	Ph	H	7.30		2.80	2.80	4.10	7.3
25g	H	Ph		6.12	2.60	2.60	4.20	7.1–7.8

(iii) IR and UV spectroscopy

The carbonyl stretching frequency in the IR for 6-oxopyrrolo[1,2-*b*]pyrazole (**24**) is 1760 cm^{-1}, abnormally high for an amide-type carbonyl, which seems to indicate that normal delocalization of the lone pair of the ring junction nitrogen atom is severely impaired (in contrast with the ^{13}C NMR data).

The UV spectrum shows strong absorption at 295 nm and 345 nm, with a much weaker peak at longer wavelength which is responsible for the color of the compound ⟨87JCS(P1)653⟩.

(iv) Mass spectroscopy

The mass spectrum of the compound (**24**) shows the molecular ion m/z 120(100%) and exhibits major peaks at $M^+ - 56$ and $M^+ - 57$ (m/z 64(36%) and 63(33%)), probably due to rapid N_2 cleavage after initial loss of CO ⟨87JCS(P1)653⟩.

8.02.2.3 Reactivity

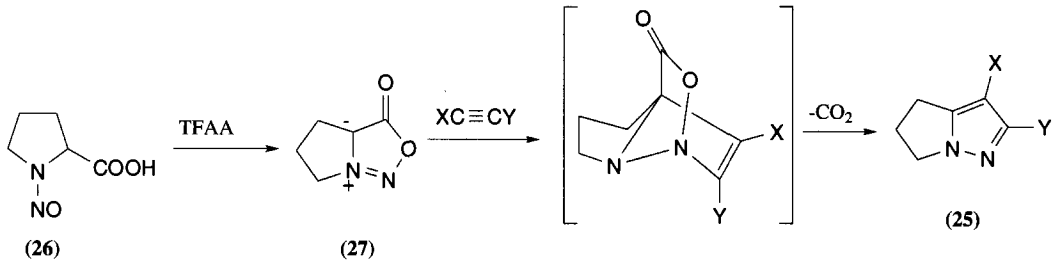
No reactions involving this system or any derivative have been reported.

8.02.2.4 Synthesis

8.02.2.4.1 Dipolar cycloadditions

The mesoionic system (**27**) (obtained by treatment of *N*-nitrosoproline (**26**) with TFAA) reacts with alkynic dipolarophiles to give smooth addition, followed by extrusion of CO_2 on refluxing in

xylene, leading to the substituted 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazoles (**25**) (Scheme 2) ⟨83TL1067⟩. This strategy was used to synthesize the alkaloid withasomnine (**25f**) ⟨85SC259, 85TL5739⟩.

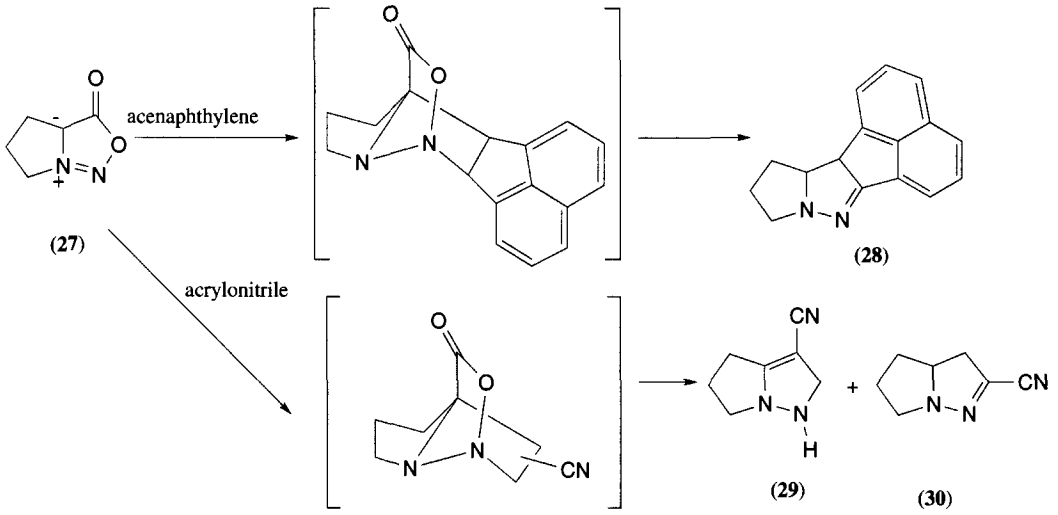


(26) (27) (25)

a)X=Y=Ph; b)X+Y=COOMe;c)X=Y=COPh;d)X=H,Y=COOEt;e)X=COOEt,Y=H;f) X=Ph,Y=H;g)X=H,Y=Ph.

Scheme 2

The compound (**27**) also reacts with alkenic dipolarophiles, such as acenaphthylene and acrylonitrile, to give the corresponding cycloadducts, with subsequent CO_2 extrusion to give compounds (**28**)–(**30**) (Scheme 3).

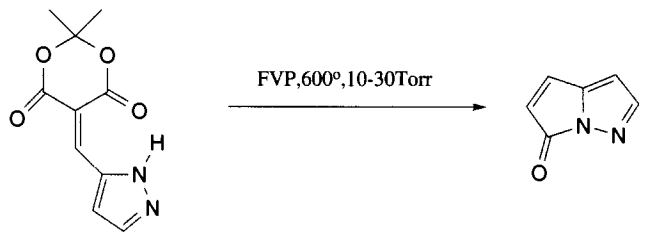


(27) (28) (29) (30)

Scheme 3

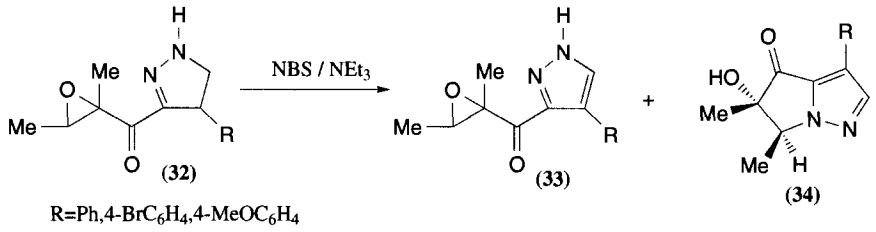
8.02.2.4.2 Formation of the pyrrolidone ring

Reaction of pyrazole-3-carbaldehyde with Meldrum's acid gave the condensation product (**31**), which was pyrolyzed in the gas phase to give 6-oxopyrrolo[1,2-*b*]pyrazole (**24**) in low yield (18%) (Equation (1)) ⟨87JCS(P1)653⟩.



(31) (24) (1)

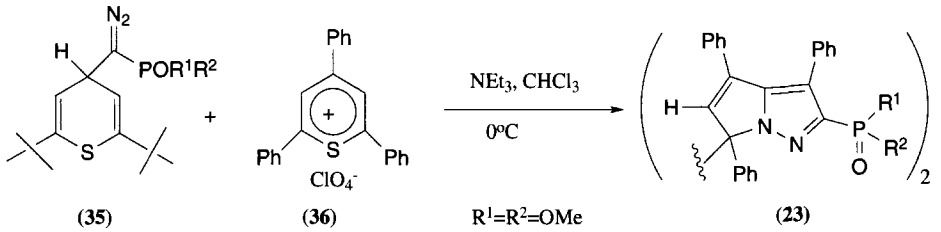
Treatment of the pyrazoline (**32**) with NBS and triethylamine gave mixtures of the pyrazole (**33**) and 5-hydroxy-5,6-dimethyl-4-oxo-3-arylpyrrolo[1,2-*b*]pyrazole (**34**) (Equation (2)) ⟨90MI 802-01⟩.



(2)

8.02.2.4.3 Simultaneous formation of two rings

The reaction of 4-(diazomethyl)-4*H*-thiapyrans (**35**) with 2,4,6-triphenylthiapyrylium perchlorate (**36**) takes an unusual course, forming the bis(6*H*-pyrrolo[1,2-*b*]pyrazole) (**23**) (Equation (3) ⟨85T811⟩.



(3)

8.02.3 PYRROLO[1,2-*a*]IMIDAZOLES

8.02.3.1 Introduction

Pyrroloimidazoles are more widely studied. Both types, pyrrolo[1,2-*a*]imidazoles and pyrrolo[1,2-*c*]imidazole derivatives, have interesting physiological activity.

8.02.3.2 Theoretical and Experimental Structural Methods

8.02.3.2.1 Theoretical methods

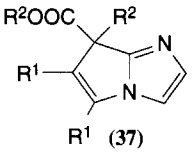
There is some preliminary data ⟨74CHE230⟩ based on the MO LCAO method within the semi-empirical self-consistent field (SCF) approximation, on 1*H*-pyrrolo[1,2-*a*]imidazoles; the maximum π-electron densities are localized on C-5 and C-7 ⟨84CHEC-I(6)979⟩. No other theoretical methods have been used.

8.02.3.2.2 Experimental methods

(i) X-ray

There are few reported structures of this system. The structure of a 7*H*-pyrrolo[1,2-*a*]imidazole derivative (**37**) has been determined by x-ray analysis ⟨90JCS(P1)1821⟩ and shows the expected data. The structures of some 6,7-dihydro ⟨87JHC561⟩ and 2,3-dihydro derivatives ⟨92JOC2347⟩ have also been elucidated by crystallographic x-ray analysis, but only some data on the crystals has been reported.

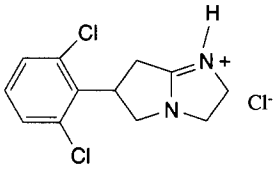
More information has been published for a 6-aryl-2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazole (**38**) ⟨83AX1426⟩. The crystalline structure of this compound showed that protonation occurs on the N-1.



(37)

R^1 = COOMe

R^2 = -$(CH_2)_2$=CH

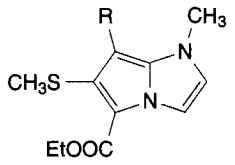


(38)

(ii) Proton NMR spectroscopy

Although no information is available on unsubstituted heterocycles, the ^{1}H chemical shifts of some 5,6,7-trisubstituted pyrrolo[1,2-*a*]imidazoles (**39**) and (**40**) have been described ⟨90H(31)977, 92JHC1473⟩. The H-2 chemical shift is at δ 6.74 in one case, and at δ 7.67 in the other case. The H-3 appears at δ 6.80 and δ 7.62 respectively. In both cases the coupling constants are 2 Hz. This data reflects a behavior similar to that of the protons of the imidazole ring. The ^{1}H NMR data of 5-oxopyrrolo[1,2-*a*]imidazole (**41**) have been assigned unambiguously; vicinal and long-range coupling constants are also reported ⟨87JCS(P1)657⟩. H-2 and H-3 appear at δ 6.96 and δ 7.03 respectively, with a J = 1.8 Hz. The δ value for H-6 is 6.02, and H-7 is a little deshielded, appearing at δ 7.23. The vicinal coupling constant is 6.1 Hz. The long-range coupling constant between H-2 and H-6 is 0.7 Hz.

The protons in nonaromatic pyrrolo[1,2-*a*]imidazoles show normal chemical shifts for this type of compound ⟨89CB95⟩. In some cases ⟨92JOC2347⟩, differential nuclear Overhauser effect (DIFNOE) experiments were used to assign signals.

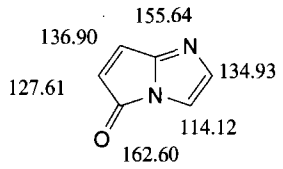


(39) R=CN

(40) R=COOEt

(iii) Carbon-13 NMR spectroscopy

There is little reported data about pyrrolo[1,2-*a*]imidazoles, and in general the information is used to confirm structures ⟨84TL3901, 89CB95, 92CB1939⟩. The most interesting analysis of ^{13}C NMR is the unambiguous assignment of parameters of 5-oxopyrrolo[1,2-*a*]imidazole (**41**) as shown in Figure 2 ⟨87JCS(P1)657⟩. Coupling constant information was utilized in this assignment.



(41)

Figure 2 Carbon-13 NMR data for (**41**) ($CDCl_3$).

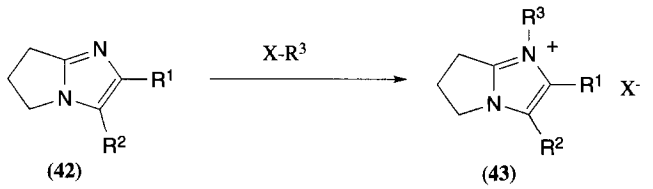
(iv) IR and UV spectroscopy

IR values of the carbonyl groups present in pyrrolo[1,2-*a*]imidazole ring systems are used to explain structural features: e.g., in the case of 5-oxopyrrolo[1,2-*a*]imidazole (**41**), the carbonyl group showed a strong absorption in the IR at 1760 cm^{-1} which indicates that normal delocalization of the lone pair in the ring junction nitrogen atom is severely impaired ⟨87JCS(P1)653⟩.

No significant data of electronic absorption spectroscopy has been reported, except in some cases where they have been used to explain the color of the compounds ⟨87JCS(P1)653⟩.

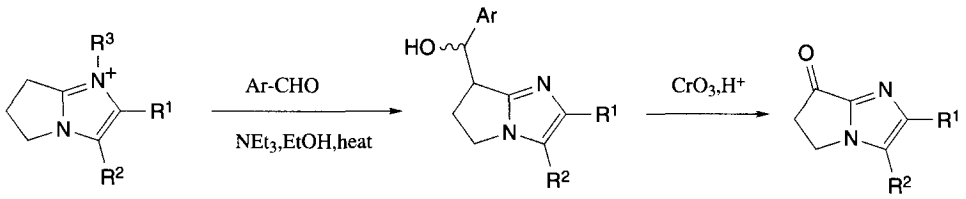
8.02.3.3 Reactivity

Pyrrolo[1,2-*a*]imidazole derivatives have been studied because of their biological activities (see ⟨89TL6599⟩ and ⟨92CB1939⟩). The most general reaction is N1-alkylation, as shown by reaction between pyrroloimidazole (**42**) and allyl bromide, methyl iodide, or benzyl bromide to give quaternary salts (**43**) (Equation (4)) ⟨89TL6599⟩.



(42) (43) (4)

The quaternization increases the acidity of the protons at C-7, facilitating subsequent reactions in this position. This method has been used to synthesize antiinflammatory pyrroloimidazole derivatives (Scheme 4).



(44) (45)

R^3=-$CH_2OCH_2CH_2OCH_3$
R^1=R^2= -p-C_6H_4F
Ar= p-$C_6H_4NO_2$

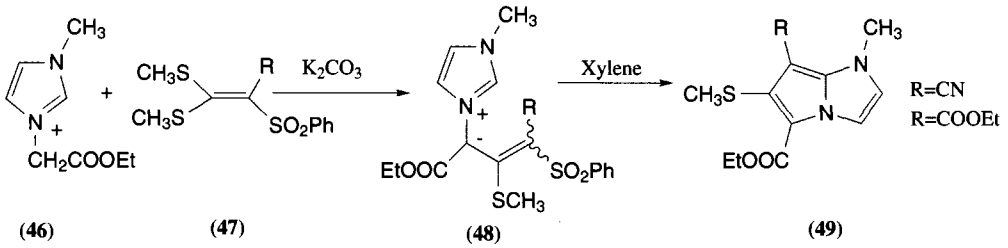
Scheme 4

8.02.3.4 Synthesis

8.02.3.4.1 Fully conjugated ring and related systems

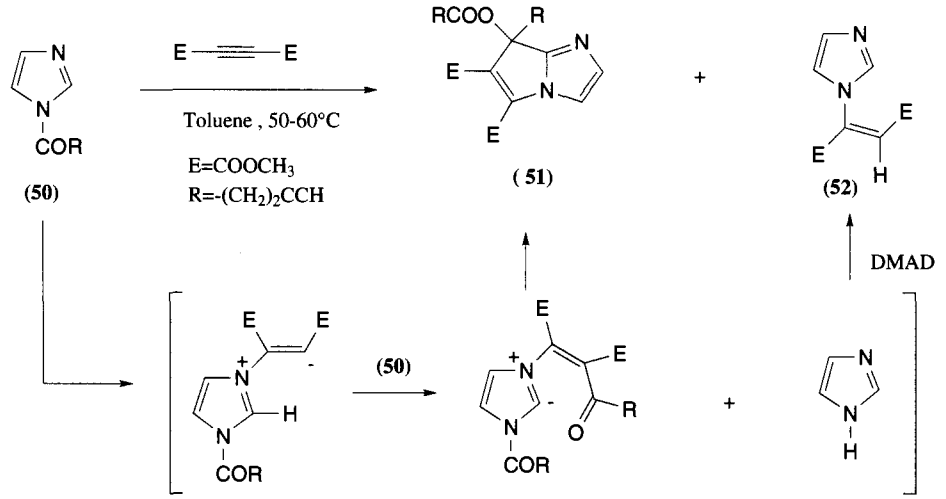
There are two examples of these syntheses, collected in CHEC-I ⟨84CHEC-I(6)973⟩, one by reaction of an imidazolium *N*-ylide with ethyl propiolate ⟨68JA3830⟩, and another by reaction of imidazole-2-carbaldehyde with vinyltriphenylphosphonium bromide in presence of NaH in THF ⟨76JHC111⟩. In the early 1990s, the intramolecular 1,5-dipolar cycloaddition reaction of the imidazolium *N*-allylides (**48**) to give the pyrrolo[1,2-*a*]imidazole (**49**) has been described. Compound (**48**) is generated

from 1-ethoxycarbonylmethylimidazolium bromide (**46**) and ketene dithioacetal (**47**) in xylene (Scheme 5) ⟨90H(31)977⟩.



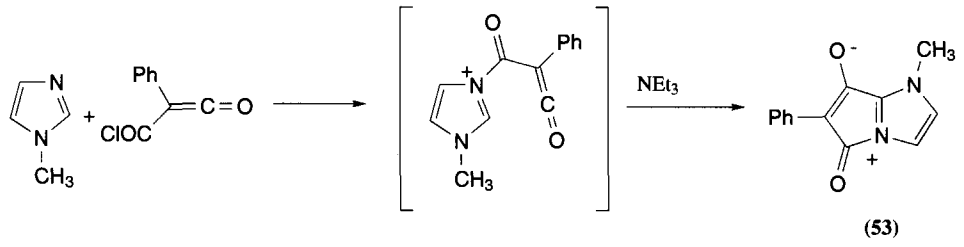
Scheme 5

Functionalized 7*H*-pyrrolo[1,2-*a*]imidazoles (**51**) are obtained directly by a double transacylation reaction of 1-acylimidazoles (**50**) and DMAD in toluene (Scheme 6) ⟨90JCS(P1)1821, 92CB1939⟩.



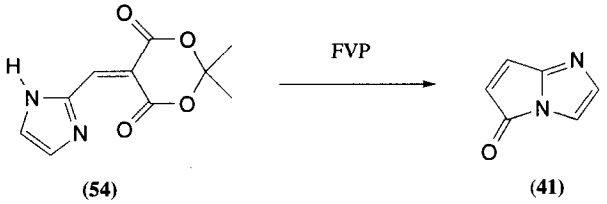
Scheme 6

New types of cross-conjugated, heterocyclic betaines such as 7-oxido-1-methyl-5-oxo-6-phenylpyrrolo[1,2-*a*]imidazolium (**53**) have been obtained by reaction of *N*-methylimidazole with chlorocarbonylphenylketene in THF at room temperature in presence of triethylamine (Scheme 7) ⟨84JOC3672⟩.



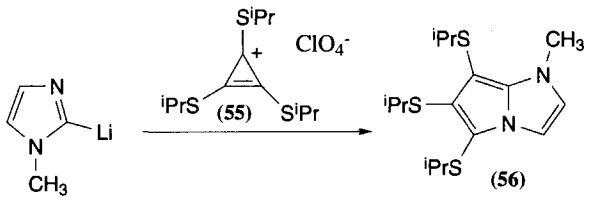
Scheme 7

An interesting procedure to obtain 5-oxopyrrolo[1,2-*a*]imidazole (**41**) has been described, by pyrolysis, in the gas phase, of compound (**54**), a condensation product of Meldrum's acid and imidazole-2-carbaldehyde (Equation (5)) ⟨87JCS(P1)653, 87JCS(P1)657⟩.



(54) (41) (5)

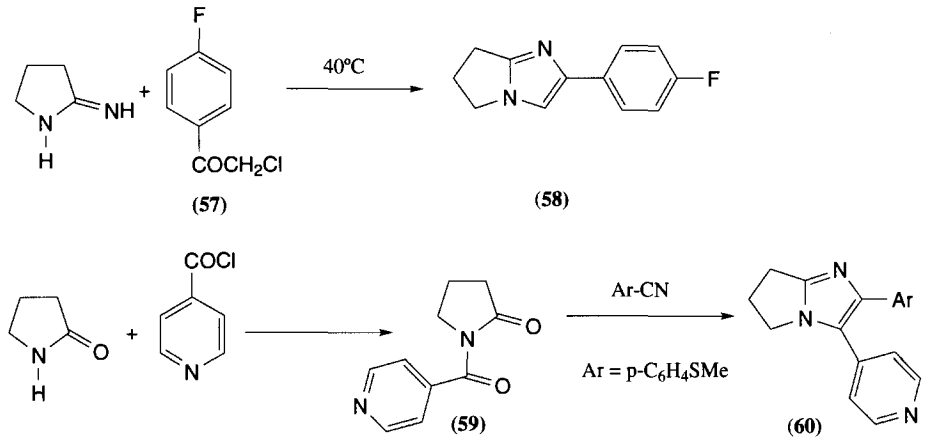
The reaction of the cyclopropenium perchlorate (**55**) with *N*-methyl-2-imidazolyllithium gives the pyrrolo[1,2-*a*]imidazole (**56**) in excellent yield, probably from a vinylcarbene intermediate (Equation (6)) ⟨92JHC1473⟩.



(55) (56) (6)

8.02.3.4.2 6,7-Dihydro-5H-pyrrolo[1,2-a]imidazoles

The most general synthesis of substituted 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles has been described in several patents. The starting materials are pyrrolidine derivatives such as the 2-iminopyrrolidine or 2-pyrrolidone (Scheme 8) ⟨89EUP306300, 92MI 802-01⟩. In the first case, the 2-iminopyrrolidine reacts with the chloroketone (**57**) at 40 °C to give the dihydro pyrrolo[1,2-*a*]imidazole (**58**). In the second case the 2-pyrrolidone was *N*-acylated by 4-picolyl chloride and the product (**59**) cyclocondensed with a nitrile to give the 2,3-diaryl-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (**60**).

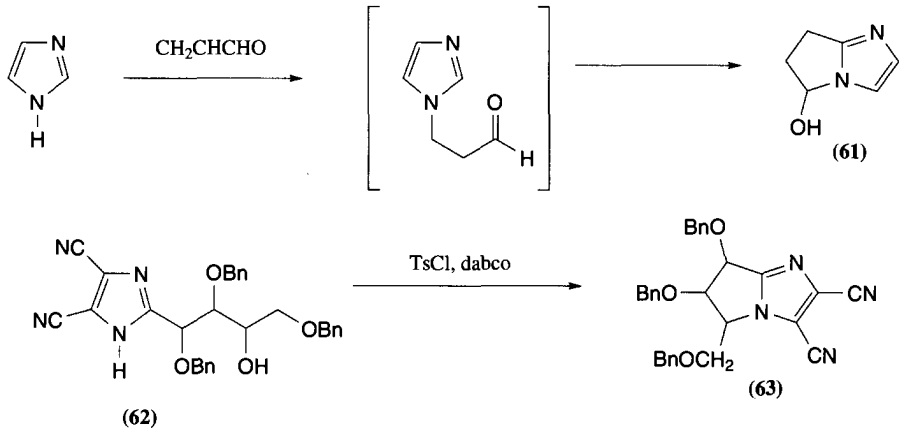


(57) (58) (59) (60)

Scheme 8

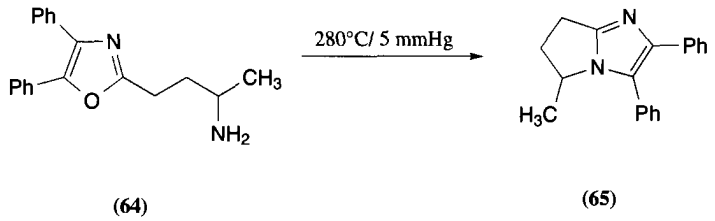
Two syntheses from an imidazole nucleus have been developed (Scheme 9). By reaction between imidazole and acrolein, 6,7-dihydro-5-hydroxy-5*H*-pyrrolo[1,2-*a*]imidazole (**61**) has been obtained in moderate yield, probably from initial Michael adducts and further cyclization ⟨87JHC561⟩. The second synthesis shows an example of intramolecular cyclization, from compound (**62**) to give (**63**) ⟨86TL323⟩.

6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles are also obtained by intramolecular dehydration of γ-aminoalkyloxazoles. When γ-aminoalkyloxazole (**64**) was directly heated at 280 °C under reduced



Scheme 9

pressure (5 torr), dihydropyrroloimidazole (**65**) was obtained in a 46% yield (Equation (7)) ⟨83JCS(P1)3027⟩.

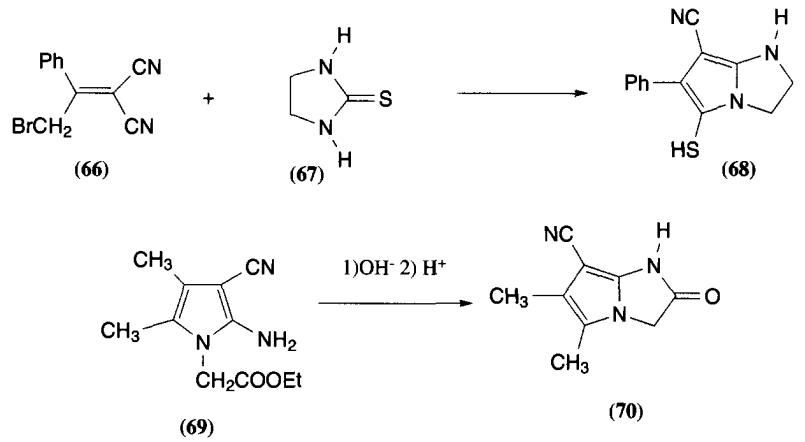


(7)

8.02.3.4.3 2,3-Dihydro-1H-pyrrolo[1,2-a]imidazoles

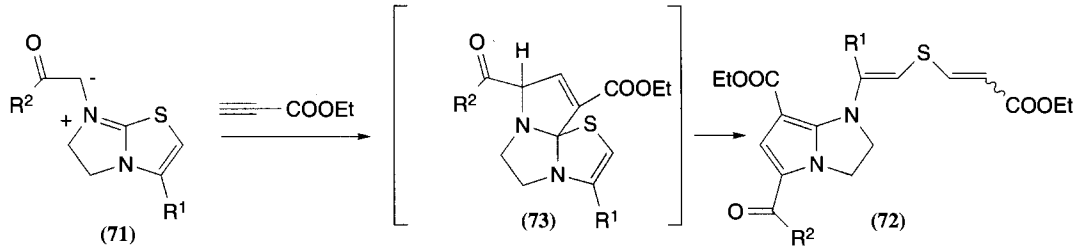
The unusual condensation of 2-bromoalkylidene malonitrile (**66**) with 4,5-dihydroimidazole-2-thione (**67**) gave a substituted 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**68**) in moderate yield ⟨84TL3901⟩. A general synthesis of these systems is shown by the intramolecular cyclization reaction of 1,3,4,5-tetrasubstituted-2-aminopyrrole (**69**) to give the corresponding pyrrolo[1,2-*a*] imidazole derivative (**70**) in good yield ⟨86JHC393⟩. Both of these reactions are shown in Scheme 10.

5,6-Dihydroimidazo[2,1-*b*]thiazolium betaines (**71**) react with alkynic dipolarophiles to form



Scheme 10

isomeric (*trans*, *cis*) 1 : 2 adducts with the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**72**) structure ⟨92JOC2347⟩. A plausible mechanism has been proposed from the 1,3-dipolar cycloadduct (**73**) initially formed (Scheme 11).



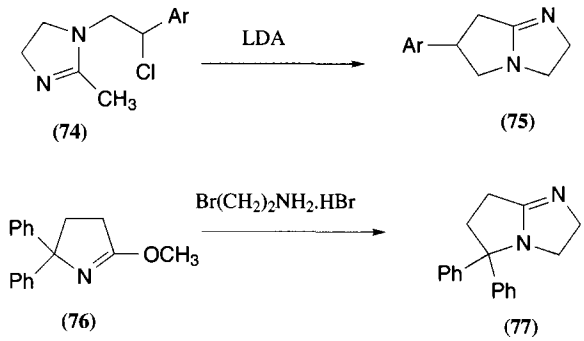
R^1=Ph, R^2=Ph, $pBrC_6H_4$,OEt
R^1=CH_3, R^2=Ph, $pBrC_6H_4$,OEt

Scheme 11

8.02.3.4.4 Tetrahydro and perhydro derivatives

(i) Nucleophilic type displacement and cyclocondensation reactions

Nucleophilic displacements have been used to synthesize tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles (**75**) as shown by the reaction of chloride (**74**) with LDA ⟨86JCS(P1)205⟩. In another case, an initial *N*-alkylation of imidate (**76**) with bromoethylamine gives pyrroloimidazole derivative (**77**) by a nucleophilic cyclization ⟨85JOC2220⟩. Both reactions are shown in Scheme 12.

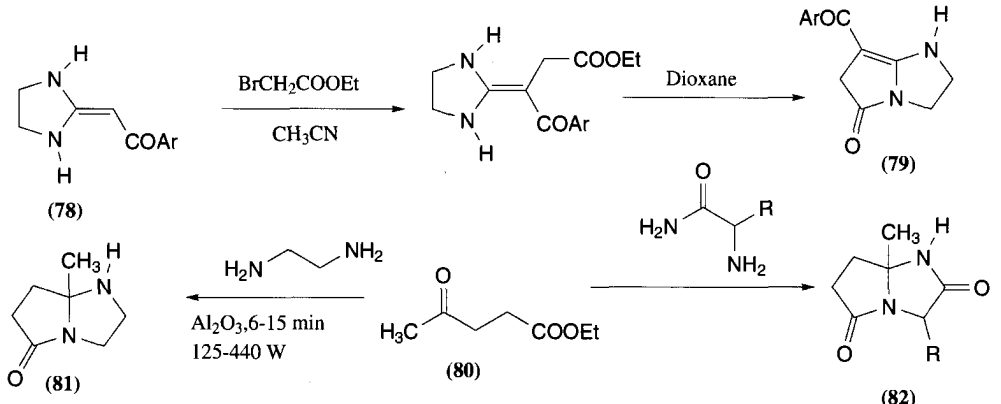


Scheme 12

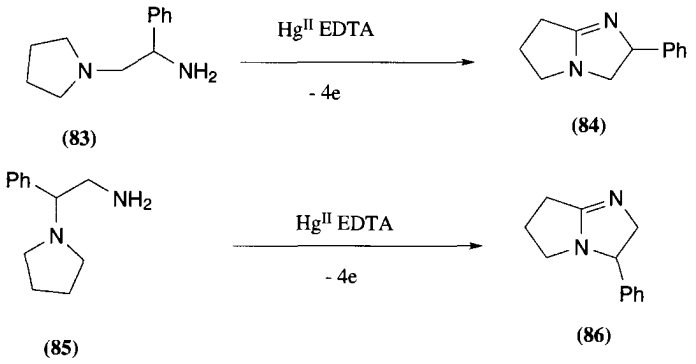
Heterocyclic ketene aminals (**78**) react smoothly with ethyl bromoacetate, and pyrroloimidazoles (**79**) are obtained by further cyclocondensation of alkylation products ⟨89CB95⟩. Another procedure is based on reaction of 1,2-ethylenediamine and ethyl levulinate (**80**) under microwave irradiation giving (**81**) ⟨92SL219⟩. Compound (**80**) also reacts with glycinamides, and alaninamides ⟨93JMC4214⟩ to give the corresponding pyrrolo[1,2-*a*]imidazolone derivatives (**82**). These reactions are shown in Scheme 13.

(ii) Oxidative cyclization methods

Mercuric EDTA dehydrogenation of isomeric 1,2- and 2,1-(aminophenyl)ethylpyrrolidines ((**83**), (**85**)) by double dehydrogenation produces amidines ((**84**), (**86**) respectively) (Scheme 14) ⟨76ZN(B)99⟩.



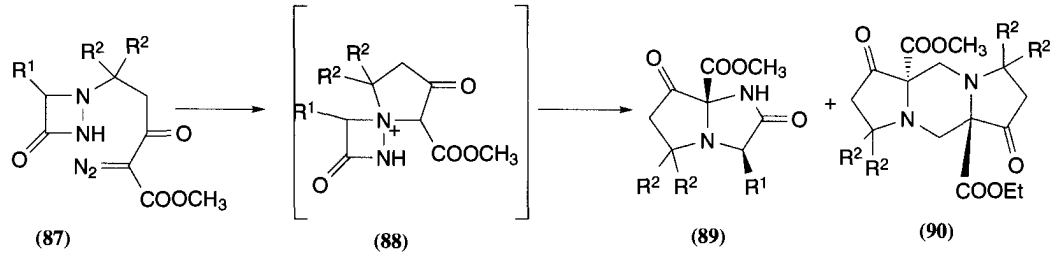
Scheme 13



Scheme 14

(iii) Ring rearrangements

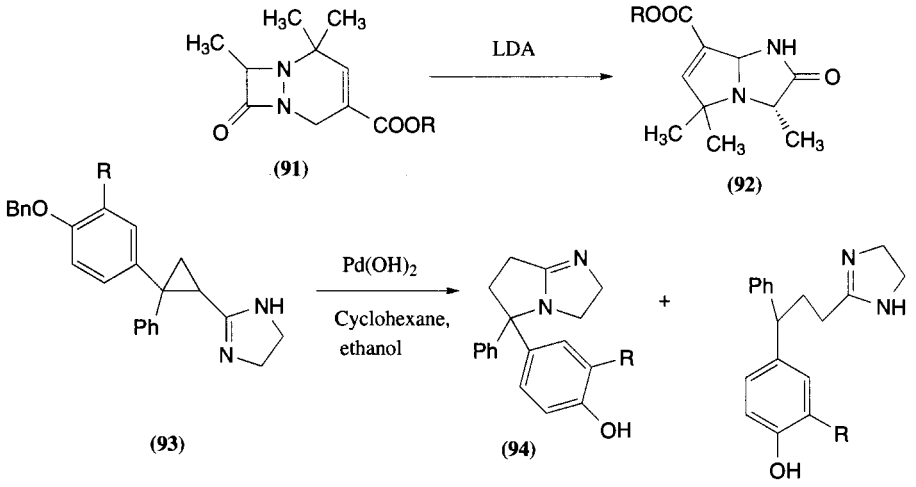
When diazoketones (**87**) are heated in benzene, in the presence of a catalytic amount of rhodium(II) acetate, they give white crystalline compounds (**89**) and (**90**). This transformation has been explained as due to the rupture of intermediate (**88**) generated probably by an initial carbenoid species (Scheme 15) ⟨84JOC113⟩.



$R^1 = H, R^2 = Ph$
$R^1 = H, R^2 = c\text{-}C_5H_{10}$
$R^1 = CH_3, R^2 = Ph$

Scheme 15

Removal of a proton from 1,2-disubstituted diazetidinones (**91**) results in an instantaneous ring-expansion to imidazolidinones (**92**) in a similar reaction to Stevens rearrangement ⟨86JOC1537⟩. Another interesting rearrangement to pyrroloimidazoles (**94**) has been described from trisubstituted aziridine (**93**) using base catalysis ⟨85JOC2220⟩. Both reactions are shown in Scheme 16.



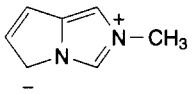
Scheme 16

8.02.4 PYRROLO[1,2-*c*]IMIDAZOLES

8.02.4.1 Theoretical and Experimental Methods

8.02.4.1.1 Theoretical methods

No advanced theoretical data has been reported for this type of system, but the pyrrolo[1,2-*c*]imidazole mesomeric betaine (**95**) has been the target of preliminary studies ⟨84CHEC-I(6)1030⟩.



(95)

8.02.4.1.2 Experimental methods

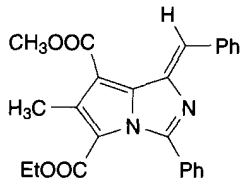
(i) X-ray

There are some resolved structures for this type of compound, for example, 1*H*-pyrrolo[1,2-*c*]imidazole (**96**) ⟨89H(29)1137⟩, and the 3,5-dioxo-2,3-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole (**97**) ⟨91JOC858⟩. Carbene rhodium(I) (**98**), or the similar cobalt(I) complexes have been elucidated by x-ray analysis, and a very interesting study of stereochemistry of these compounds has been made ⟨83JOM(250)C9, 85JOM(296)173⟩. The copper complex (**99**) of 3-oxo-1-thioxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole has been studied ⟨84ZN(B)586⟩.

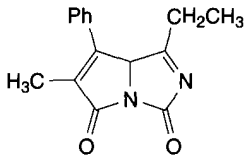
(ii) Proton and carbon-13 NMR spectroscopy

There are a great number of recorded spectra for this type of compound, but they were used only to confirm the structures; there are no systematic studies.

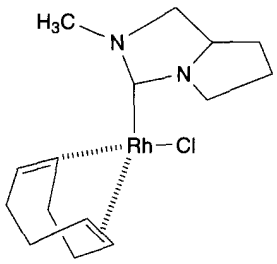
The most interesting data is displayed in Tables 3 and 4. Proton chemical shifts of H-1 and H-3 in compound (**100**) are similar to those of the imidazole ring, and an ABX_2 system is exhibited for protons H-7, H-6, and H-5, the most significant feature being H-5 shielding at 4.79 ppm. Salt (**101**) showed strong deshielding for H-3. Data for 5-oxopyrrolo[1,2-*c*]imidazole (**102**) have been studied and show a long-range coupling constant for H(3)-H(7) of 0.7 Hz.



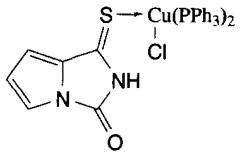
(96)



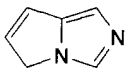
(97)



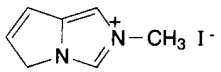
(98)



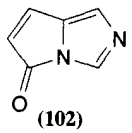
(99)



(100)



(101)



(102)

Table 3 Proton NMR spectral data of some pyrrolo[1,2-*c*]imidazoles.

Structure	*H-1*	*H-3*	*H-5*	*H-6*	*H-7*	*Other*	*Ref.*
100[a]	6.78 (s)	7.65 (s)	4.49 (m)	6.18 (dd)	6.52 (dd)		89JCS(P1)957
101[b]	7.74 (s)	9.11 (s)	5.06 (s)	6.82 (s)	6.82 (s)	4.01 (s)	89JCS(P1)957
102[c]	6.81 (s)	7.76 (d)		5.86 (d)	7.32 (dd)		87JCS(P1)657

[a]$CDCl_3$, $J_{6,7} = 6$ Hz, $J_{6,5} = 2$ Hz, $J_{7,5} = 2$ Hz. [b]CD_3OD. [c]$CDCl_3$, $J_{3,7} = 0.7$ Hz, $J_{6,7} = 5.9$ Hz.

Table 4 Carbon-13 NMR specral data of some pyrrolo[1,2-c]imidazoles.

Structure	*C-1*	*C-3*	*C-5*	*C-6*	*C-7*	*C-7a*	*Other*	*Ref.*
100[a]	113.0	119.7	55.7	137.2	137.2	134.3	37.3	89JCS(P1)957
101[b]	126.5	134.4	162.4	123.4	138.0	135.0		87JCS(P1)657

[a]CD_3OD. [b]$CDCl_3$, data for coupling constants is reported.

Carbon-13 NMR spectral data were used to monitor the base-catalyzed exchange of deuterium for hydrogen at positions 3, 5, and 7 in the salt (**101**), via a mesomeric betaine ⟨89JCS(P1)957⟩.

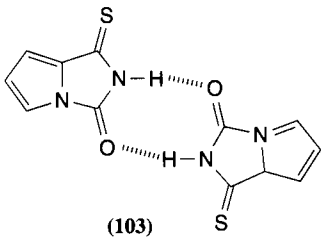
There are a number of reports on the synthesis of the saturated ring system, and NMR spectra were used to determine the structure. In some cases, the stereochemistry has been established by spectroscopic analysis ⟨90JOC2254⟩. Some oxo derivatives, such as (**97**), have been studied by attached proton test (APT) and heteronuclear shift correlation (HETCOR) experiments ⟨91JOC858⟩. Pyrrolidine ring conformation in two 2,3-dioxoperhydropyrrolo[1,2-*c*]imidazoles were analyzed from ^1H NMR data using a generalized Karplus equation ⟨85BSB187⟩.

(iii) IR and UV spectroscopy

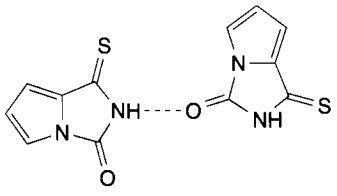
5-Oxopyrrolo[1,2-*c*]imidazole (**102**) shows carbonyl stretching frequency in the IR region at 1750 cm^{-1}, abnormally high for an amide-type carbonyl, since the carbonyl chemical shift in ^{13}C NMR

is in the normal range at 162.41 ppm ⟨87JCS(P1)653, 87JCS(P1)657⟩. This behavior is consistent with lack of delocalization of the lone pair in the ring junction nitrogen atom, as in 5-oxopyrrolo[1,2-*a*]imidazole (see Section 8.02.3.2.2(iv)).

The IR spectra of 3-oxo-1-thioxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole in the solid form and in solution have been measured as a function of temperature, and a direct correlation has been obtained between the two phases and the type and extent of hydrogen bonding. It was suggested that the compound exists as cyclic dimer (**103**) in the solid state (below 310 K) and in dilute solution by formation of two equivalent hydrogen bonds. At transition temperature, the cyclic dimer changes to the noncyclic dimer (**104**) and persists in this structure till 410 K. In addition, thermodynamic functions ΔG°, ΔH°, and ΔS° have been estimated using spectral data in solution ⟨84CJC1845⟩.



(103)



(104)

Little data has been reported of UV spectroscopy for this type of compound. It has been observed that some 1*H*-pyrrolo[1,2-*c*]imidazoles ⟨89H(29)1137⟩ are stable crystalline compounds with UV–visible absorption at 400–500 nm, and some of these compounds also display fluorescence with emission at 500–600 nm. Some data for pyrrolo[1,2-*c*]imidazole mesomeric betaines have also been reported. All mesomeric betaines display strong UV–visible absorption between 389 nm and 210 nm and fluorescence emission at 452–502 nm ⟨90JOC910⟩. The dioxo derivative analogues, like compound (**97**), are yellow crystalline compounds with UV–visible absorption, which also display characteristic fluorescence ⟨91JOC858⟩.

(iv) Mass spectrometric methods

The Edman phenylisothiocyanate method for determination of successive NH_2 terminal amino-acid residues in peptides and proteins gives, when the terminal aminoacid is proline, a 1-oxo-3-thioxoperhydropyrrolo[1,2-*c*]imidazole, and these compounds have been studied by chromatographic methods ⟨83JC371, 84JC279, 84JC359, 84JC534, 85JC77, 85JC99, 86JC383⟩ and chemical ionization mass spectroscopy ⟨83MI 802-02⟩.

8.02.4.2 Reactivity

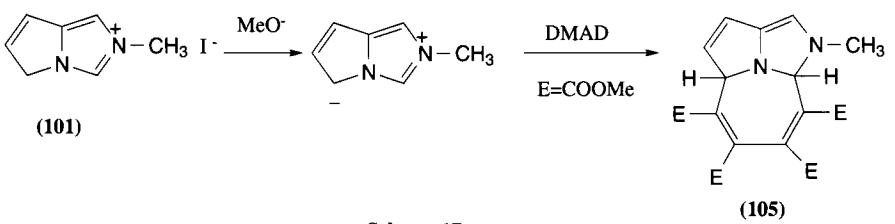
Three different types of reactions have been studied with this basic system:

(i) reactions of pyrrolo[1,2-*c*]imidazole mesomeric betaines;

(ii) asymmetric synthesis using chiral aminals derived from proline (perhydropyrazolo[1,2-*c*]imidazole); and

(iii) formation of coordination compounds.

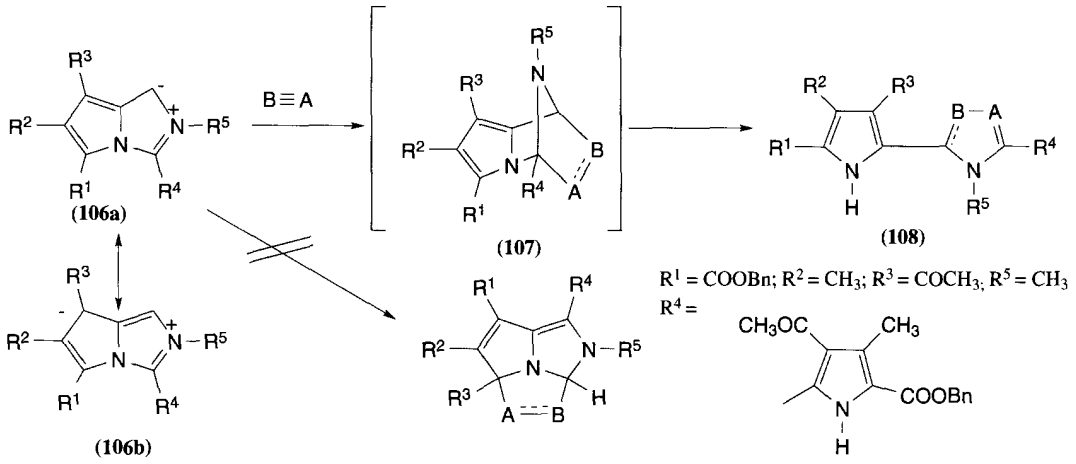
The simple mesomeric betaine generated from the iodide (**101**) with an excess of methanolic sodium methoxide at 0 °C, reacts with DMAD to give the 2 : 1 cycloadduct (**105**) in low yield (Scheme 17) ⟨89JCS(P1)957⟩.



(101) (105)

Scheme 17

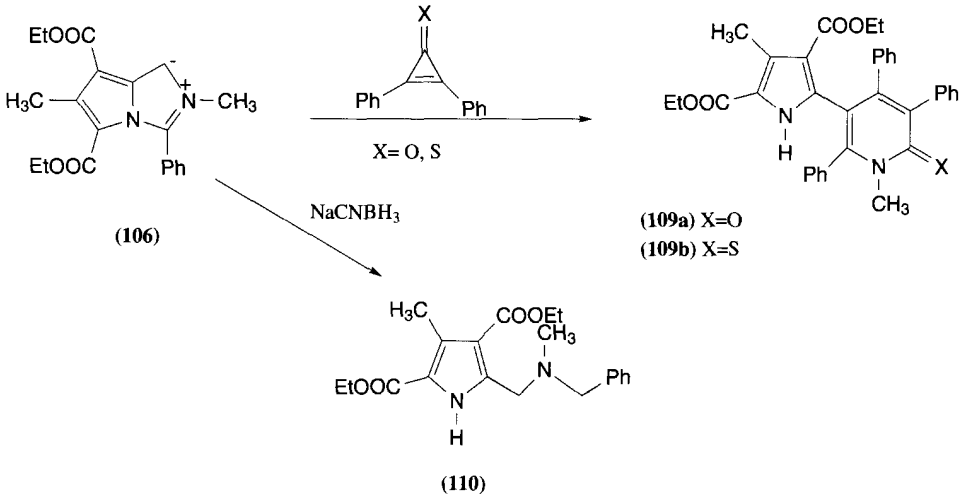
Peri-, regio-, and stereoselectivity of cycloaddition reactions of substituted mesomeric betaines (**106**) have been studied with different alkynic and alkenic dipolarophiles. High periselectivity has been observed in cycloaddition with both series of dipolarophiles, with the dipolarophile adding exclusively across the 1,3-azomethine ylide dipole (**106a**). The formation of 2,2′-bipyrroles (**108**) could be explained by a rearrangement of initial bicyclic cycloadduct (**107**) ⟨90JOC910⟩. All these reactions are shown in Scheme 18.



Scheme 18

Reactions of these mesomeric betaines with diphenylcyclopropenone and diphenylcyclopropenethione give 2-(1*H*)-pyridones (**109a**), 2-(1*H*)-pyridinethiones (**109b**) and other products, via an interesting series of intermediates ⟨91JOC110⟩.

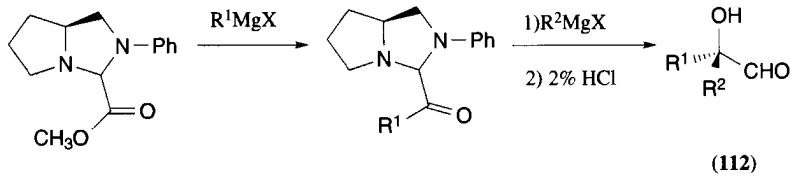
A ring-opening reaction of compounds (**106**) has been described by treatment with sodium cyanoborohydride in acetonitrile, in presence of acetic acid at room temperature to afford aminomethylpyrroles (**110**) (Scheme 19) ⟨90JOC910⟩.



Scheme 19

Chiral perhydropyrrolo[1,2-*c*]imidazoles derived from proline have been used in asymmetric synthesis. The function of the heterocyclic system is to act as a chiral building block and protecting group of the aldehyde function. Nucleophilic addition to the carbonyl group in aminal (**111**) is stereoselective, giving, by further hydrolysis, the corresponding chiral aldehyde (**112**) with high optical yields (Scheme 20). A great variety of examples of this method are in the literature ⟨82TL4953, 83CL93, 84BSF(2)77, 91BCJ2739⟩.

In the presence of various *N*-bases, 3-oxo-1-thioxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole (**103**)

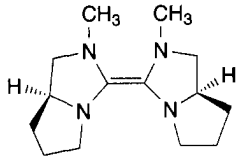


(111) (112)

Scheme 20

reacts with Co(II), Co(III), Cu(II), and Ni(II) ions to give a series of interesting complexes ⟨83IJC(A)24, 83IJC(A)1050, 86MI 802-01⟩. In some cases, structures have been resolved by x-ray analysis ⟨84ZN(B)586⟩. By reaction of compound (**103**) with Ru(III), Rh(I), Rh(II), Pd(I), Pd(II), and Pt(IV), a great number of coordination compounds have been obtained, ⟨84IJC(A)204⟩. Similar results have been described with 1,3-dithioxo-2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazole ⟨84IJC(A)122⟩.

An optically active electron-rich olefin (**113**) derived from pyrrolo[1,2-*c*]imidazole is converted into a carbenemetal (Rh(I) or Co(II)) complex with retention of optical integrity ⟨83JOM(250)C9, 85JOM(296)173⟩, the structure of these compounds has been elucidated by x-ray diffraction.

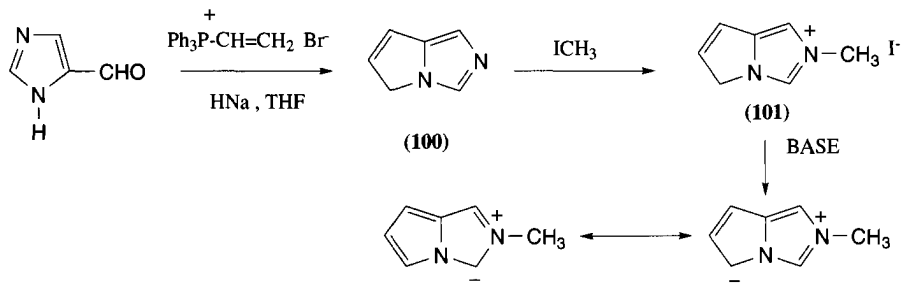


(113)

8.02.4.3 Synthesis

8.02.4.3.1 Heteropentalenic mesomeric betaines, 5H-, 3H-, and 1H-pyrrolo[1,2-c]imidazoles and related systems

The most general procedure to obtain heteropentalenic mesomeric betaines is the basic treatment of *N*-methyl-5*H*-pyrrolo[1,2-*c*]imidazole iodide (**101**). The dipolar intermediate has been trapped with DMAD ⟨89JCS(P1)957⟩. Iodide (**101**) is obtained by methylation of 5*H*-pyrrolo[1,2-*c*]imidazole (**100**), easily obtained by reaction of imidazole-4-carbaldehyde with vinyltriphenylphosphonium bromide in the presence of NaH in THF (Scheme 21) ⟨76JHC111⟩.

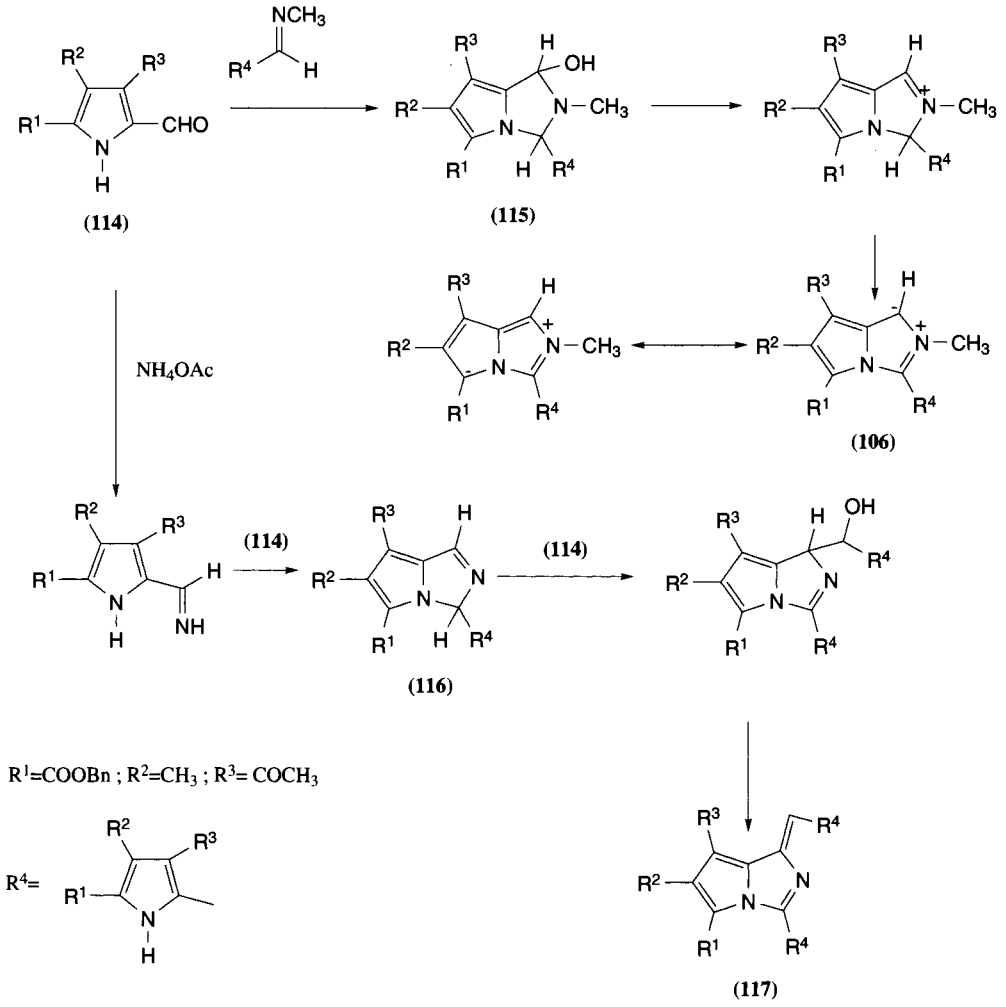


(100) (101)

Scheme 21

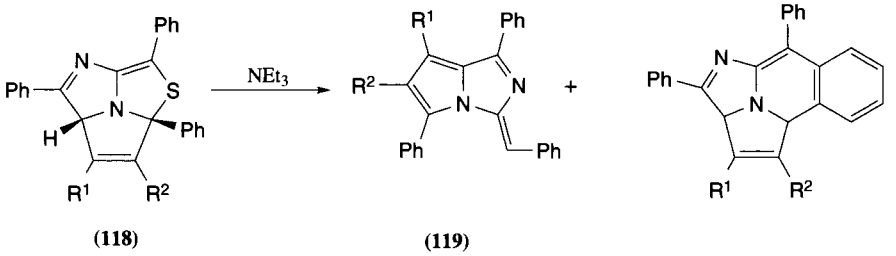
A series of pyrrolo[1,2-*c*]imidazole mesomeric betaines (**106**) have been prepared in good yield by condensation of 2-formylpyrroles (**114**) with aromatic imines. Mechanistically, the reaction might proceed by condensation of the imines with 2-formylpyrroles to give 2,3-dihydro-1*H*-pyrrolo[1,2-

c]imidazoles (**115**), followed by dehydration and deprotonation giving heteropentalenic mesomeric betaines (**106**) (Scheme 22) ⟨90JOC910⟩.



Scheme 22

1*H*-Pyrrolo[1,2-*c*]imidazoles (**116**) and (**117**) have been obtained by condensation of 2-formylpyrroles (**114**) and ammonium acetate (Scheme 22) ⟨89H(29)1137⟩. Compound (**119**) was obtained in the desulfuration of tricyclic system (**118**) ⟨83CL763⟩.

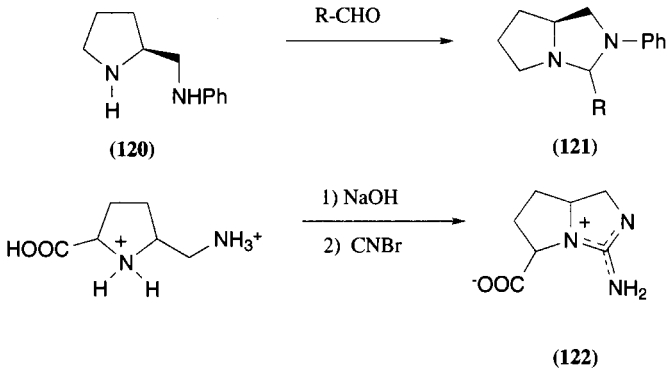


(8)

An interesting procedure to obtain 5-oxopyrrolo[1,2-*c*]imidazole (**102**) is by pyrolysis in the gas phase of the condensation product of Meldrum's acid and imidazole-4(5)-carbaldehyde (**54**) (Equation (5)) ⟨87JCS(P1)653, 87JCS(P1)657⟩.

8.02.4.3.2 Perhydropyrrolo[1,2-c]imidazoles

The general procedure to obtain perhydropyrrolo[1,2-*c*]imidazoles (**121**) is based on condensation between (*S*)-2-(anilinomethyl)pyrrolidine (**120**) and the corresponding aldehyde (Scheme 23) ⟨82TL4953, 83CL93, 84BSF(2)77, 91BCJ2739⟩.



(120) (121)

(122)

Scheme 23

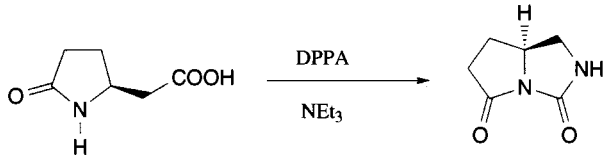
The zwitterionic perhydropyrrolo[1,2-*c*]imidazole (**122**) has been obtained by reaction of 2-aminomethylpyrrolidine-5-carboxylic acid chloride with sodium hydroxide and cyanogen bromide (Scheme 23) ⟨84MI 802-02⟩.

8.02.4.3.3 Oxo and dioxo derivatives

Synthesis of (*S*)-1-oxoperhydropyrrolo[1,2-*c*]imidazole (**124**) has been described by reaction of (*S*)-proline ethyl ester in a solution of dichloromethane and gaseous ammonia dissolved in methanol. The intermediate (**123**) has been postulated (Scheme 24) ⟨90JOC2254⟩.

In a similar sequence, reaction between proline amide (**125**) and acetone in toluene at reflux gave dimethyl derivative (**126**) ⟨85T611⟩. Intramolecular cyclization of amido ester (**127**) gave the cyclic urea (**128**) (Scheme 24) ⟨85JMC434⟩.

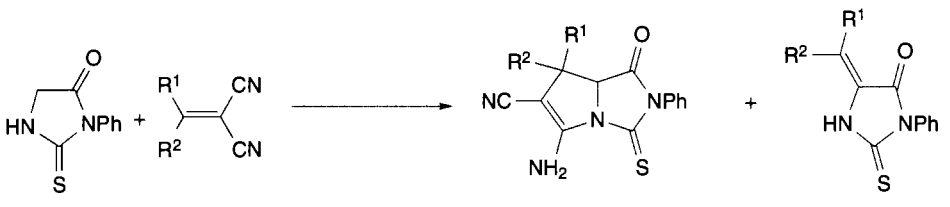
3,5-Dioxo-derivatives (**130**) can be obtained from proline derivatives. Curtius rearrangement using diphenyl phosphorazide (DPPA) of 2-oxopyrrolidinyl-5-acetic acid (**129**) afforded lactam (**130**) (Equation (9)) ⟨92H(33)619⟩.



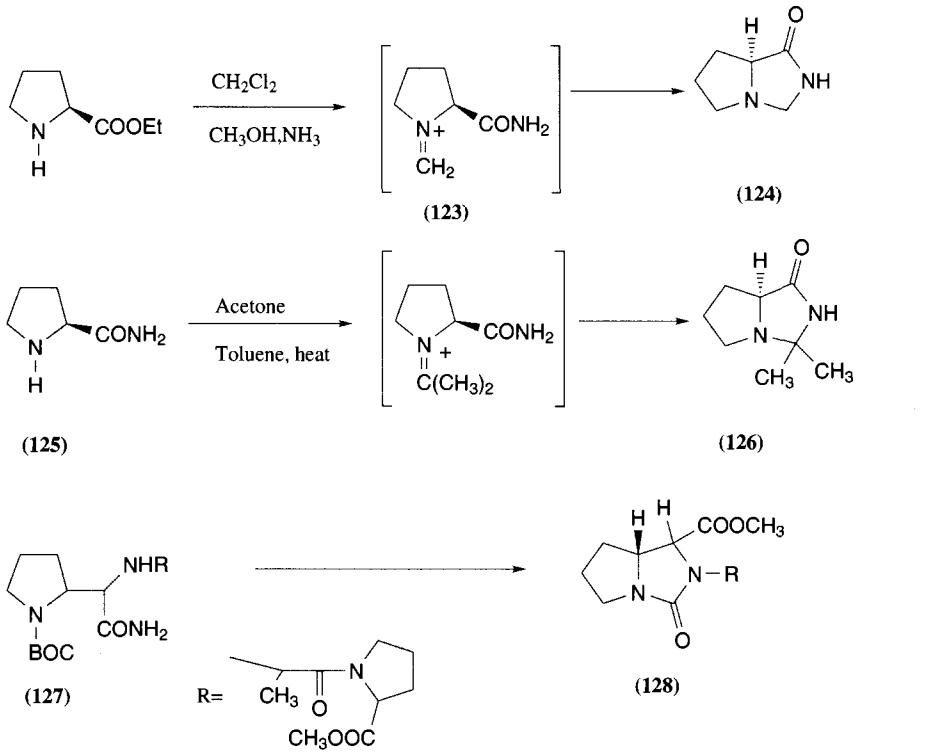
(129) (130) (9)

A synthesis of 3,5-dioxo-2*H*,3*H*-pyrrolo[1,2-*c*]imidazoles (**132**) has been developed by reaction between the imidazolones (**131**) and anhydrides in NaH/DMF (Scheme 25) ⟨91JOC858, 92JMC1267⟩.

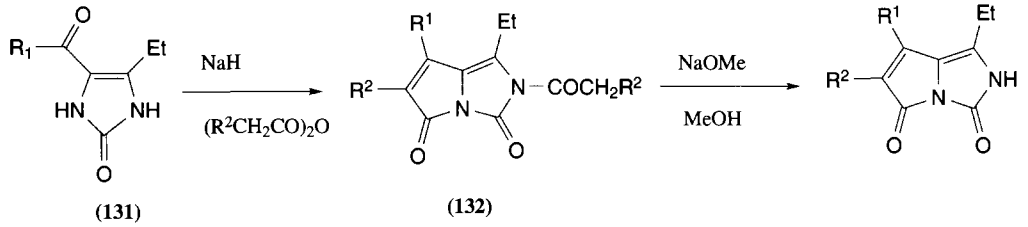
A series of 1-oxo-3-thioxo-2,3,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles (**133**) have been obtained by reaction of 2-thiohydantoin with activated alkenes. The formation of this pyrroloimidazole can be explained by an initial addition of 2-thiohydantoin to the activated double bond to yield an acyclic intermediate with subsequent cyclization (Equation (10)) ⟨82S502, 83LA1468⟩.



(133) (10)

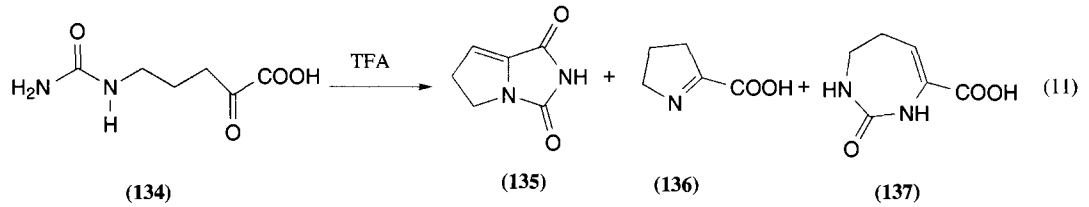


Scheme 24

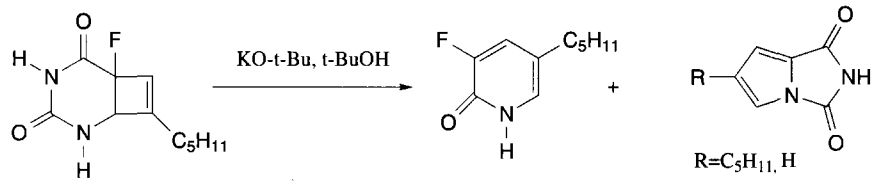


Scheme 25

The α-ketoacid (**134**) reacts with TFA to give 1,3-dioxo-5,6-dihydro-1*H*,2*H*-pyrrolo[1,2-*c*]-imidazole (**135**), 1-pyrroline-2-carboxylic acid (**136**), and 1,3-diazepine (**137**) (Equation (11)) ⟨83LA1623⟩.



An interesting rearrangement of some 2,4-diazabicyclo[4,2,0]oct-7-ene-3,5-diones (**138**) by reaction with potassium *t*-butoxide gave the corresponding 2-pyridones and 1,3-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-*c*]imidazoles (**139**) (Equation (12)) ⟨83JOC2337⟩.



(138) (139) (12)

8.02.5 PYRROLO[1,2-*b*]ISOXAZOLES

8.02.5.1 Introduction

In CHEC-I ⟨84CHEC-I(6)973⟩ there are only two examples of this system ⟨63JCS4693, 66CC607⟩. Several perhydro-, 3a,4,5,6-tetrahydro-, and 2-oxoperhydropyrrolo[1,2-*b*]isoxazoles have been described since, but the parent pyrrolo[1,2-*b*]isoxazole is not known.

8.02.5.2 Theoretical and Experimental Structural Methods

8.02.5.2.1 Theoretical methods

There are no theoretical calculations on this type of compound.

8.02.5.2.2 Experimental methods

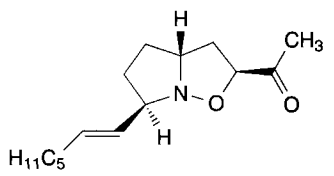
(i) X-ray

There is one example of a perhydropyrrolo[1,2-*b*]isoxazole in which the structure has been established by x-ray analysis, but no crystallographic data was reported ⟨85HCA2299⟩.

(ii) Proton NMR spectroscopy

No general studies have been made in this field, but there are some examples in which the NMR data have been used to resolve structural problems: e.g., the NMR data of the picrates of two 2-aryl-perhydropyrrolo[1,2-*b*]isoxazole diastereomers have been used to establish the ratio of each stereoisomer in the reaction mixture ⟨84JOC2412⟩.

The structures of the two epimeric adducts (**140a**) and (**140b**) were established using homonuclear shift correlation (COSY) and DIFNOE techniques ⟨89JCS(P1)2415⟩.



(**140a**)
(**140b**) epimeric at C2

The most interesting work is the determination of stereochemistry of 5α and 5β diastereomers of (2α,3β,3aα)-ethylperhydro-2-(1,2,3,4-tetraacetoxybutyl)-5,6,6-trimethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate by use of (^{1}H-^{1}H)COSY, (^{13}C-^{1}H) HETCOR, and nuclear Overhauser effect difference spectroscopy (NOEDS) techniques ⟨91MRC645⟩.

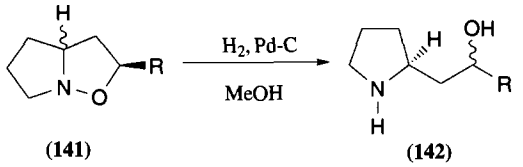
8.02.5.3 Reactivity

8.02.5.3.1 Ring openings and N—O bond cleavage

There are three methods for N—O bond cleavage in the saturated system: (i) hydrogenolysis, (ii) oxidative cleavage, and (iii) reductive cleavage. These methods have been used in the synthesis of a variety of natural products.

(i) Hydrogenolysis

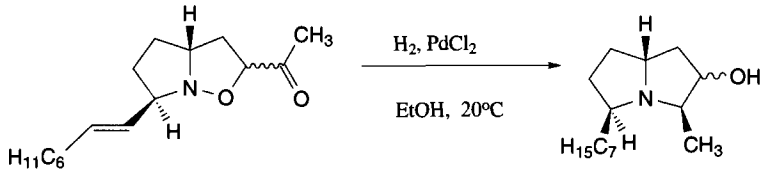
The diastereoisomeric mixture of perhydropyrrolo[1,2-*b*]isoxazoles (**141**), hydrogenolyzed over 10% Pd-C in methanol, gave aminoalcohols (**142**) as a mixture of isomers (α and β —OH) (Equation (13)) ⟨83CC271, 83CL1195, 84JOC2412⟩.



(141) (142) (13)

R=3,4-$(MeO)_2C_6H_5$

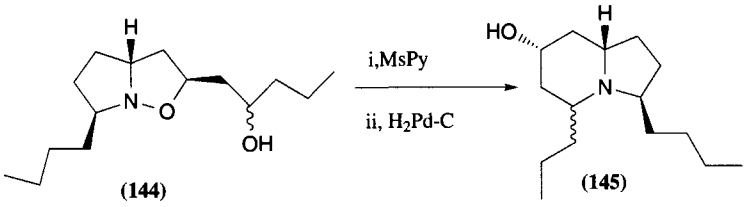
Reduction of (**140a**) and (**140b**) separately with $H_2/PdCl_2$ in ethanol afforded the epimeric pyrrolizines (**143a**) and (**143b**) (Equation (14)); the stereochemistry at C-5 is presumably due to a face-selective reduction of an intermediate cyclic iminium ion ⟨89JCS(P1)2415⟩.



(140a)
(140b) epimeric at C2

(143a)
(143b) epimeric at C6 (14)

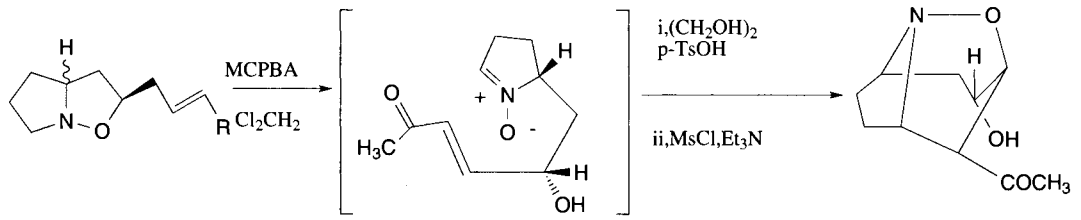
An interesting route to indolizidines (**145**) is based on N—O bond cleavage of perhydropyrrolo[1,2-*b*]isoxazole (**144**) by hydrogenolysis of the mesylated intermediate (Equation (15)) ⟨89JOC1748⟩.



(144) (145) (15)

(ii) Oxidative cleavage

Oxidative cleavage of the isoxazoline ring in perhydropyrrolo[1,2-*b*]isoxazole (**146**) with *m*-chloroperbenzoic acid gives (**148**) as the sole identifiable product in 79% yield, probably via the nitrone (**147**) which overcomes the normal predilection for 6-membered ring closure, in intramolecular cycloadditions of nitrones, to afford the adduct ⟨84JA7979, 85T3447⟩.



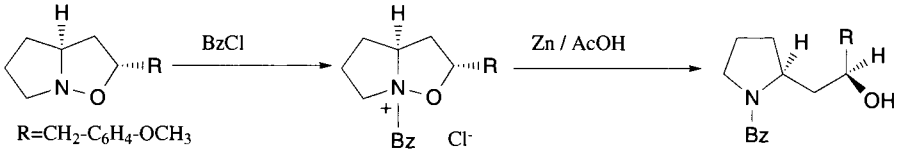
R=$COCH_3$

(146) (147) (148)

Scheme 26

(iii) Reductive cleavage

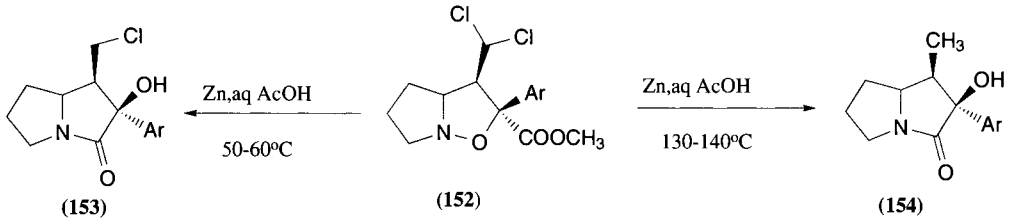
Isoxazolidine (**149**) was converted into β-aminoalcohol (**151**) via reductive N—O bond cleavage of the quaternary salt (**150**) with Zn and aqueous acetic acid (Scheme 27) ⟨85JCS(P1)261⟩.



(149) (150) (151)

Scheme 27

Another example is provided by the quaternization of a saturated pyrrolo[1,2-*b*]isoxazole with methanesulfonyl chloride and further treatment with Zn powder in aqueous acetic acid ⟨82T2627⟩. When compound (**152**) was treated with Zn in aqueous acetic acid at 50–60 °C, the isoxazolidine underwent reductive N—O bond cleavage with *in situ* cyclization to afford pyrrolizidine (**153**) in 86% yield. When (**152**) is treated directly with Zn in 90% aqueous acetic acid at higher temperature (130–140 °C) and prolonged reaction time, pyrrolizidine (**154**) is obtained (Scheme 28) ⟨85CPB351⟩.



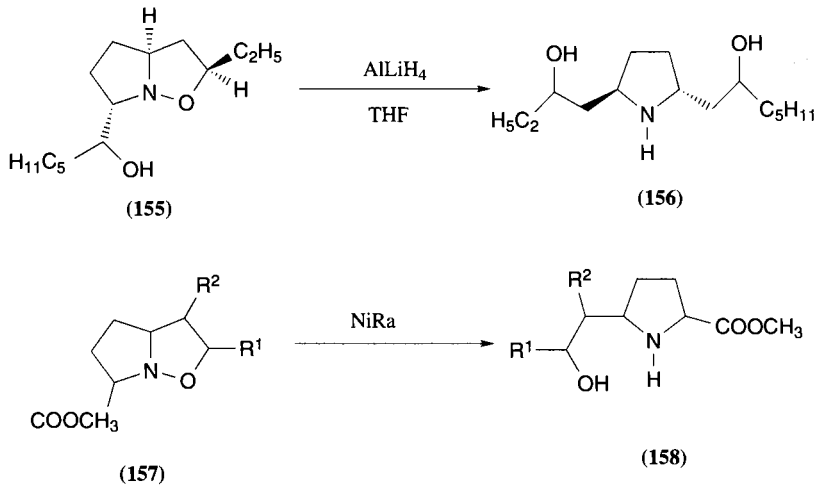
(153) (152) (154)

Scheme 28

Amino diol (**156**) is obtained by reduction of pyrroloisoxazole (**155**) with lithium aluminum hydride in refluxing THF ⟨86TL1489⟩. A similar reduction is described from compound (**157**) to (**158**) using Raney Ni (Scheme 29) ⟨84T4513⟩.

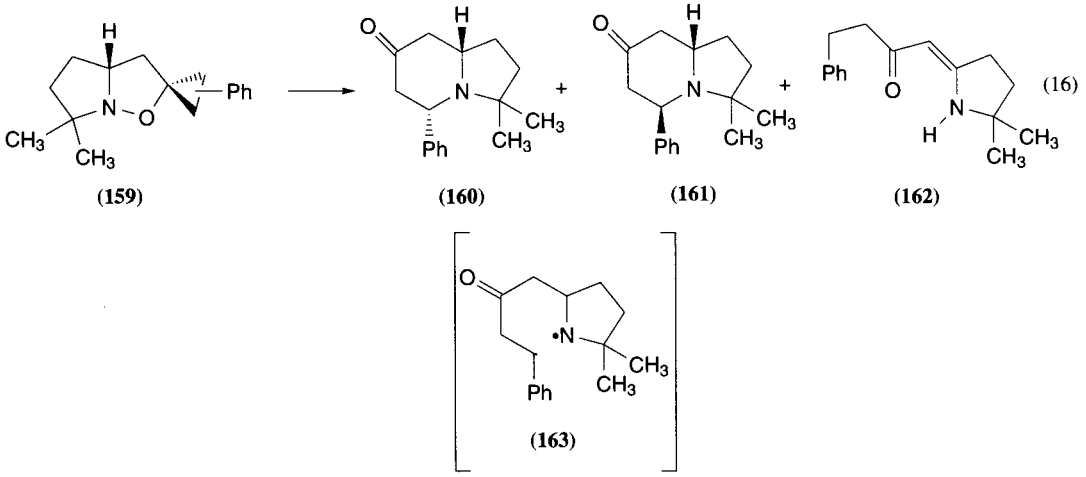
8.02.5.3.2 Thermal rearrangements

2-Spirocyclopropane perhydropyrrolo[1,2-*b*]isoxazole derivatives (**159**) undergo thermal rearrangement in mild conditions to 3,5-substituted indolizidinones (**160**) and (**161**) by regioselective cleavage of the cyclopropane ring, through the more stabilized secondary radical (**163**). Isomeric enaminones (**162**) are also formed from the same intermediate (Equation (16)) ⟨86TL1727, 90JOC1762⟩.



(155) (156) (157) (158)

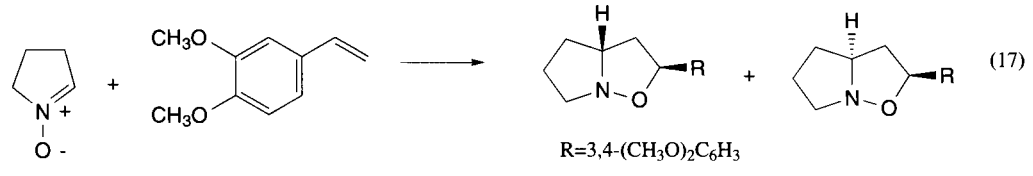
Scheme 29



(159) (160) (161) (162) (163) (16)

8.02.5.4 Synthesis

A general method is described for synthesis of perhydropyrrolo[1,2-*b*]isoxazoles through 1,3-dipolar cycloaddition of cyclic nitrones with dipolarophiles. This cycloaddition has high regio- and stereoselectivity and has been used in control of stereochemistry in synthesis of natural products containing nitrogen or other atoms. As one representative example of regioselective (3 + 2) cycloaddition, reaction between pyrroline *N*-oxide (**164**) and 3,4-dimethoxystyrene (**165**) in boiling toluene gave a diastereisomeric mixture of pyrroloisoxazoles (**166**) and (**167**), in nearly quantitative yield with preferential formation of (**166**) (Equation (17)).

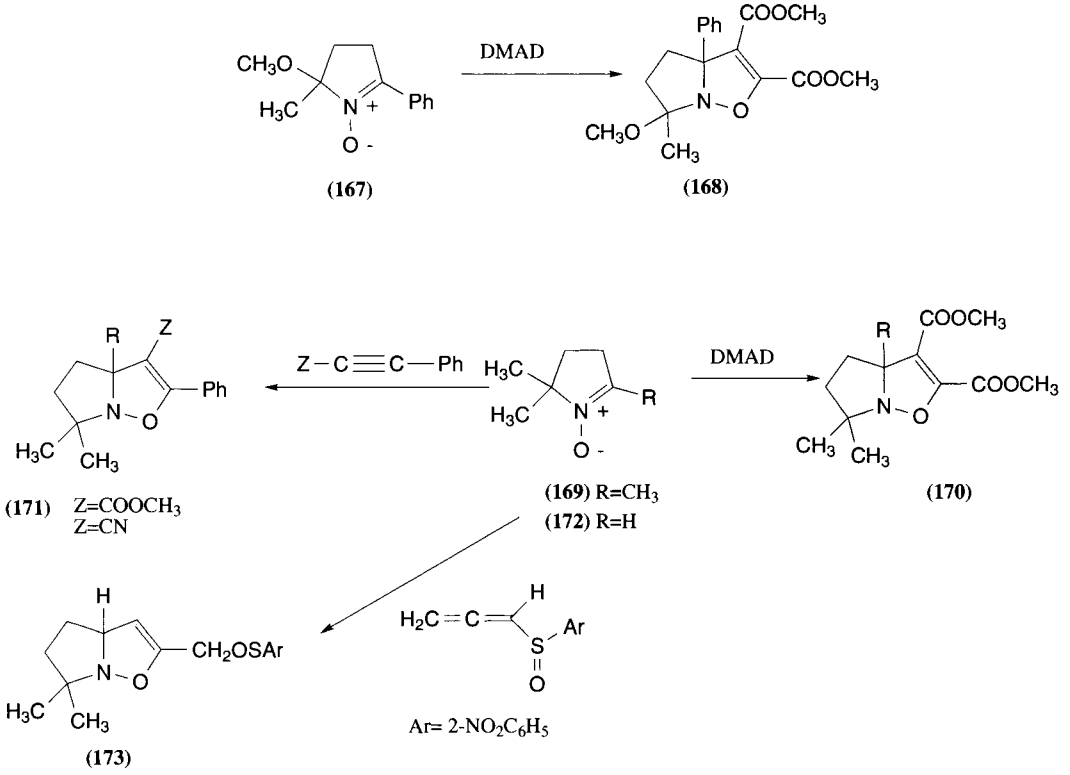


(164) (165) (166) (167) (17)

A large variety of alkenes have been used as dipolarophiles, dienes, allylsilanes, ethyl and methyl acrylates, styrenes, methylene cyclopropanes, vinylketones, polyfunctionalized acrylates, etc., giving

a great number of perhydropyrroloisoxazoles ⟨82T2627, 83CC271, 83CL1195, 84JA7979, 84JOC2412, 84T4513, 85CL957, 85CL1049, 85HCA2299, 85T3447, 86TL1727, 89JCS(P1)2415, 89JOC1748, 90JOC1762, 91MRC645⟩.

A tetrahydro system (**168**) has been obtained by reaction of nitrone (**167**) and DMAD ⟨83JCS(P1)1275⟩. In a similar manner 2,5,5-trimethylpyrroline *N*-oxide (**169**) reacted with DMAD or methyl phenylpropiolate to give the corresponding adducts (**170**) and (**171**) ⟨84JOC3127, 85JOC3076⟩. Nitroarylsulfinyl-substituted allenes react with 5,5-dimethylpyrroline 1-oxide (**172**) to give the corresponding tetrahydropyrrolo[1,2-*b*]isoxazole (**173**) ⟨91JOC4252⟩. All these reactions are shown in Scheme 30.



Scheme 30

8.02.6 PYRROLO[2,1-*b*]OXAZOLES

8.02.6.1 Introduction

Very little work has been done with this type of compound, and the results are concerned only with perhydro derivatives, mainly 5-oxoperhydro compounds, also called Meyers bicyclic lactams, which are used for asymmetric synthesis.

8.02.6.2 Theoretical and Experimental Structural Methods

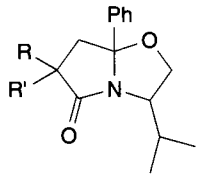
8.02.6.2.1 Theoretical methods

No molecular calculations are available for these systems.

8.02.6.2.2 Experimental methods

(i) X-ray

A few structures have been resolved in the study of the stereochemistry of compounds—as, for example, the Meyers chiral bicyclic lactam (**174**) ⟨84JA1146⟩—but no crystal data was reported.



(174) (SS) for R=R'=H

(ii) NMR spectroscopy

A great number of reports have appeared involving perhydro compounds, because of their use in asymmetric synthesis; NMR spectral data is used as the main means to determine the structures and the position of substituents. The features of the spectra are normal for saturated bicyclic heterocyclic compounds. Some unambiguous assignments were done by DIFNOE experiments ⟨89AP93, 91AP(324)191⟩.

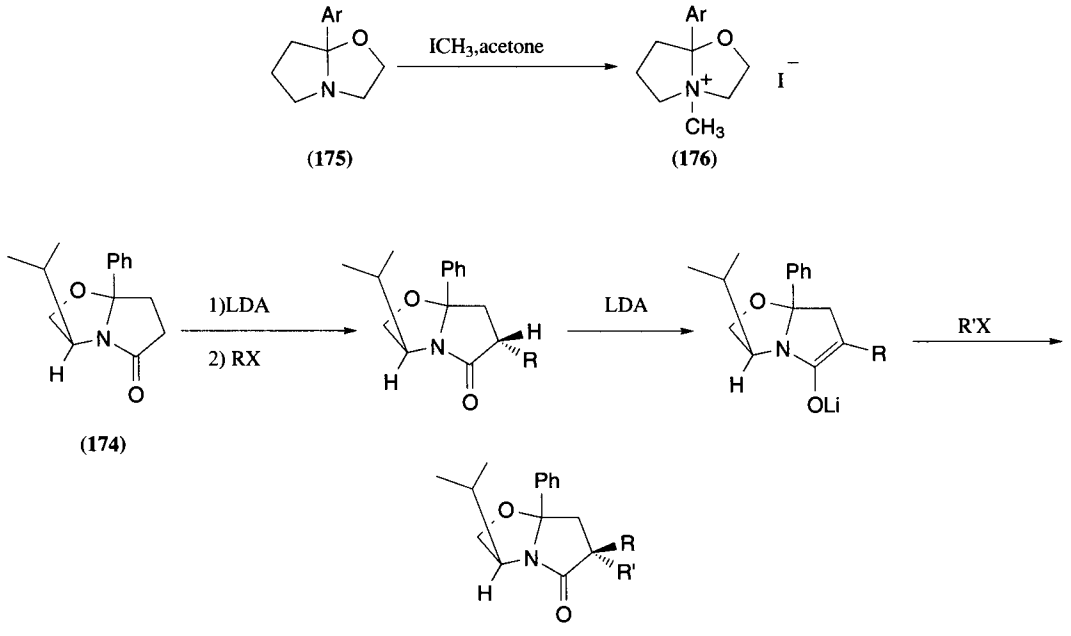
8.02.6.3 Reactivity

The studies of the reactivity of saturated pyrrolo[2,1-*b*]oxazoles are in general associated with the reactivity of Meyers chiral bicyclic lactams and their applications in asymmetric synthesis.

8.02.6.3.1 Reactions with electrophiles

(i) Nitrogen and carbon alkylation

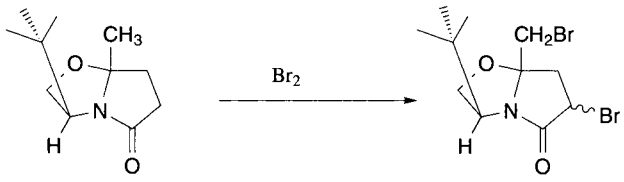
Reactions of perhydro derivatives with alkylating agents give the corresponding quaternary salt: for example, 7a-aryl-perhydropyrrolo[2,1-*b*]oxazoles (**175**) react with iodomethane in acetone to give the corresponding iodide (**176**) in high yield ⟨85AJC1591⟩. Meyers lactams react with alkylating agents in strong basic medium giving *C*-alkyl derivatives. Metalation of (**174**) (LDA, THF, −78 °C) and addition of alkyl, allyl, or benzyl halides and other electrophiles gives chiral monosubstituted lactams, that can again be metalated (LDA, THF, −78 °C) and alkylated to give disubstituted derivatives with good to excellent stereoselectivity (Scheme 31) ⟨84JA1146, 85TL2047, 87T5663, 90T4951⟩.



Scheme 31

(ii) Bromination

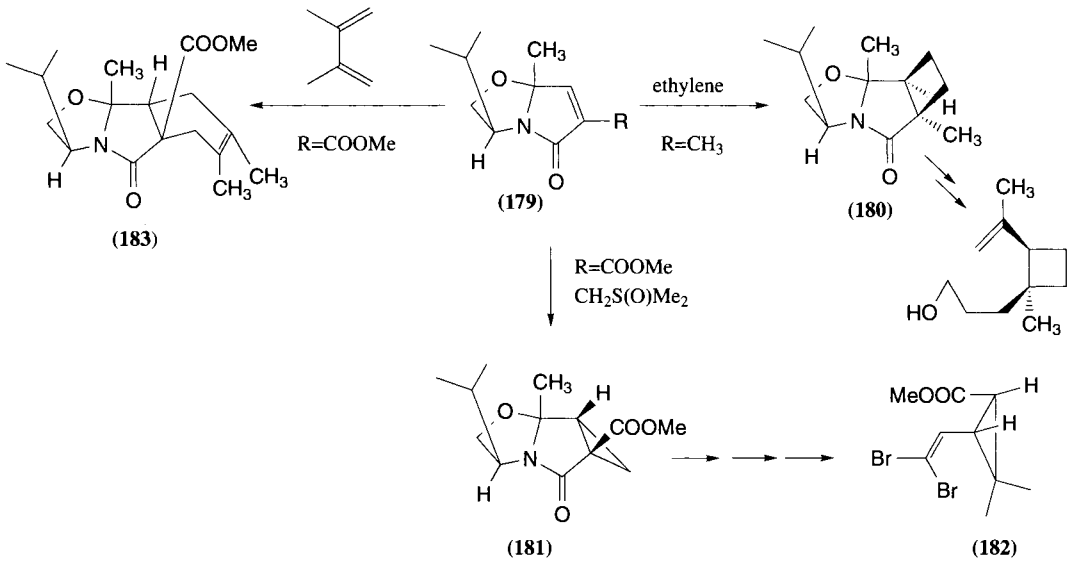
Bicyclic lactam (**177**) reacts with bromine to give the lactam (**178**) brominated in the α position and the angular methyl group (Equation (18)) ⟨90T4951⟩.



(177) (178) (18)

(iii) Cycloaddition

The L-valinol-derived unsaturated lactams (**179**) act as excellent chiral enophiles in asymmetric [2 + 2] photocycloaddition using ethylene to give cycloadduct (**180**) ⟨86JA306⟩, and in [2 + 1] cycloaddition ⟨88JA7245, 89TL1745, 90T4951⟩ to give the natural products (**181**) and (**182**). The dienophile (**179**) has been used in an asymmetric Diels–Alder reaction with 2,3-dimethylbuta-1,3-diene to give the tricyclic adduct (**183**) as a single diastereoisomer ⟨91JCS(P1)2299⟩. All these reactions are shown in Scheme 32.



Scheme 32

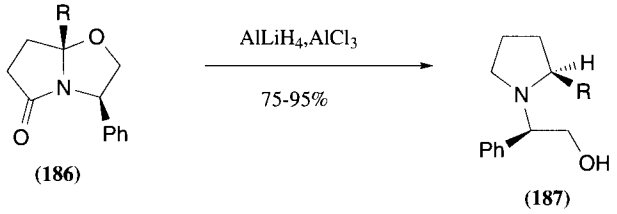
(iv) Ring opening

Meyers bicyclic lactams react with acids in alcohols to give new substituted 4-ketoesters (**184**) ⟨84JA1146, 85TL2047⟩. In another reaction lactams (**186**) react with red-Al, with further treatment with $BuNH_2PO_4$ to give 4-ketoaldehydes (**185**) ⟨86JOC1541⟩.

Cleavage of the oxazoline ring can be achieved by treatment of bicyclic lactams with lithium aluminum hydride and aluminum trichloride to obtain α-substituted pyrrolidines (**187**) (Equation (19)) ⟨91JOC2294, 92T3945⟩.

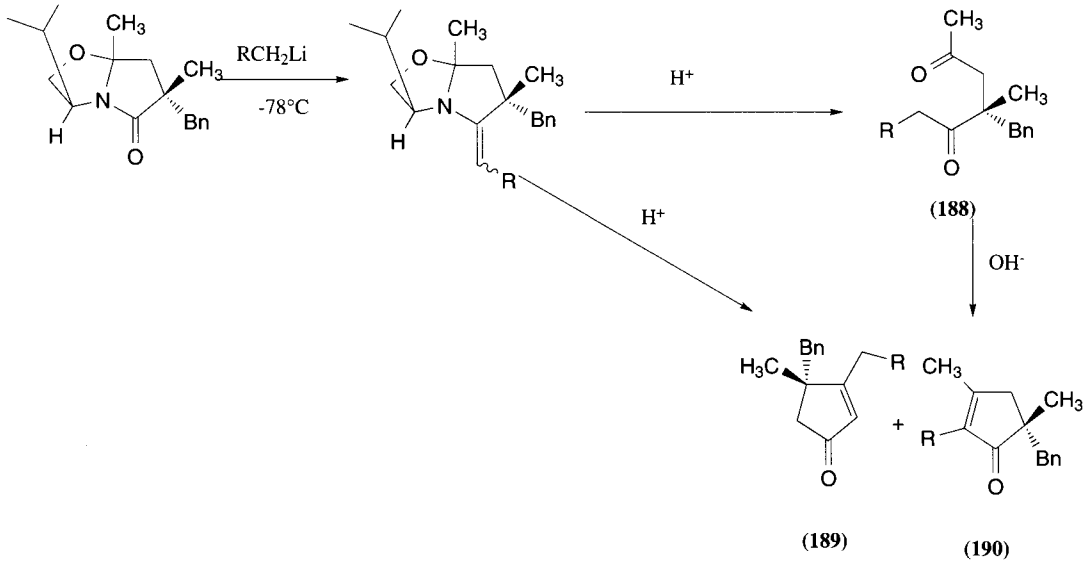


(184) (185)



(186) (187) (19)

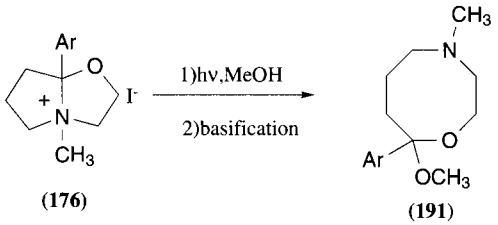
Treatment of 6,6-disubstituted lactams with a lithioderivative and further acid treatment gives 1,4-diketones (**188**), which cyclized spontaneously to afford cyclopentenones (**189**) and (**190**) (Scheme 33) ⟨87T5663⟩.



(188) (189) (190)

Scheme 33

An unusual ring opening has been observed in photosolvolysis of iodide (**176**) in methanol to obtain 1,4-oxazocine (**191**) (Equation (20)) ⟨85AJC1591⟩.



(176) (191) (20)

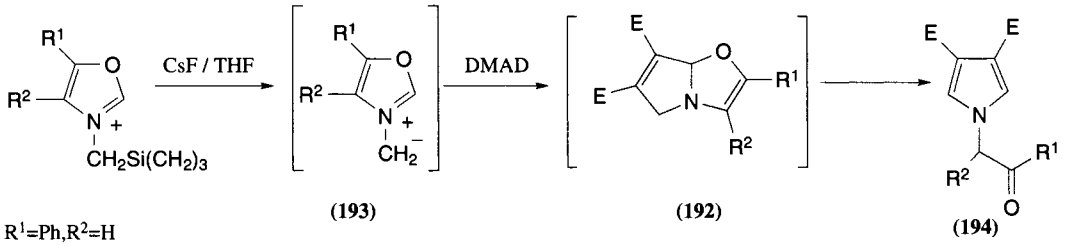
8.02.6.4 Synthesis

8.02.6.4.1 Aromatic and unsaturated systems

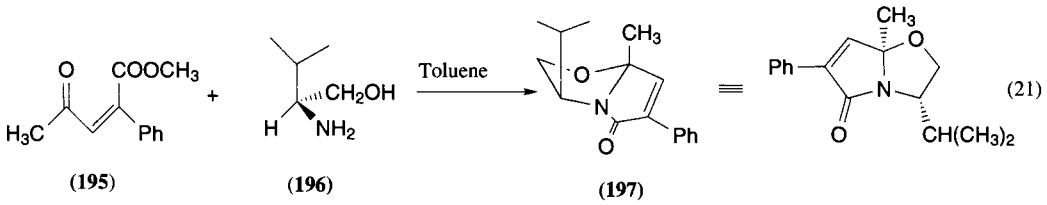
Aromatic pyrrolo[2,1-*b*]oxazoles are unknown compounds. A dihydro derivative (**192**) has been postulated as an intermediate in the reaction of an oxazolium *N*-ylide (**193**) with DMAD, to give trisubstituted pyrrole (**194**) (Scheme 34) ⟨85CC1108⟩.

Chiral unsaturated bicyclic lactams are obtained by various methods. In one case, compound

(**197**) was obtained directly by cyclodehydration of methyl 4-oxo-2-phenylpent-2-enoate (**195**) with L-valinol (**196**) (Equation (21)) ⟨90T4951⟩.

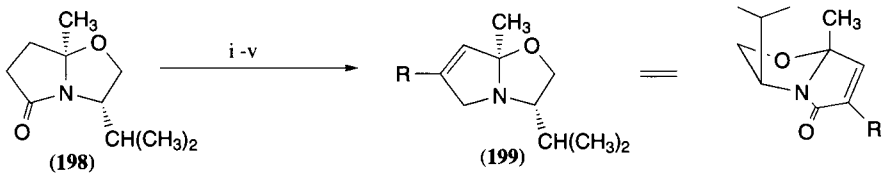


Scheme 34



(21)

A more general route for this type of chiral bicyclic lactam is based on a metalation from a Meyers lactam (**198**) followed by alkylation, acylation, or sulfenylation to give the α-substituted bicyclic unsaturated lactams. These compounds were converted to α,β-unsaturated derivatives (**199**) by a metalation–selenation–oxidative elimination sequence that proceeded in good overall yields (Scheme 35) ⟨90T4951⟩.



i=LDA/THF ; ii=R-X; iii=LDA /THF ; iv=PhSeBr ; v=H_2O_2,pyr;

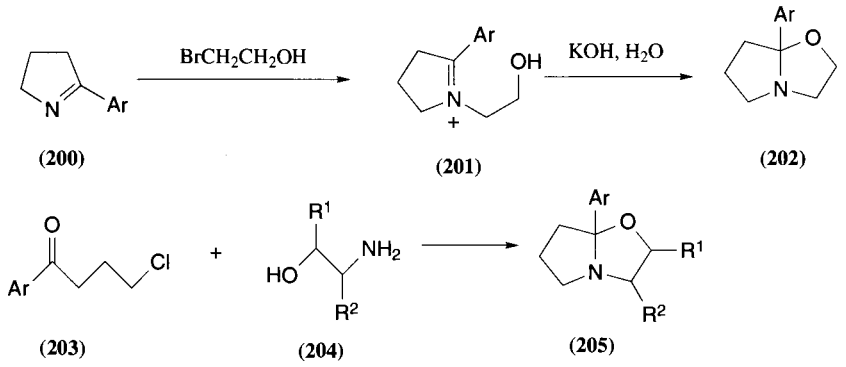
Scheme 35

8.02.6.4.2 Saturated systems

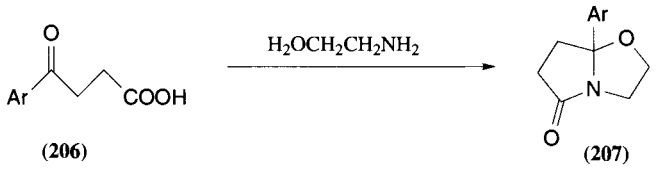
(i) Nucleophilic type displacement and cyclocondensation reactions

The 7a-phenylsubstituted perhydropyrrolo[2,1-*b*]oxazoles (**202**) were obtained by reaction of 3,4-dihydro-2*H*-pyrrole derivatives (**200**) with 2-bromoethanol in acetonitrile solution and further treatment of the salts obtained with an aqueous solution of potassium hydroxide ⟨85AJC1591⟩. Reactions of 4-chlorobutyrophenones (**203**) with aminoethanols (e.g., (**204**)) were used to obtain 7a-arylperhydropyrrolo[2,1-*b*]oxazoles (**205**) in moderate yields ⟨79MI 802-01⟩. All these reactions are shown in Scheme 36.

A limited number of 5-oxo-7a-phenylperhydropyrrolo[2,1-*b*]oxazoles (**207**) were obtained by condensation of the corresponding oxoacid with an alkanolamine (Equation (22)) ⟨76JMC436, 91EJM85⟩.



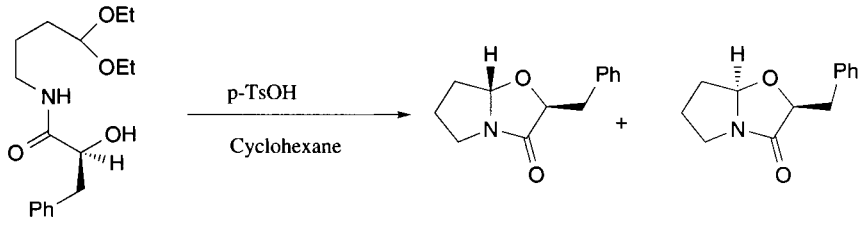
Scheme 36



(22)

When this method is applied to a chiral aminoalcohol such as (*S*)-valinol ⟨84JA1146, 85TL2047⟩ or (*S*)-*t*-leucinol ⟨89TL1745⟩ and levulinic acid or another 4-ketoacid ⟨86JOC1541⟩ with azeotropic removal of water, the corresponding Meyers chiral bicyclic lactams are obtained (formally, (3*S*,7a*R*) 3-alkyl-7a-methyl-5-oxo-perhydropyrrolo[2,1-*b*]oxazoles) ⟨90T4951, 91SL863⟩. These Meyers chiral bicyclic lactams have been extensively used in asymmetric synthesis of a great number of natural products ⟨86JA306, 86JOC1541, 87T5663, 88JA7245, 90JOC791, 90T4951, 91JCS(P1)2299⟩.

A similar series of bicyclic lactams were obtained in high chemical and optical yields by heating 3-acylpropionic acids with (*R*)-phenylglycinol in toluene ⟨91JOC2294⟩. Another similar method, illustrated in Equation (23), is the cyclocondensation of the chiral amidoketals in the presence of *p*-toluenesulfonic acid ⟨89AP93, 91AP(324)191⟩.



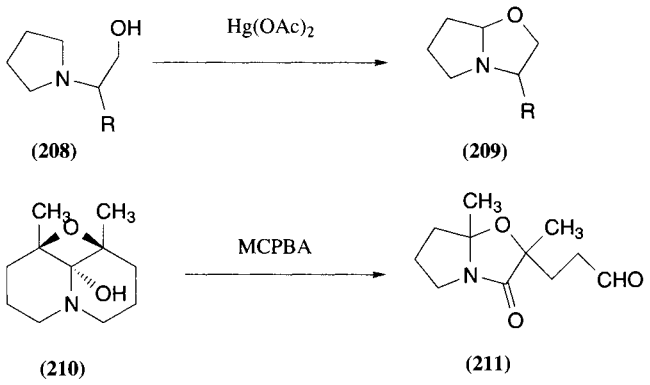
(23)

(ii) Oxidative cyclization methods

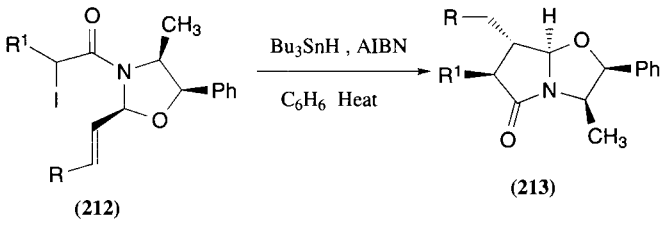
The mercuric acetate oxidation of many pyrrolidino alcohols, such as (**208**), gives bicyclic oxazolidines (**209**) in low yield ⟨60JA5148⟩. A curious example is shown in the reaction of MCPBA with an oxetane compound (**210**) to give the aldehyde (**211**) ⟨85CB1927⟩. These reactions are shown in Scheme 37.

(iii) Radical cyclization

Radical mediated cyclization of norephedrine-derived α-iodoamides (**212**) is found to give bicyclic lactams (**213**) with high stereoselectivity (Equation (24)) ⟨92T3945⟩.



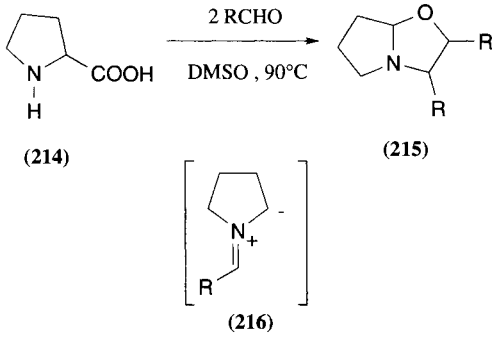
Scheme 37



(24)

(iv) 1,3-Dipolar cycloaddition

2,3-Disubstituted perhydropyrrolo[2,1-*b*]oxazoles (**215**) can be obtained by reaction between proline and some aromatic and nonenolizable aldehydes. An azomethine ylide (**216**) has been postulated as intermediate in this reaction (Equation (25)) ⟨85G569⟩.



(25)

8.02.7 PYRROLO[1,2-*c*]OXAZOLES

8.02.7.1 Introduction

Aromatic pyrrolo[1,2-*c*]oxazoles cannot be drawn, and the basic structures 1*H*,3*H*-, 3*H*,5*H*-, and 3*H*,7*H*- are unknown. All the compounds described are perhydro, mainly oxo derivatives.

8.02.7.2 Theoretical and Experimental Structural Methods

8.02.7.2.1 Theoretical Methods

No molecular calculations are available for these systems.

8.02.7.2.2 Experimental methods

(i) X-ray

A single stereoisomer of 1-oxo-7-hydroxybenzyl-3-*t*-butylperhydropyrrolo[1,2-*c*]oxazole, with three asymmetric carbon atoms, was synthesized with very high diastereoselectivity (94% *ds*); its structure is the only one that has been resolved by x-ray ⟨83JA5390⟩.

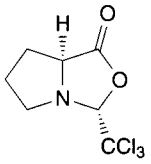
(ii) NMR spectroscopy

The structures of some of these compounds have been established by proton and carbon-13 spectroscopy ⟨83JA5390⟩. In some cases nuclear Overhauser effect (NOE) ⟨85T603⟩ or ^{2}D NMR (NOESY) experiments ⟨94CC1383⟩ have been used.

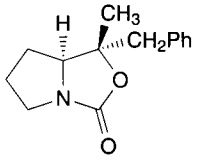
(iii) Circular dichroism and IR spectroscopy

The circular dichroism spectrum of (**217**) shows strong negative CE near 220 nm. This result is interpreted as due to the predominance of the E conformation of the oxazolidine ring ⟨85T603⟩.

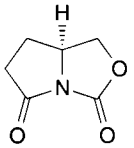
IR spectral data have been used to assign the position of the carbonyl group in oxo derivatives. While compound (**217**) showed strong absortion at 1822 cm^{-1} (CCl_4) ⟨85T603⟩, a similar compound with the carbonyl group in the C-3 position (**218**) showed absorption at 1735 cm^{-1} ⟨83JCS(P1)395⟩. When there is another carbonyl group at C-5 (**219**) the carbonyl absorptions are at 1800, 1730, and 1710 cm^{-1} (KBr) ⟨92H(33)619⟩.



(**217**)



(**218**)



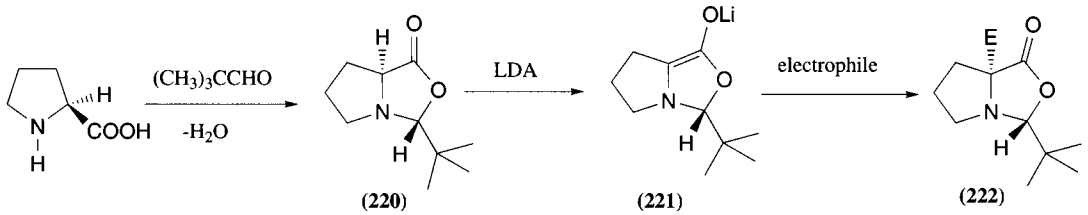
(**219**)

8.02.7.3 Reactivity

The principal systems described with a pyrrolo[1,2-*c*]oxazole structure are the perhydro-1-oxo, -3-oxo, and dioxo derivatives. Reactivity of these types of compound is based on the carbonyl chemistry.

8.02.7.3.1 Reactions with electrophiles; alkylations and related reactions

1-Oxo-perhydropyrrolo[1,2-*c*]oxazole (**220**) can be deprotonated with LDA to give a chiral non-racemic enolate (**221**), which reacts with different electrophiles to functionalize the C-7a position giving compounds (**222**) (Scheme 38) ⟨83JA5390, 85HCA155⟩.

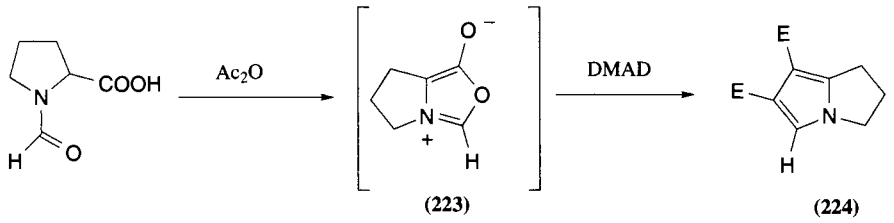


(**220**) (**221**) (**222**)

Scheme 38

8.02.7.3.2 Cycloaddition reactions

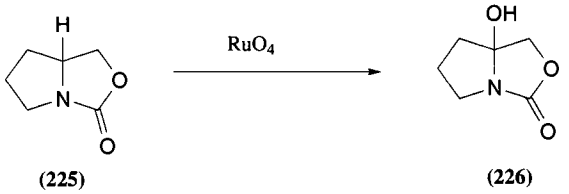
The mesoionic pyrrolo[1,2-*c*]oxazolium oxide (**223**), postulated as intermediate in the reaction of an *N*-substituted proline and acetic anhydride, reacts with DMAD to give a 1,3-dipolar adduct, which by extrusion of carbon dioxide afforded the diester (**224**) (Scheme 39) ⟨85TL1295⟩.



Scheme 39

8.02.7.3.3 Oxidation reactions

The ruthenium tetroxide oxidation of 3-oxoperhydropyrrolo[1,2-*c*]oxazole (**225**) gave the 7a-hydroxyl derivative (**226**) in high yield (Equation (26)) ⟨85CPB5042⟩.



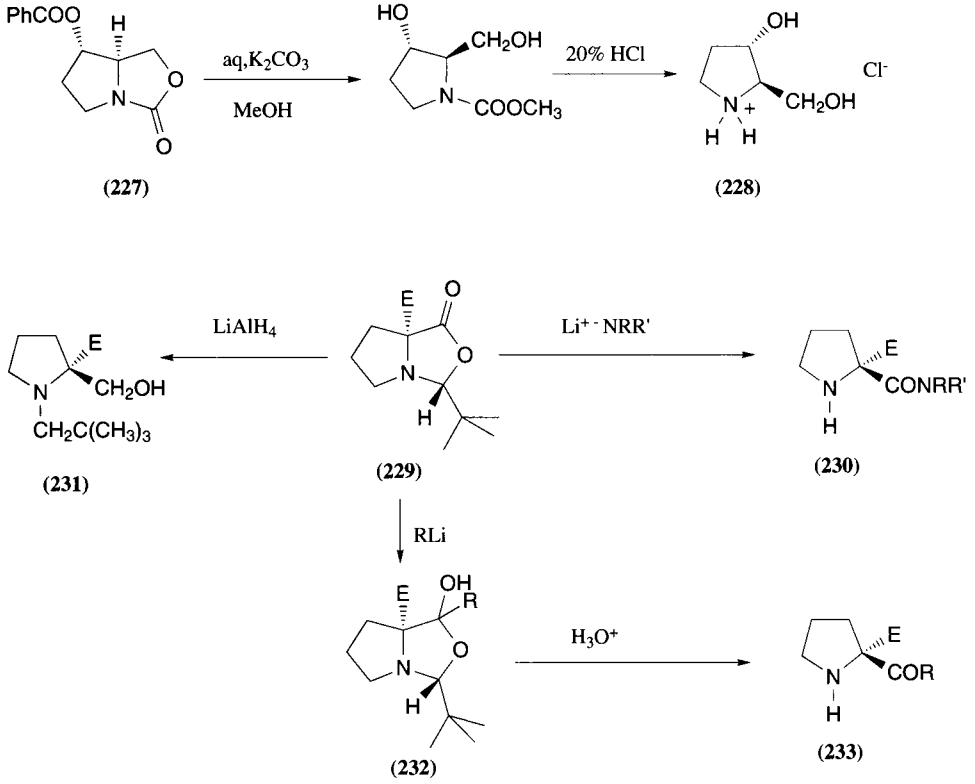
(26)

8.02.7.3.4 Ring-opening reactions

The basic hydrolysis of the 3-oxoperhydropyrrolo[1,2-*c*]oxazole (**227**) and subsequent acid hydrolysis afforded the corresponding 2-hydroxymethylpyrrolidinium salt (**228**) ⟨89CL1449⟩. However, the hydrolytic cleavage of the 7a-substituted 1-oxoperhydropyrrolo[1,2-*c*]oxazole (**229**) turns out to be most difficult. In this case the treatment with lithium amides gives α-substituted proline amides (**230**). Other strong nucleophilic reagents also lead to cleavage of the ring. Thus, lithium aluminum hydride gives aminoalcohol (**231**), and methyl or phenyllithium add to give, after nonacidic aqueous workup, the stable hemiacetals (**232**). Upon treatment with acid, or thermally during the distillation, the ketones (**233**) have been obtained ⟨83JA5390⟩. These reactions are shown in Scheme 40. In a similar manner, disubstituted 5-oxoperhydropyrrolo[1,2-*c*]oxazoles react with lithium aluminum hydride to give cleavage of the oxazoline ring ⟨86JOC3140⟩.

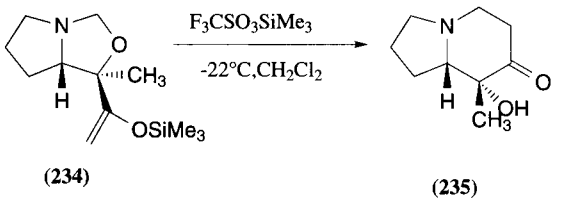
8.02.7.3.5 Ring cleavage and ring closure reactions

Several perhydropyrrolo[1,2-*c*]oxazoles, such as (**234**), described by Overman *et al.* in the context of synthesis of indolizine alkaloids, can be transformed into perhydroindolizines (**235**) by treatment



Scheme 40

with trimethylsilyl trifluoromethanesulfonate ⟨84JA5360⟩ or camphorsulfonic acid (Equation (27)) ⟨84JA4192⟩.



(27)

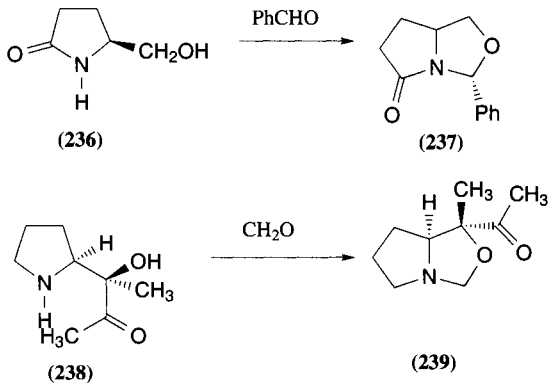
8.02.7.4 Synthesis

8.02.7.4.1 Perhydropyrrolo[1,2-c]oxazoles

These systems are reported as cyclopentaoxazolidines and can be obtained by conventional azeotropic dehydration of aldehydes with amino alcohols ⟨85TL5303⟩: for example, (*S*)-5-Hydroxymethyl-2-pyrrolidinone (**236**) was condensed with benzaldehyde to obtain the corresponding chiral 5-oxo-2-phenylperhydropyrrolo[1,2-*c*]oxazole (**237**) in excellent yield ⟨86JOC3140⟩. Similar treatment of enantiomerically pure amino ketone (**238**) with paraformaldehyde or formalin under a variety of Mannich conditions yielded (**239**) ⟨84JA5360⟩. These reactions are shown in Scheme 41.

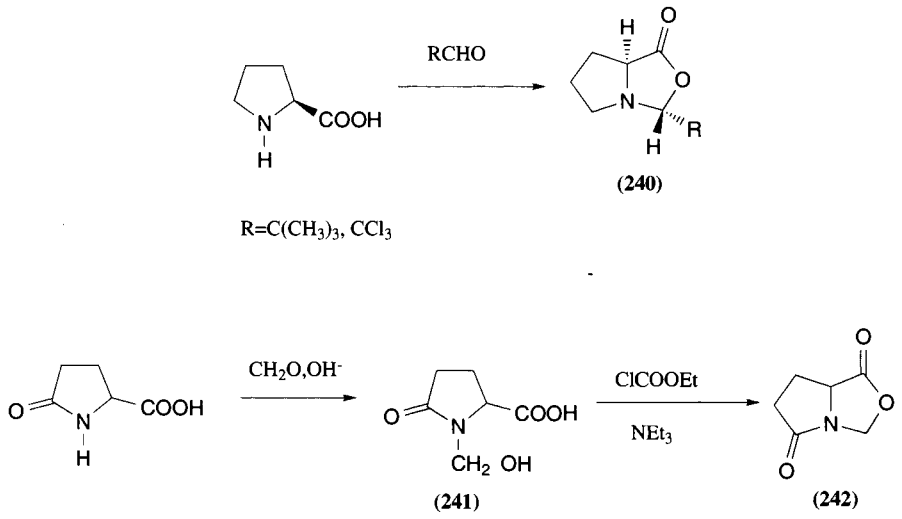
8.02.7.4.2 1-Oxoperhydropyrrolo[1,2-c]oxazoles

Proline and some derivatives have been condensed with several aldehydes to give in each case a single stereoisomer with the 1-oxoperhydropyrrolo[1,2-*c*]oxazole structure (**240**). These compounds have been used for asymmetric synthesis ⟨83JA5390, 85HCA155, 85T603⟩.



Scheme 41

The pyrrolone (**241**) cyclizes in the presence of ethyl chloroformate and triethylamine to give the azlactone (**242**) which polymerizes above 95 °C ⟨84JHC1393⟩. All these reactions are shown in Scheme 42.



Scheme 42

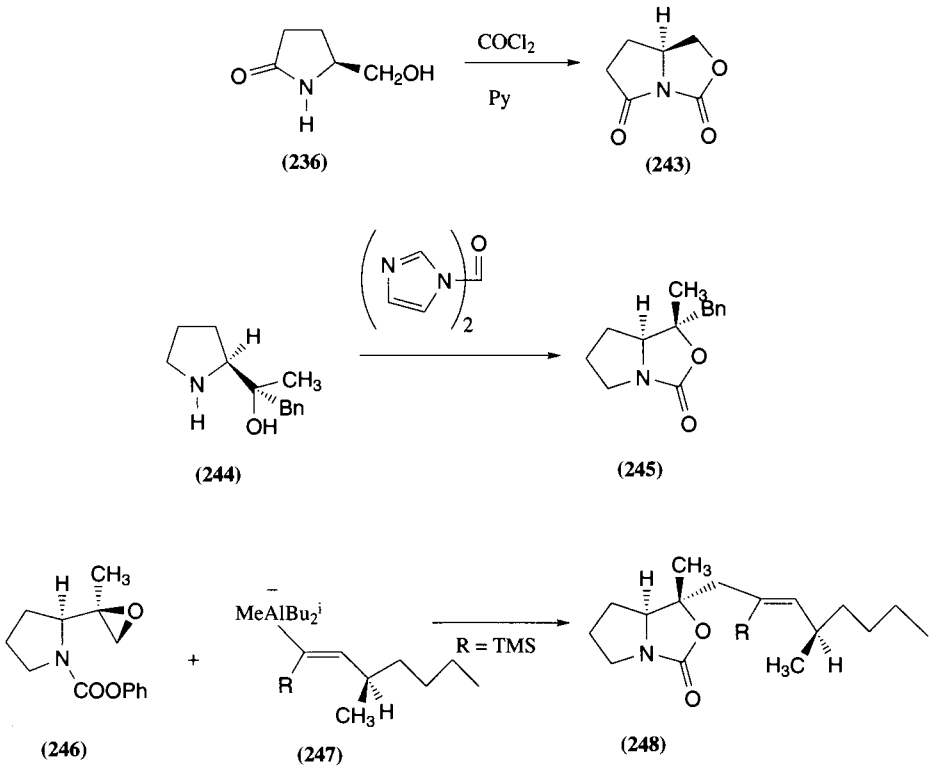
8.02.7.4.3 3-Oxoperhydropyrrolo[1,2-c]oxazoles

(i) Condensation cyclizations

The reactions of (*S*)-5-hydroxymethyl-2-pyrrolidinone (**236**) with phosgene or phosgene dimer (trichloromethylchloroformate) in the presence of pyridine afforded (+)-(*S*)-3,5-dioxoperhydropyrrolo[1,2-*c*]oxazole (**243**) in moderate yield ⟨92H(33)619⟩. In a similar manner, trisubstituted oxazolidinones have been obtained ⟨84EUP128120⟩.

When the amino alcohol (**244**) derived from proline reacted with *N*,*N*′-carbonyldiimidazole, the bicyclic carbamate (**245**) was obtained. This reaction was applied to the synthesis of some pumiliotoxin A alkaloids ⟨83JCS(P1)395⟩. A similar cyclization described by Overman, is based on the

reaction between the enantiomerically pure epoxide (**246**) and the vinyl alanate (**247**) to give the bicyclic carbamate (**248**). This reaction has been used in the synthesis of several indolizine alkaloids ⟨84JA4192, 85JOC3669, 85JMC482⟩. All these reactions are shown in Scheme 43.



Scheme 43

(ii) Intramolecular ring closure

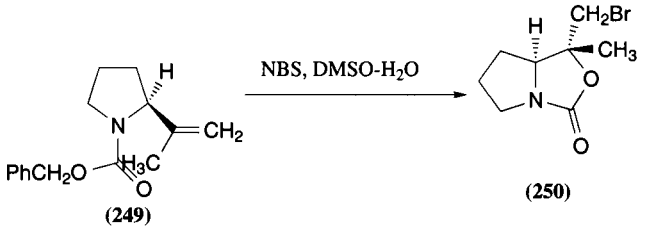
The chiral allylic carbamate (**249**) reacts with NBS in DMSO-H_2O with high 1,2-relative asymmetric induction, via carbonyl participation, to give the chiral 3-oxo-1,1-disubstituted perhydropyrrolo[1,2-*c*]oxazole (**250**) in a particular case of halolactonization used in the synthesis of the pumiliotoxin A alkaloids class ⟨82TL4887, 84JA4192⟩. Similar reactions of halonium-initiated cyclization using brominium dicollidine perchlorate have been studied ⟨83JA654⟩.

C-5 monosubstituted carbamates (**251**) react with iodine in ether containing $NaHCO_3$, to give bicyclic oxazolidones (**252**) in one step, presumably after intermediate cyclization to pyrrolidinones which undergo a further spontaneous cyclization ⟨88JOC5491⟩.

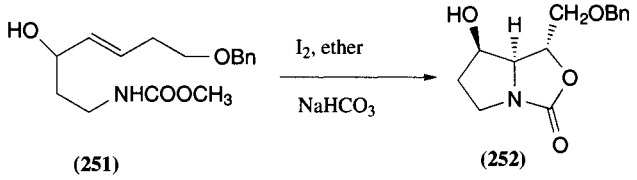
Another strategy is based on the creation of the pyrrolidine ring in the last step. Thus, debenzylation (H_2, $PdCl_2$) of 2-oxazolidinone (**253**) followed by subsequent *O*-sulfonylation and cyclization (NaH, THF) furnished 3-oxo-7-substituted perhydropyrrolo[1,2-*c*]oxazole (**254**) ⟨89CL1449⟩. All these reactions are shown in Scheme 44.

(iii) Radical cyclizations

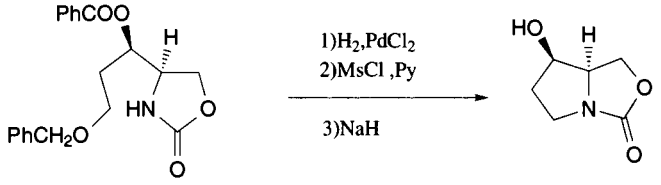
As one application of cobalt-mediated radical carbon-to-carbon bond forming reactions, the reaction between 2-oxazolidinone (**255**) and cobaloxime(I) gave an inseparable mixture of (*Z*) and (*E*) 3-oxo-6,7-disubstituted perhydropyrrolo[1,2-*c*]oxazole (**256**) in high yield, and variable amounts of the α,β-unsaturated esters (**257**) (Equation (28)) ⟨92T9373⟩.



(249) (250)

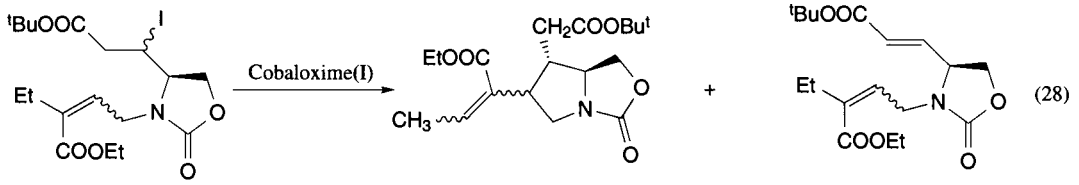


(251) (252)



(253) (254)

Scheme 44



(255) (256) (257) (28)

Diastereoselective synthesis of compounds (**259**) has been accomplished by an application of α-acylaminoradical cyclization at a silylated triple bond in compound (**258**) ⟨86CL735⟩. Desilylation of (**259**) (TFA-CH_2Cl_2) gave a quantitative yield of (**260**) as a single diastereoisomer. A similar reaction of the aldehyde (**261**) with tributyltin hydride in presence of AIBN gave a mixture of diastereoisomers (**262**) and (**263**) in 86% yield (without diastereoselectivity at the C-7 position). A particularly noteworthy feature is that the radical cyclization proceeds with complete facial selectivity ⟨94CC1383⟩. These reactions are shown in Scheme 45.

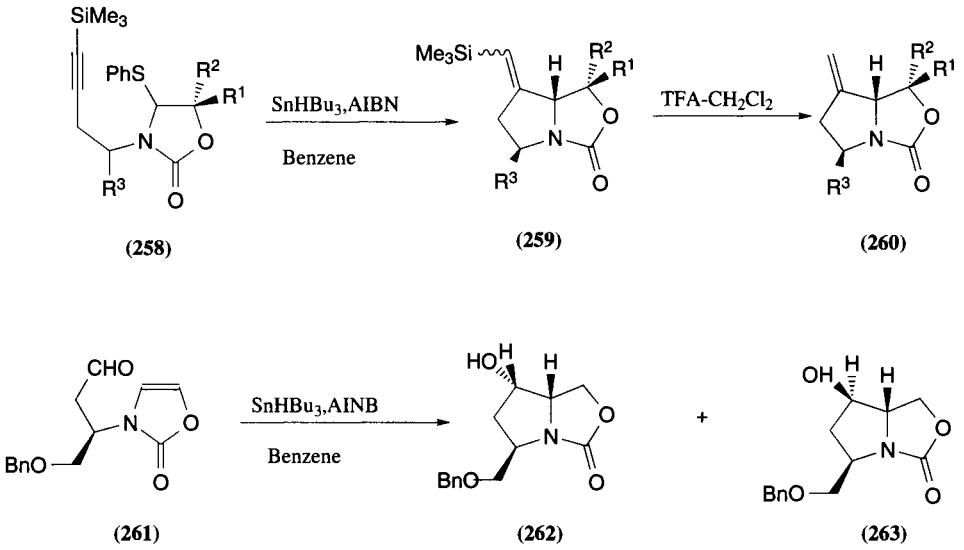
8.02.7.4.4 1,3-Dioxoperhydropyrrolo[1,2-c]oxazoles

Several 1,3-dioxoperhydropyrrolo[1,2-*c*]oxazoles (**266**) have been synthesized. The more common procedure is by reaction of *C*-substituted prolines (**264**) with phosgene, followed by ring closure with 2,6-lutidine ⟨83JPS(A)1699⟩ or Ag_2O (Scheme 46) ⟨83MI 802-01⟩.

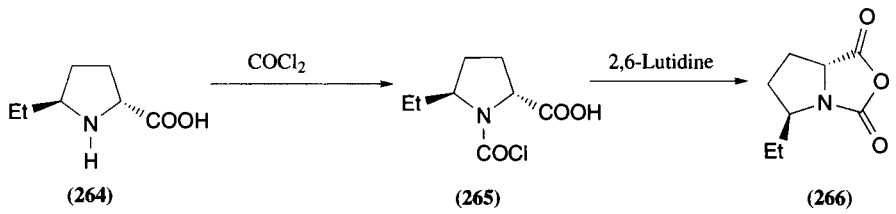
8.02.8 PYRROLO[2,1-*b*]THIAZOLES

8.02.8.1 Introduction

Pyrrolo[2,1-*b*]thiazoles have fully conjugated rings; a few derivatives are described, but the parent compound is unknown. More saturated compounds are known.



Scheme 45



Scheme 46

8.02.8.2 Theoretical and Experimental Structural Methods

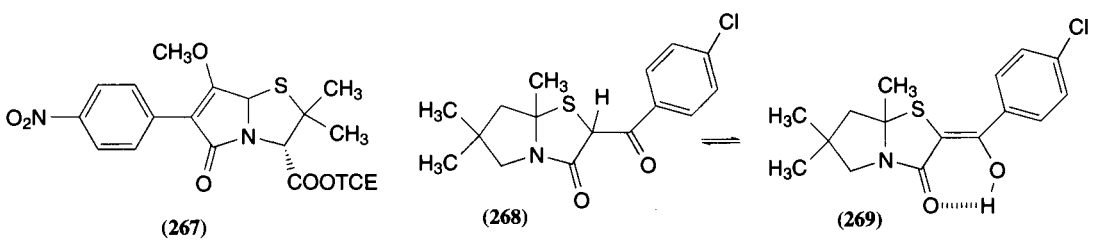
8.02.8.2.1 Theoretical methods

Theoretical calculations of this type of compound have not been reported.

8.02.8.2.2 Experimental methods

(i) X-ray

There are some resolved structures but not of the fully conjugated compounds: for example, the compound (**267**), but no data has been reported ⟨86JCS(P1)2195⟩. The crystal data of 3-oxo-2-(4-chlorobenzoyl)-6,6,7a-trimethylperhydropyrrolo[2,1-*b*]thiazole (**268**) suggest intramolecular H-bonding which gives the preferred structure as (**269**) ⟨87AP(320)1278⟩.



(ii) NMR spectroscopy

The ^{1}H chemical shifts of some substituted pyrrolo[2,1-*b*]thiazoles are summarized in Table 5 ⟨73JCS(P1)657, 86JCS(P1)1255⟩.

Table 5 Proton NMR spectral data for substituted pyrrolo[2,1-*b*]thiazoles (solvent $CDCl_3$).

Compound	*H-2*	*H-3*	*H-5*	*H-6*	*H-7*	*Others*
3Me,6Bu^t	6.13		6.85		6.15	1.30; 2.90
2Me,3Me,6Me			6.77		5.98	2.18; 2.23
2Me,3Me,5Me,6Me					5.85	2.09; 2.19; 2.38; 2.46
6Me,5CHS	6.93	9.07			6.33	10.37; 2.40
7Me,6Me,5CHS	6.93	9.69				10.23; 2.30; 2.13
3Me,6Bu^t,7CHS	6.63		6.94			11.11; 2.47;1.48
5Me,6Me,7CHS	7.09	7.41				10.62; 2.33; 2.27

A significant feature is the shielding of the aromatic protons, indicating a π-excessive character for this system. As can be seen in Table 5, when the 5-position is substituted by a thioaldehyde function, H-3 is significantly deshielded by the anisotropic current of the thiocarbonyl group.

The H(2)-H(3) coupling constant is 3–4 Hz ⟨94H(38)2017⟩. Long-range coupling between H-3 and H-7 is 0.5 Hz and between different methyl groups with aromatic protons $J_{5,6Me} = 1.2$ Hz, $J_{7,6Me} = 0.8$ Hz, $J_{2,3Me} = 1.2$ Hz. A long-range coupling 7H-CHS ($J = 0.8$ Hz) has also been observed ⟨86JCS(P1)1255⟩. Restricted rotation about the ring—CHO bond was detected in some substituted pyrrolo[2,1-*b*]thiazole-5-carbaldehydes. Spectroscopic examination of these compounds established proportions of O,N-*syn* and *anti* rotational isomers ⟨86JCS(P1)1255⟩. In a similar manner pyrrolo[2,1-*b*]thiazole-5-thiocarbaldehydes and -7-thiocarbaldehydes have been studied ⟨73JCS(P1)657⟩. Some spectra of substituted pyrrolo[2,1-*b*]thiazoles are recorded in TFA giving the substituted 5*H*-pyrrolo[2,1-*b*]thiazolium cations ⟨73JCS(P1)657⟩.

In 2-substituted 2,3-dihydro-3-oxopyrrolo[2,1-*b*]thiazoles, chemical shifts of aromatic protons are similar to those of 1,2-disubstituted pyrroles ⟨83JHC591⟩.

The nonaromatic pyrrolo[2,1-*b*]thiazoles showed chemical shifts expected for this type of system. A number of reports have appeared on synthesis of these saturated ring systems, and spectroscopic data were used as the main means to determine structure and position of substitution. In some cases NOE experiments were used ⟨86CC409, 86TL3453, 89T4537⟩.

There are few reports, for aromatic pyrrolo[2,1-*b*]thiazoles, of ^{13}C NMR spectra ⟨92JHC1473, 94H(38)2017⟩. In partial or completely saturated pyrrolo[2,1-*b*]thiazoles, ^{13}C NMR spectra are available and were used to prove structures of compounds ⟨86JCS(P1)2195, 89T4537⟩.

(iii) IR spectroscopy

The most interesting feature is the comparison of IR spectra of 3,6-dimethylpyrrolo[2,1-*b*]thiazole-5-carbaldehydes with *N*-methylpyrrole-2-carbaldehyde, confirming that the mesomeric effect (O,N-*sym*, O,N-*anti*) is more pronounced in the pyrrolo[2,1-*b*]thiazole system ⟨86JCS(P1)1255⟩.

In saturated systems such as dihydro, tetrahydro, or perhydro oxopyrrolo[2,1-*b*]thiazoles, carbonyl absorption appears in the normal range. Only in 3,5-dioxoperhydropyrrolo[2,1-*b*]thiazole do carbonyl absorptions appear at higher values, at 1782 and 1720 cm^{-1} ⟨87JMC498⟩.

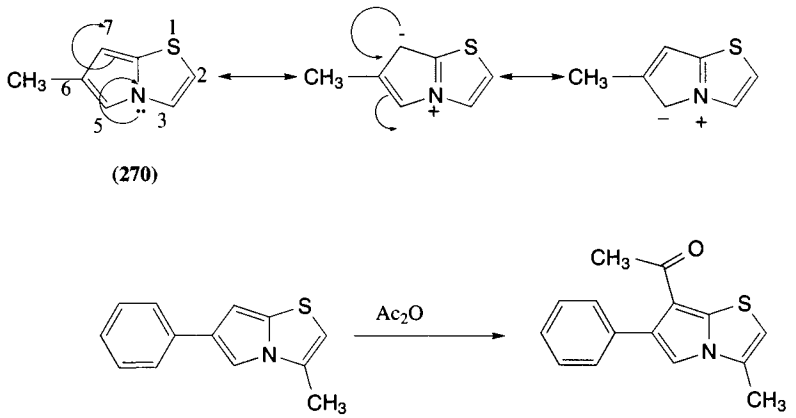
8.02.8.3 Reactivity

There are few studies of pyrrolo[2,1-*b*]thiazoles. In the fully conjugated series, electrophilic substitutions have been described. For saturated compounds work has been mainly in synthesis of penicillin analogues and other compounds with interesting biological properties.

8.02.8.3.1 Fully conjugated pyrrolo[2,1-b]thiazoles—electrophilic substitution

Pyrrolo[2,1-*b*]thiazoles undergo electrophilic substitution readily ⟨64LA(679)139⟩ first at the 5-position, then at the 7-position, ⟨66JCS(C)1908⟩. The 5- and 7-positions are conjugated with both

sulfur and nitrogen atoms, and maximum delocalization from each should make the 5-position more reactive, as should the greater activation of methyl across the 5,6-bond, which is indicated by the valence bond structure (**270**) to be of higher order ⟨87JCS(P2)591⟩. The rate of deuteration of 6-methylpyrrolo[2,1-*b*]thiazole (7- and 5-position) under standard conditions may be calculated as 1.19×10^{17} and 1.68×10^{18} respectively. The corresponding σ^+ values are -1.95 and -2.08 ⟨87JCS(P2)591⟩. Examples of acetylation were described ⟨64LA(679)139⟩ and protonation with TFA in simple pyrrolo[2,1-*b*]thiazoles has been described and shown by NMR to give 5*H*-pyrrolo[2,1-*b*]thiazolium salts (Scheme 47) ⟨73JCS(P1)657⟩. Vilsmeier formylation and thioformylation have been studied in various substituted pyrrolo[2,1-*b*]thiazoles ⟨73JCS(P1)657, 86JCS(P1)1255⟩.

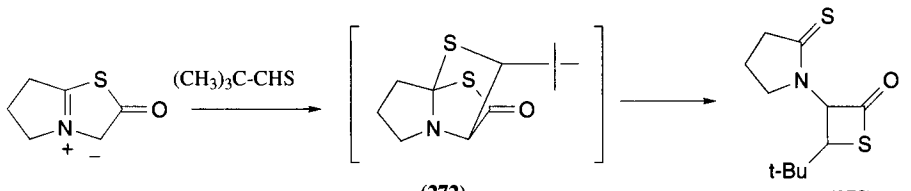


(270)

Scheme 47

8.02.8.3.2 Saturated pyrrolo[2,1-b]thiazoles

The bicyclic thiomunchnone (**271**) (generated from the thiolactam carboxylate salt and MsCl, followed by 1 equiv. of triethylamine) has been used as 1,3-dipole in reaction with thiopivaldehyde to give compound (**273**), derived from an initial adduct (**272**) (Scheme 48) ⟨86JOC117⟩.

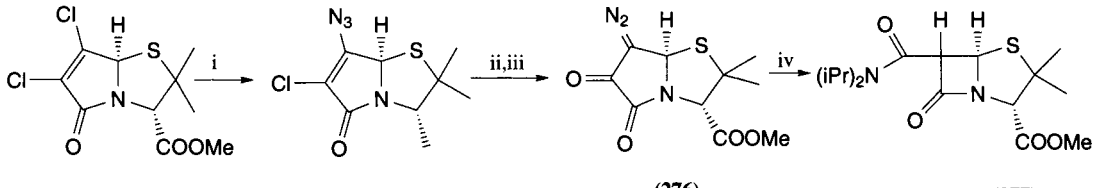


(271) (272) (273)

Scheme 48

Some transformations of pyrrolo[2,1-*b*]thiazole (**274**) have been described in relation to penicillin chemistry. Treatment of (**274**) with potassium azide in acetonitrile containing a trace of dibenzo-18-crown-6 gave azide (**275**). This product is converted easily to diazopyrrolinone (**276**) and by photolysis in THF in the presence of diisopropylamine to give the β-lactam (**277**) (Scheme 49) ⟨83JOC3365⟩.

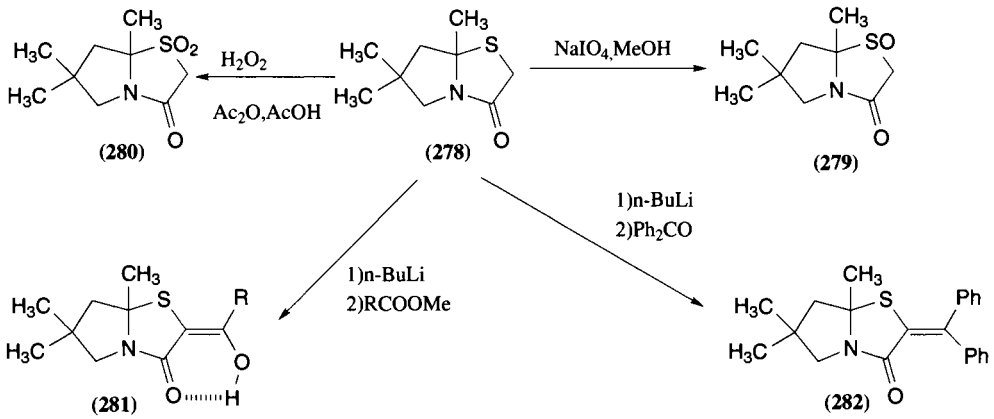
Perhydropyrrolo[2,1-*b*]thiazol-3-one (**278**) can be oxidized to the sulfoxide (**279**) with sodium periodate or to the sulfone (**280**) with H_2O_2. By reaction with *n*-butyllithium an enolate has been obtained. By reaction of this enolate with some electrophiles, such as esters or ketones, the corresponding 2-substituted perhydropyrrolo[2,1-*b*]thiazolones (**281**) or (**282**) have been obtained. These reactions are shown in Scheme 50.



(274) (275) (276) (277)

i=KN_3,CH_3CN,dibenzo-18-crown-6,-12°C,4days;ii=$NaBH_4$,CH_2Cl_2,-12°C;iii=$NaNO_2$,aq HCl,CH_2Cl_2;; iv=hν,THF, i-Pr_2NH

Scheme 49



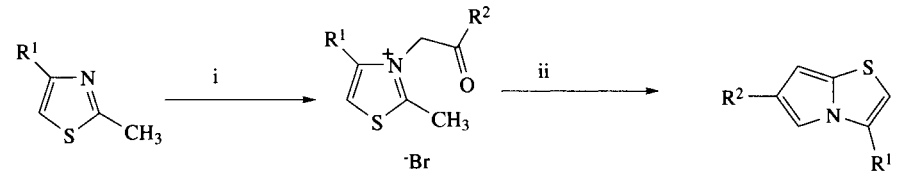
Scheme 50

8.02.8.4 Synthesis

8.02.8.4.1 Pyrrolo[2,1-b]thiazoles

(i) C—C bond formation

2,4-Disubstituted thiazoles (**283**) react with α-bromoketones to give the corresponding salts. These salts (**284**), by treatment with sodium carbonate or hydroxide in water or methanol, or with sodium acetate in acetic anhydride, give 6-substituted pyrrolo[2,1-*b*]thiazoles (**285**) (Scheme 51) 〈64LA(679)139, 65JCS65, 73JCS(P1)657, 86JCS(P1)1255〉.



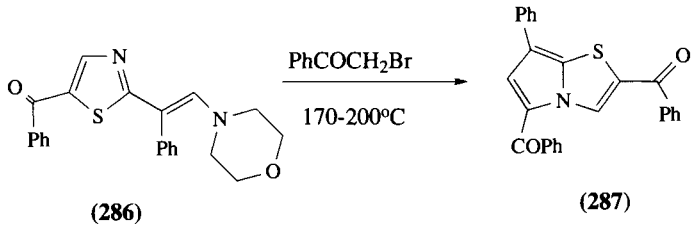
(283) R^1	R^2
Me	Ph
Me	C_6H_4Br-p
Me	Me
C_6H_4Cl-p	Me

(284) ·Br

i=$BrCH_2COR^2$; ii=$AcONH_4$,Ac_2O,head

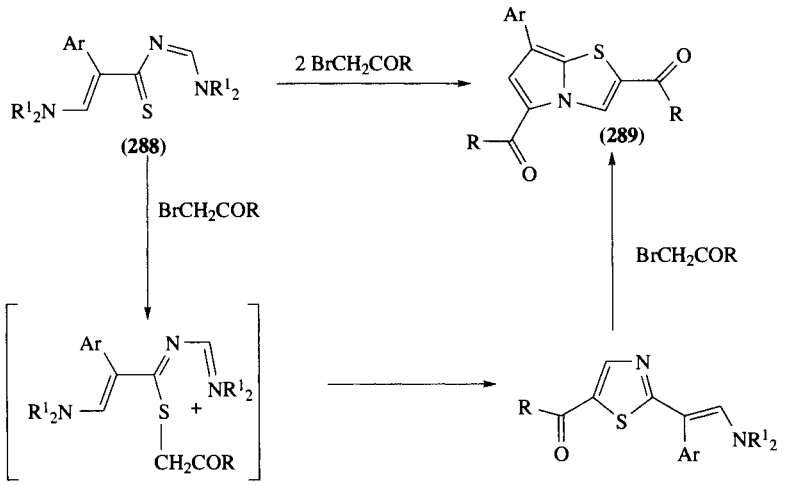
Scheme 51

The 5-benzoyl-2-(2-morpholino-1-phenylethenyl)thiazole (**286**) reacts with phenacyl bromide at 170–200 °C to give the trisubstituted pyrrolo[2,1-*b*]thiazoles (**287**) (Equation (29)) 〈88EGP262863〉.



(29)

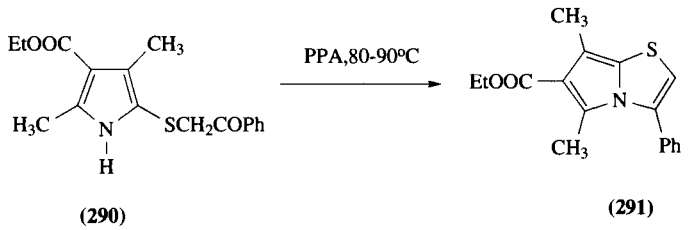
A general synthesis of 2,5,6-trisubstituted pyrrolo[2,1-*b*]thiazoles from *N*-(3-amino-thioacryl)formamidines (**288**) has been described by reaction with aromatic α-haloketones. The pyrrolo[2,1-*b*]thiazoles (**289**) have been obtained in moderate yield (33–77%) (Scheme 52) ⟨88ZC214⟩.



Scheme 52

(ii) C—N bond formation

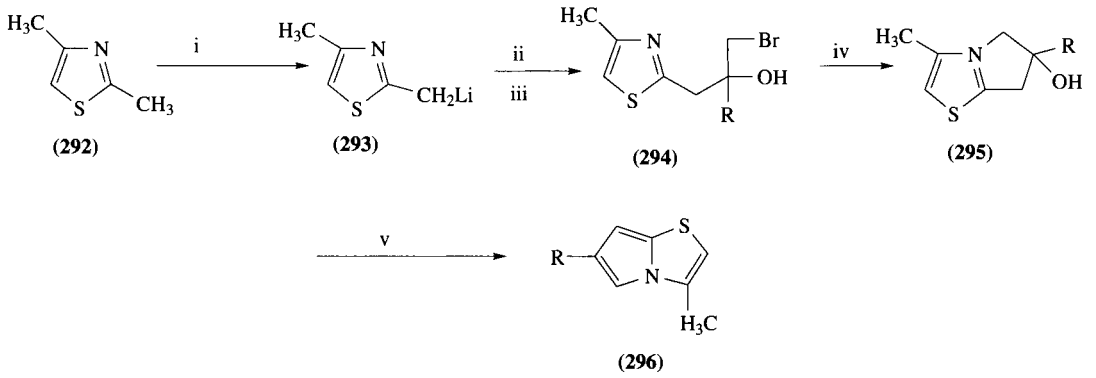
The sulfide (**290**) cyclizes smoothly on heating with polyphosphoric acid (ppa) to give the poly-substituted pyrrolo[2,1-*b*]thiazoles (**291**) (Equation (30)) ⟨84AJC1473⟩.



(30)

(iii) Intramolecular alkylation

3,6-Disubstituted pyrrolo[2,1-*b*]thiazoles (**296**) have been obtained by treatment of the lithio derivative (**293**) of 2,4-dimethylthiazole (**292**) with α-haloketones at −55 °C giving (**294**). Cyclization to (**295**) and dehydration under mild conditions afforded the corresponding pyrrolothiazole (**296**) in good yield (63–65%) (Scheme 53) ⟨86JCS(P1)1255⟩.

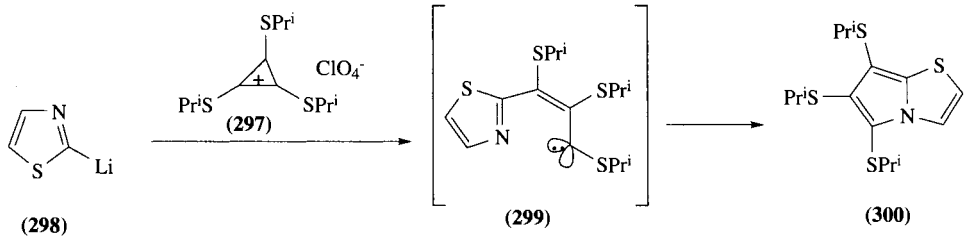


i = n-BuLi,THF,-55°C; ii = $PhCOCH_2Br$,-55°C;CH_3COCH_2,-55°C; iii = AcOH,-55°C; iv = acetone,heat;
v = NaOH-H_2O-MeOH;

Scheme 53

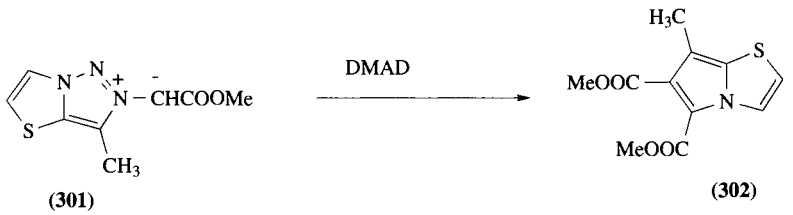
(iv) Nucleophilic type displacements

Reaction of tris-(isopropylthio)cyclopropenium perchlorate (**297**) with 2-thiazolylithium (**298**) in dry THF gave pyrrolo[2,1-*b*]thiazole (**300**) in good yield (71%). This reaction is said to proceed via the vinylcarbene (**299**) (Scheme 54) ⟨92JHC1473⟩.



Scheme 54

The compound (**302**) has been synthesized by reaction between the triazolopyridinium ylide (**301**) and DMAD (Equation (31)) ⟨94H(38)2017⟩.

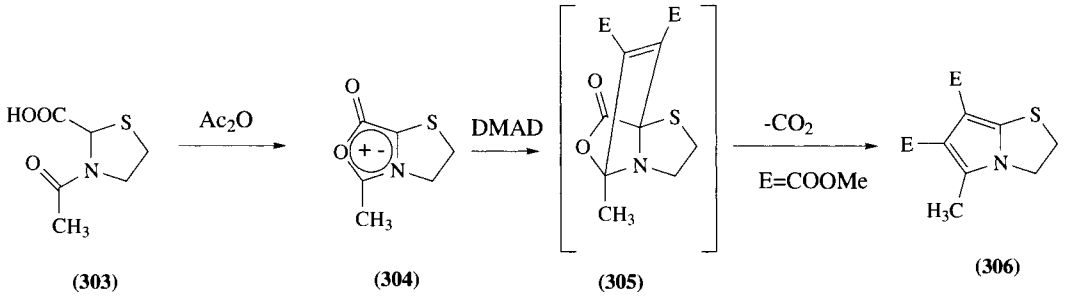


(31)

8.02.8.4.2 Dihydropyrrolo[2,1-b]thiazoles

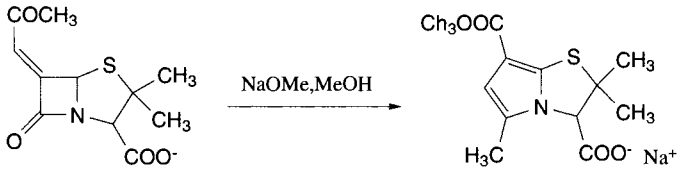
Only 2,3-dihydropyrrolo[2,1-*b*]thiazoles have been described. Reaction of *N*-acetylthiazolidine-2-carboxylic acid (**303**) in the presence of acetic anhydride provides mesoionic oxazolone intermediates (**304**) which undergo 1,3-dipolar cycloaddition with DMAD, to give unstable intermediate (**305**) which rapidly eliminates carbon dioxide to give 2,3-dihydro-5-methylpyrrolo[2,1-*b*]thiazole-6,7-dicarboxylate (**306**) (Scheme 55) ⟨88JMC1427⟩.

The 6-acetylmethylenepenicillanic acid (**307**) reacts with sodium methoxide to give pyrrolo[2,1-*b*]thiazoline (**308**) by a ring expansion of the β-lactam ring (Equation (32)) ⟨83BJ(211)447⟩.



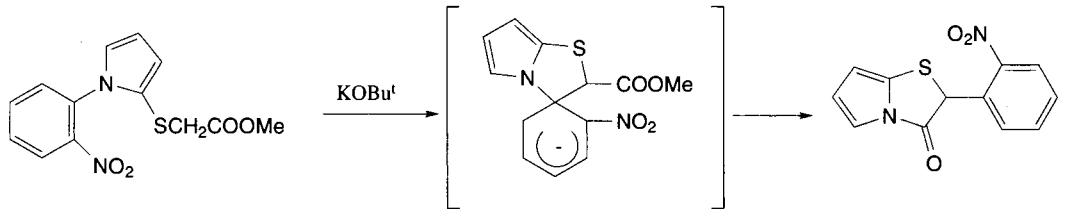
(303) (304) (305) (306)

Scheme 55



(307) (308) (32)

An unusual synthesis of the 3-oxo derivative (**311**) has been reported by a rearrangement of the pyrrolothioacetate (**309**) with potassium *t*-butoxide in DMSO. The key to this reaction is a Meisemheimer-type intermediate (**310**), in which the thiazolidine ring is cleaved and recyclized (Scheme 56) ⟨83JHC591⟩.



(309) (310) (311)

Scheme 56

A thiomunchnone (**312**) has been synthesized by reaction of the thiolactam carboxylate salts with MsCl, followed by one equivalent of triethylamine ⟨86JOC117⟩.

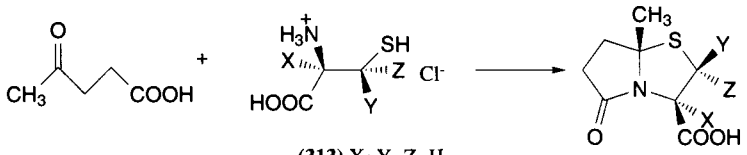


(312)

8.02.8.4.3 Tetra- and perhydropyrrolo[2,1-b]thiazoles

(i) Nucleophilic-type displacement

The cysteine derivatives (**313**) react with levulinic acid to afford the lactams (**314**) (Equation (33)) ⟨86CC409⟩.

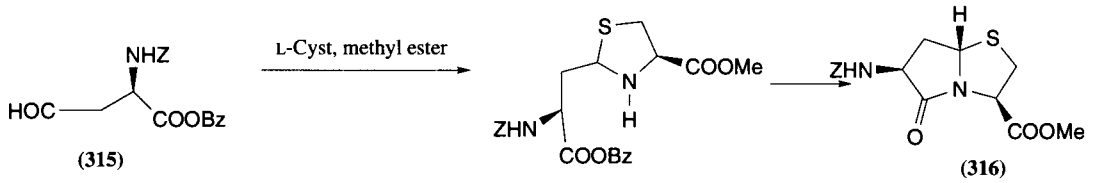


(313) X=Y=Z=H
X=Y=H, Z=D
X=Z=H, Y=D

(314)

(33)

In a similar manner the synthesis of γ-lactam analogues of penems (**316**) from *N*-benzyloxycarbonyl-*L*-aspartic semi-aldehyde benzyl ester (**315**) has been described (Scheme 57) ⟨86TL3461, 89T4537⟩.

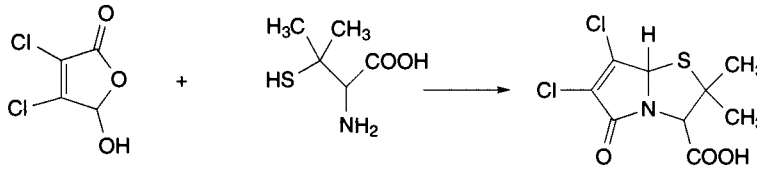


(315)

(316)

Scheme 57

Another 1,4-bielectrophile used is mucochloric acid (**317**) which, on condensation with penicillamine, afforded pyrrolinone (**318**) in one step (Equation (34)) ⟨83JOC3365⟩.

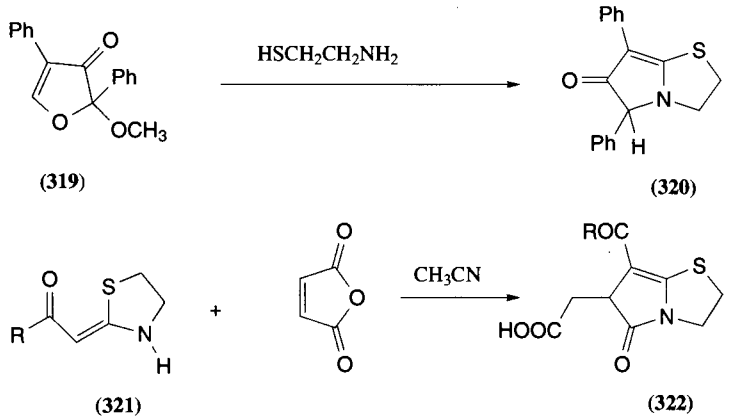


(317)

(318)

(34)

The 2-methoxy-3-(2*H*)furanone (**319**) reacts with 2-aminoethanethiol to give pyrrolo[2,1-*b*]thiazole (**320**) ⟨85H(23)1073⟩. Reaction of cyclic S,N-acetals (**321**) with maleic anhydride in boiling acetonitrile gave the pyrrolo[2,1-*b*]thiazole derivative (**322**) ⟨88S284⟩. These reactions are shown in Scheme 58.



(319)

(320)

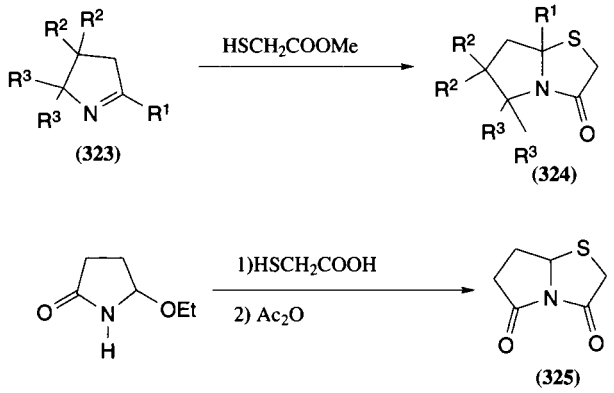
(321)

(322)

Scheme 58

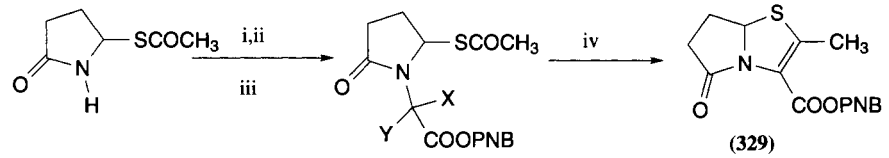
(ii) Aldol-type condensation

(a) C—N bond formation. Reaction of methyl thiolacetate with unsaturated pyrrolidine (**323**) gave perhydropyrrolo[2,1-*b*]thiazolones (**324**) ⟨87AP(320)799⟩. A similar reaction of 5-ethoxypyrrolidine and thiolacetic acid gave 3,5-dioxoperhydro[2,1-*b*]thiazole (**325**) (Scheme 59) ⟨87JMC498⟩.



Scheme 59

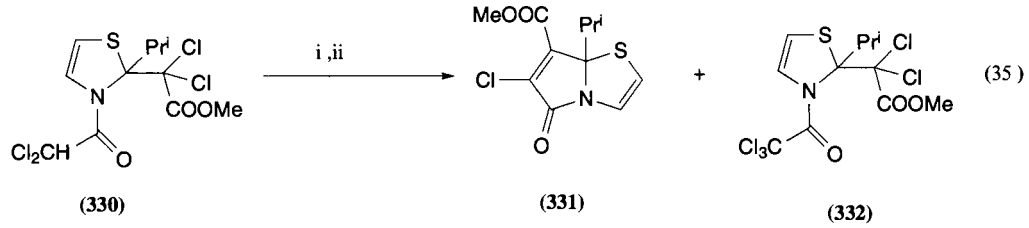
Condensation of thioacetate (**326**) with *p*-nitrobenzylglyoxylate afforded the hemiaminal (**327**) as a mixture of diastereoisomeric alcohols. Treatment with thionyl chloride gave the corresponding chlorides which were transformed into phosphorane (**328**). This phosphorane, after cyclization, gave the pyrrolo[2,1-*b*]thiazole (**329**) (Scheme 60) ⟨86TL3453⟩.



i=HOC-COOPNB,Toluene 110°C;ii=$SOCl_2$,THF,Lutidine;iii= $P(Ph)_3$,dioxane,2,6-lutidine
iv=Toluene,heat

Scheme 60

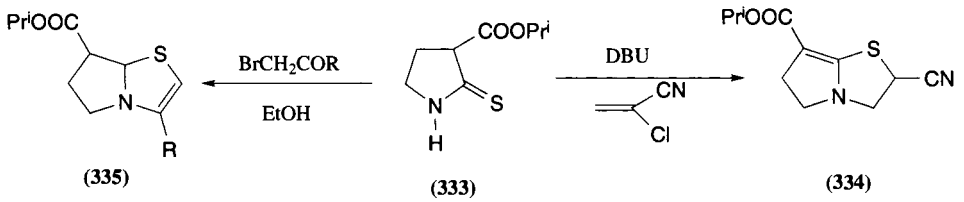
When *N*-acylthiazolines (**330**) are treated with LDA/THF at −78 °C and DMSO was added, the thiazoline (**332**) and compound (**331**) were obtained (Equation (35)) ⟨84H(22)2341⟩.



(35)

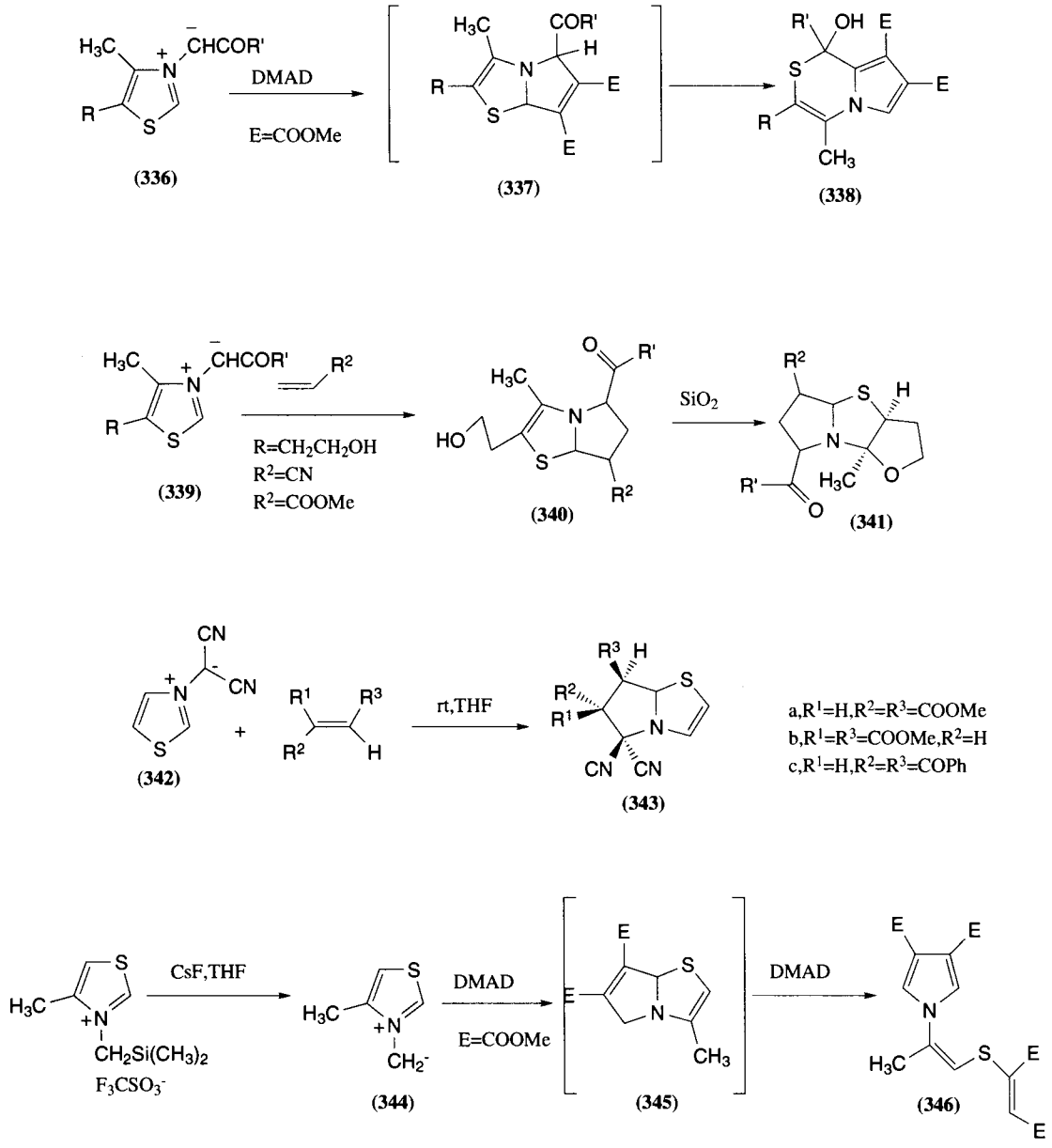
i=LDA,THF,-78°C ;ii=DMSO

(b) C—S bond formation. Reaction of the pyrrolidinethione (**333**) with 1-cyano-1-chloroethene gave the 2,3,4,5-tetrahydropyrrolo[2,1-*b*]thiazole (**334**) ⟨92JAP(K)04261186⟩. When this thione reacted with α-bromoketones, 5,6-dihydropyrrolo[2,1-*b*]thiazoles (**335**) were formed (Scheme 61) ⟨92JAP(K)04145086, 92JAP(K)04208290⟩.



Scheme 61

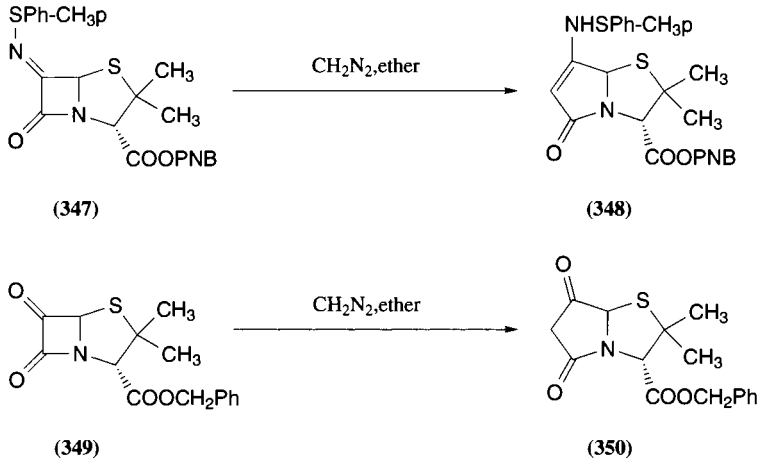
(c) 1,3-Dipolar cycloaddition with azomethine ylides. In CHEC-I ⟨84CHEC-I(6)973⟩ there are some examples of this type of reaction. Condensation of thiazolium *N*-ylides (**336**) with dipolarophiles such as DMAD gave pyrrolo[2,1-*c*]thiazines (**338**) by a rearrangement of the initial pyrrolo[2,1-*b*]thiazole cycloadduct (**337**) ⟨76JOC187⟩. From thiazolium ylides (**339**) and olefinic dipolarophiles 5,6,7,7a-tetrahydropyrrolo[2,1-*b*]thiazoles (**340**) have been obtained isolated as the tricyclic system (**341**) when the crude product is purified by silica chromatography ⟨81TL2727, 85T3537⟩. The cycloaddition of a stable thiazolium *N*-dicyanomethylide (**342**) with acyclic alkenic dipolarophiles such as dimethyl fumarate or maleate, or *trans*-1,2-dibenzoylethylene proceeded in a stereoselective manner to give the corresponding endo (3 + 2) cycloadducts with the structure of tetrahydropyrrolo[2,1-*b*]thiazoles (**343**) ⟨82H(19)2259⟩. By treatment of this ylide, or similar ylides, with *N*-methyl maleimide, tricyclic cycloadducts have been obtained in quantitative yield ⟨83H(20)1907⟩. A complete study of the stereochemistry of this type of reaction was reported by Tsuge *et al.* ⟨85BCJ3137, 85BCJ3320⟩. Cycloaddition of the nonstabilized *N*-thiazolium ylide (**344**) was achieved by stirring a THF solution of silylthiazolium trifluoromethanesulfonate with caesium fluoride at room temperature in the presence of DMAD. The initial cycloadduct (**345**) was not isolated but instead underwent a ready 1,4-elimination to give a substituted pyrrole (**346**) ⟨85CC1108⟩. All these reactions are shown in Scheme 62.



Scheme 62

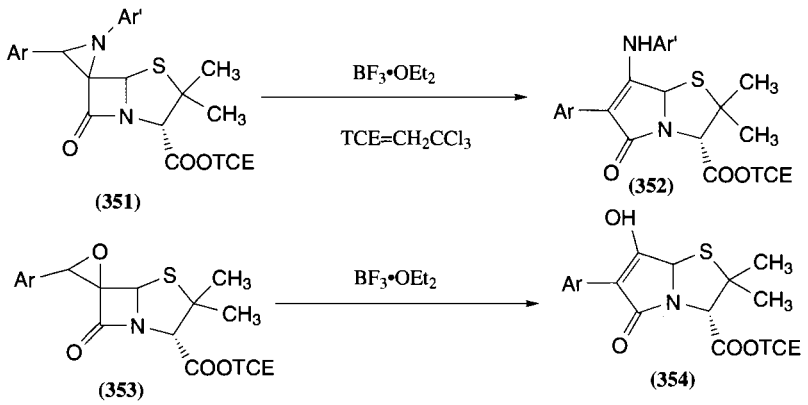
8.02.8.4.4 Ring interconversion

Reaction of a 6-sulfeniminopenicillanic acid ester (**347**) with diazomethane induces a β-lactam ring expansion rearrangement which proceeds via methylene insertion into the C(6)—C(7) bond, giving compound (**348**) ⟨83TL3419⟩. A similar reaction is shown by the reaction of 6-oxopenicillinate (**349**) with diazomethane to give compound (**350**) ⟨83CC250⟩. These reactions are shown in Scheme 63.



Scheme 63

Aziridines (**351**) and oxiranes (**353**) derived from β-lactam compounds react with aromatic amines in a boron trifluoride-diethylether catalyzed reaction to give enaminopyrrolo[2,1-*b*]thiazoles (**352**) and the pyrrolothiazole (**354**) respectively (Scheme 64) ⟨86JCS(P1)2195⟩.



Scheme 64

8.02.9 PYRROLO[1,2-*c*]THIAZOLES

8.02.9.1 Introduction

There are very few studies of this type of compound, and once again there are no systematic results.

Theoretical calculations have not been reported, and molecular experimental data are used to confirm the proposed structures in the synthesis of some compounds, but there are no significant studies ⟨87JMC2109⟩.

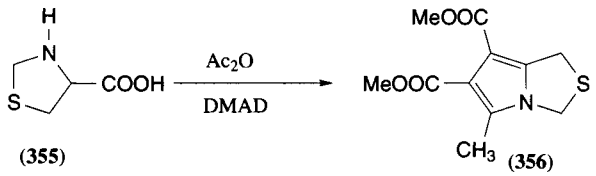
8.02.9.2 Reactivity

The only example of reactivity of this type of compound is provided by the oxidation reactions of a series of 5,6,7-trisubstituted-1,3-dihydropyrrolo[1,2-*c*]thiazoles obtaining sulfoxide and sulfone derivatives ⟨87JMC2109⟩.

8.02.9.3 Synthesis

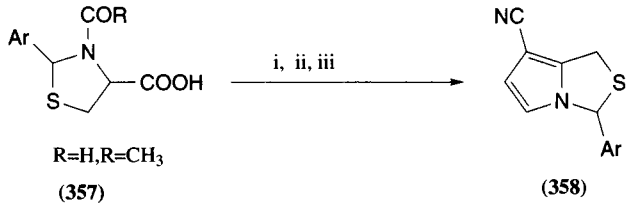
8.02.9.3.1 Cycloaddition to electron-deficient alkenes and alkynes

A synthesis of pyrrolo[1,2-*c*]thiazoles was described in CHEC-I and is based on reaction of thiazoline-4-carboxylic acid (**355**) in boiling acetic anhydride in the presence of DMAD, giving 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles (**356**) (Equation (36)) ⟨80JOC5396⟩.



(36)

A general reaction with *N*-acyl or formyl thiazolidine-4-carboxylic acid (**357**) has been described using different dienophiles such as DMAD ⟨87JMC2109⟩, 1-chlorocyanoacrylate ⟨89FRP2626004⟩, or ethyl 2,3-dichloropropenoate giving compounds (**358**) (Equation (37)) ⟨88EUP252823, 88EUP253711⟩.

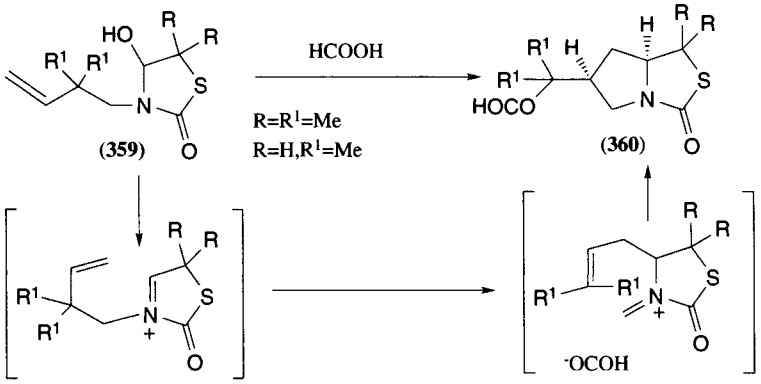


(37)

i=Et_3N,$(ClCH_2)_2$; ii=p-$MeC_6H_4SO_2Cl$; iii=CH_2=C(Cl)CN

8.02.9.3.2 Intramolecular ring closure

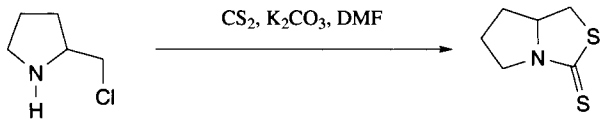
An intramolecular cyclization has been described by ring closure of OH-lactams (**359**) possessing an allyl-substituted alkene function by formic acid, giving only pyrrolizidines (**360**) in high yield via a 2-aza-Cope rearrangement (Scheme 65) ⟨82TL3807, 82TL3811, 85T1999, 85T2861⟩.



Scheme 65

8.02.9.3.3 Nucleophilic-type displacements—C—S bond formation

The chloride derived from proline reacted, with potassium carbonate in DMF solution, with carbon disulfide to give 3-thioxoperhydropyrrolo[1,2-*c*]thiazole (**361**) (Equation (38)) ⟨63JOC981, 91GEP(O)4002366⟩.



(38)

(**361**)

8.02.10 APPLICATIONS

8.02.10.1 Applications as Pharmaceuticals

This section covers information about pharmacological activity and potential pharmaceutical applications described from the mid-1980s to the mid-1990s, for bicyclic 5-5 systems with one ring junction nitrogen atom, and one extra heteroatom.

8.02.10.1.1 Enzyme inhibitors

Any compound that slows down or blocks enzyme catalysis is an enzyme inhibitor. Some pyrrolo[1,2-*c*]imidazoles have been described as α-chymotrypsin ⟨82JPP752⟩ and aldose reductase inhibitors ⟨92JAP(K)04297478⟩.

8.02.10.1.2 Cognition activators

These are drugs which can improve mental functions such as attention and memory. Antiamnesic activity has been reported for dioxoperhydropyrrolo[1,2-*a*]imidazoles ⟨89EUP335483, 93JMC4214⟩ and dioxoperhydro[1,2-*c*]imidazoles ⟨86EUP174136, 92H(33)619, 92JAP(K)04103585⟩. Analogous dioxoperhydropyrrolo[2,1-*b*]thiazoles were synthesized and evaluated for their possible ability to reverse electroconvulsive-shock-induced amnesia, but proved inactive ⟨87JMC498⟩.

8.02.10.1.3 Central nervous system activity

7a-Phenyl-5-oxoperhydropyrrolo[2,1-*b*]oxazole has been evaluated for CNS depressant activity ⟨76JMC436⟩ and some 1-oxoperhydropyrrolo[1,2-*c*]oxazoles have been found useful as antidepressants ⟨84EUP128120⟩.

8.02.10.1.4 Analgesics and antiinflammatories

3-Aroyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-7-carboxylic acid derivatives are useful as analgesics and antiinflammatories ⟨89EUP307034⟩. Pyrrolo[1,2-*a*]imidazoles have been described as 5-lipoxygenase pathway inhibitors ⟨89EUP306300, 90EUP364204⟩, acting as antiinflammatories or platelet aggregation inhibitors and analgesics ⟨82JAP(K)57123183⟩. 1*H*,3*H*-Pyrrolo[1,2-*c*]thiazole derivatives have antiallergic and antiinflammatory activity ⟨84EUP115979⟩.

8.02.10.1.5 Immunomodulators

Selected 2,4,7-substituted 2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles are effective immune enhancers, immuno suppressants, and virucides ⟨85SAP8404299⟩.

8.02.10.1.6 Antineoplastic activity

5-Methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-biscarbamates have been described as active compounds against murine P388 lymphocytic leukemia ⟨87JMC2109⟩. Several 5-aryl-2,3-dihydropyrrolo[2,1-*b*]thiazole-6,7-dimethanol-6,7-bis(isopropylcarbamate)s were tested for growth inhibitory activity with the HL-60 human promyelocytic leukemia cell line. The 5-phenyl, 5-(4-fluorophenyl), and 5-(3,4-dichlorophenyl) have antileukemic activity. These compounds were also cytotoxic to HT-29 human colon carcinoma cells ⟨88JMC1427⟩.

Some pyrrolo[1,2-*a*]imidazoles, described as aromatase inhibitors, are useful in treating gynecomastia and breast cancer or benign prostatic hyperplasia and estrogen-dependent tumors ⟨85EUP165904, 93MI 802-01⟩.

8.02.10.1.7 Antibacterial agents

Some pyrrolo[2,1-*b*]thiazoles have been synthesized as γ-analogues of the penems in hope of discovering a new class of antibiotics related to the β-lactams. Some act as bactericides ⟨88EGP262863⟩ or have antibacterial activity against both gram positive bacteria (*S. aureus*) and gram negative bacteria (*E. coli ESS*) ⟨86TL3461⟩ but others were shown to be inactive ⟨83CC250, 83TL3419, 86TL3453, 89T4537, 89TL4019⟩.

8.02.10.1.8 Cardiovascular activity

The class of 6-aryl-2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles were shown to be α-2 agonists with a central mechanism of action like clonidine ⟨83AX1426, 84MI 802-01, 85MI 802-01⟩, acting as antihypertensive agents. 3,5-Dioxopyrrolo[1,2-*c*]imidazoles act as phosphodiesterase (PDE) inhibitors, with inotropic effects ⟨90USP4937258, 92JMC1267⟩.

1*H*,3*H*-Pyrrolo[1,2-*c*]thiazole-7-carboxamides are platelet-activating factor (PAF) antagonists ⟨84FRP2539417, 88EUP252823, 88EUP253711, 90EUP388309, 91JAP(K)03193785, 91JAP(K)03287587, 93JAP(K)05222057, 93JAP(K)05230069⟩.

8.02.10.1.9 Hepato protectives

Some pyrrolo[2,1-*b*]thiazole derivatives are effective in suppressing denaturation and hepatocytes necrosis and in improving hepatic injury, and they show high safety when administered orally ⟨91EUP410224⟩. Other pyrrolo[2,1-*b*]derivatives orally prevented D-galactosamine-induced hepatitis in rats, as shown by much lowered GPT value ⟨92JAP(K)04145086, 92JAP(K)04208290, 92JAP(K)04261186⟩.

8.02.10.2 Applications as Agrochemicals

8.02.10.2.1 Herbicides

Oxo-derivatives of pyrrolo[1,2-*a*]imidazoles ⟨82EUP65724, 87EUP218048⟩, perhydropyrrolo[1,2-*c*]imidazoles ⟨84EUP104532, 89GEP(O)3809390, 92EUP493323⟩ and pyrrolo[2,1-*b*]thiazoles ⟨88EGP262863⟩ have been described as herbicides, but there is very little data in the literature.

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8.03
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 2 : 0

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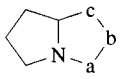
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8.03.1 INTRODUCTION

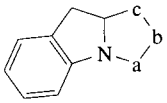
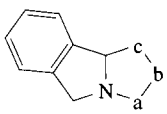
This chapter reviews bicyclic systems containing two fused 5-membered rings with one bridgehead nitrogen and two extra heteroatoms in the same ring. Of the large number of systems of this type which are theoretically possible, only 15 have been reported in the literature and these are shown in Table 1 together with the names of the parent (fully unsaturated) heterocycle and selected references. Some of these systems, for example, (**4**) and (**8**)–(**12**) have received little attention and are reported in only one or two references, whereas others, for example, (**13**) have been studied extensively. In addition, tricyclic systems, derived from (**1**)–(**7**), (**9**), and (**13**) by benz ring fusion onto the pyrrole ring, have been reported. These are named either as indole or isoindole derivatives depending on the position of the benz ring fusion (Table 2).

Table 1 Ring systems (**1**)–(**15**).



Ring system (structure number)	*Heteroatom location*	*Ref.*
Pyrrolo[1,2-*c*][1,2,3]triazole (**1**)	a=b=N	65JA749, 77TL1783, 90JOC571, 92JCR(S)52
Pyrrolo[1,2-*b*][1,2,4]triazole (**2**)	a=c=N	72UKZ1142, 73S414, 75UKZ1053, 84JHC889
Pyrrolo[2,1-*c*][1,2,4]triazole (**3**)	b=c=N	57CB909, 74UKZ245, 82JHC193, 84T2703
Pyrrolo[2,1-*b*][1,3,4]oxadiazole (**4**)	a=N, c=O	81JAP(K)81125390
Pyrrolo[1,2-*d*][1,2,4]oxadiazole (**5**)	b=N, c=O	84MI 803-01, 94T5159
Pyrrolo[1,2-*b*][1,2,4]oxadiazole (**6**)	a=O, c=N	72TL4191, 73AJC2473, 76JA1478
Pyrrolo[2,1-*b*][1,3,4]thiadiazole (**7**)	a=N, c=S	86JCS(P1)1499, 88JCS(P2)821, 89H(29)133
Pyrrolo[1,2-*b*][1,2,5]thiadiazole (**8**)	a=S, b=N	93GEP(O)4141218
Pyrrolo[2,1-*c*][1,2,4]thiadiazole (**9**)	b=S, c=N	86GEP(O)3528583, 92JCS(P1)181
Pyrrolo[1,2-*c*][1,3,2]diazaphosphole (**10**)	a=P, b=N	87JOC5320
Pyrrolo[1,2-*c*][1,3,2]diazasilole (**11**)	a=Si, b=N	74CB2804
Pyrrolo[1,2-*b*][1,4,2]dioxazole (**12**)	a=c=O	88T5209
Pyrrolo[1,2-*c*][1,3,2]oxazaborole (**13**)	a=B, b=O	80SR1479, 85JOM(294)1, 88JOC2861
Pyrrolo[1,2-*c*][1,3,2]oxazaphosphole (**14**)	a=P, b=O	84CB2328
Pyrrolo[1,2-*c*][1,2,3]oxathiazole (**15**)	a=S, b=O	90TA877, 90TA885, 92TL5895

Table 2 Benz fused ring systems (**16**)–(**26**).

Ring system (structure number)	*Heteroatom location*	*Ref.*
(a) *Indoles*		
[1,2,3]Triazolo[1,5-*a*]indole (**16**)	a=b=N	76CR(C)967
[1,2,4]Triazolo[4,3-*a*]indole (**17**)	b=c=N	84T2703, 85AP(318)556, 94T5159
[1,3,4]Oxadiazolo[3,2-*a*]indole (**18**)	a=N, c=O	83IJC(B)477
[1,2,4]Oxadiazolo[4,5-*a*]indole (**19**)	b=N, c=O	84MI 801-01, 94T5159
[1,2,4]Oxadiazolo[2,3-*a*]indole (**20**)	a=O, c=N	67CB3520
[1,3,2]Oxazaborolo[3,4-*a*]indole (**21**)	a=B, b=O	88TL4453, 92TA347
(b) *Isoindoles*		
[1,2,3]Triazolo[5,1-*a*]isoindole (**22**)	a=b=N	77TL1783, 90JOC571
[1,2,4]Triazolo[5,1-*a*]isoindole (**23**)	a=c=N	85UKZ94, 87IJC(B)1130
[1,3,4]Oxadiazolo[2,3-*a*]isoindole (**24**)	a=N, c=O	87IJC(B)1130
[1,3,4]Thiadiazolo[2,3-*a*]isoindole (**25**)	a=N, c=S	85LA1679
[1,2,4]Thiadiazolo[3,4-*a*]isoindole (**26**)	b=S, c=N	92JCS(P1)181

No reviews have been published dealing specifically with these ring systems, although some systems have been covered by more general reviews. A review of (5,5)-fused ring systems containing a bridgehead nitrogen covered the literature up to the end of 1972 ⟨77HC(30)1⟩ but the only (2:0) system mentioned was the pyrrolo[1,2-*b*][1,2,4]triazole (**2**). The chemistry of aromatic azapentalenes has been reviewed and included work on the three pyrrolotriazoles (**1**)–(**3**) prior to 1976 ⟨78AHC(22)183⟩. Only five of the ring systems in Table 1, i.e., (**1**)–(**4**), (**6**) were reported in the chapter on classical heteropentalenes in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CH(6)973⟩, a reflection of the relative novelty of the majority of the compounds discussed in this chapter. This review will concentrate on the literature which has appeared since the publication of the above mentioned reviews but also includes important earlier work where appropriate.

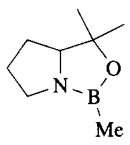
A variety of methods have been used in the primary literature to number (5,5) bicyclic heterocycles. For consistency, the authors have adopted the system used in the *Chemical Abstracts Ring Systems Handbook* (1993 Edition).

8.03.2 THEORETICAL METHODS

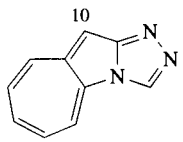
Little has been reported on the application of theoretical methods to ring systems (**1**)–(**26**), although work on oxazaborolidine (**27**) and pyrrolotriazoles (**28**)–(**30**) is worthy of mention.

For the oxazaborolidine (**27**), *ab initio* molecular orbital calculations ⟨94JA8516⟩ and semiempirical methods ⟨93JOC799, 94TA903⟩ have been used to investigate possible transition-state assemblies that correspond to catalyst–borane complexes in asymmetric reduction pathways. Various key intermediates have been proposed depending on the level of theory adopted.

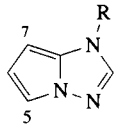
Simple Hückel molecular orbital (HMO) calculations on the pyrrolo[2,1-*c*][1,2,4]triazole (**28**) suggest that electrophilic attack would occur most readily at C-10, and this prediction was borne out by observations that acid-catalyzed deuteration and bromination by NBS in the dark both occur at this position ⟨85JCR(S)363⟩. Various reactivity indices have been calculated for a number of pyrrolo[1,2-*b*][1,2,4]triazoles (**29**) and pyrrolo[2,1-*c*][1,2,4]triazoles (**30**) using the MO LCAO method within the semiempirical SCF approximation. These indicate that the 5-position is most susceptible to electrophilic attack, followed by the 7-position ⟨74CHE230⟩.



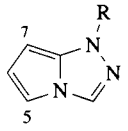
(27)



(28)



(29)



(30)

8.03.3 EXPERIMENTAL STRUCTURAL METHODS

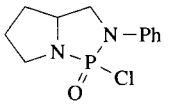
NMR spectroscopy has found widespread use in the structural investigation of a number of the systems discussed in this chapter. The technique has been particularly useful in determining the stereochemistry of ring fusion, assigning absolute configurations and measuring diastereomeric excesses. Other methods, for example, IR, UV, MS, and x-ray spectroscopy, have been of limited use in providing structural information on these systems and are not considered worthy of mention here.

8.03.3.1 Proton NMR Spectroscopy

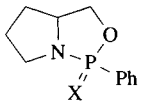
The diastereomers of diazaphospholidine (**31**) and the oxazaphospholidines (**32**) and (**33**) were assumed to exist in the energetically favorable *cis* fused configuration (see Section 8.03.4) and were assigned absolute configurations around phosphorus by comparison of the chemical shifts of the C-6 protons ⟨81TL477, 87JOC5320⟩. In phosphorus-containing heterocycles, protons in a 1,3-*cis* relationship to a P=X group are deshielded ⟨76OMR(8)399, 77JOC1022⟩.

Evidence for predominantly *cis* fusion of the two 5-membered rings in pyrrolothiadiazole (**34**) was obtained by both ^{1}H and ^{13}C NMR spectroscopy ⟨88JCS(P2)821⟩ and the configurations of

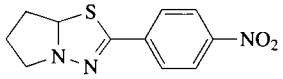
sulfamidite (**35**) and sulfamidate (**36**) have also been determined ⟨90TA885⟩. The *cis* fused isomer of (**36**) is believed to adopt a twist-envelope like configuration with sulfur at the apex of the flap (**37**) ⟨75BCJ1878⟩.



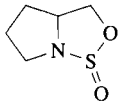
(**31**)



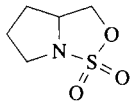
(**32**) X = O
(**33**) X = S



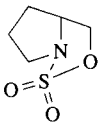
(**34**)



(**35**)



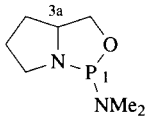
(**36**)



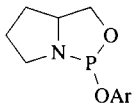
(**37**)

8.03.3.2 Carbon-13 NMR Spectroscopy

The oxazaphospholidine (**38**), prepared from (*S*)-prolinol and tris(dimethylamino)phosphine, was shown to be a single diastereomer which was assigned the (1*R*,3a*S*) configuration by ^{13}C NMR studies ⟨87NJC573⟩. The assignment was based on the observation that the magnitude of $^{2}J_{PC}$ coupling constants in cyclic phosphines is strongly dependent on the dihedral angle between the lone pair on phosphorus and the carbon atom in the β-position. For example, the configurations of the diastereomers of (**39**) can be assigned since the coupling is quite different when C-6 and the phosphorus lone pair are in a synperiplanar relationship ($^{2}J_{PC} = 40$ Hz) from that when they are anticlinal ($^{2}J_{PC} = 0$ Hz) ⟨88OM59⟩.



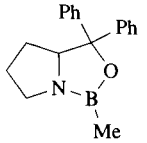
(**38**)



(**39**)

8.03.3.3 Boron-11 NMR Spectroscopy

The oxazaborolidine (**40**) was originally believed to exist as a mixture with a dimeric species, since the ^{11}B NMR spectrum showed two distinct signals ⟨89TL6275⟩. The extra signal was subsequently ascribed to the presence of an impurity in the original sample and the spectrum of pure (**40**) was shown to consist of a single signal at 34.3 ppm ⟨91JOC751⟩.

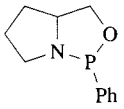


(**40**)

8.03.3.4 Phosphorus-31 NMR Spectroscopy

The enantiomeric purities of compounds related to (**31**), where the chlorine atom has been replaced by an alkylamino group, have been determined by ^{31}P NMR studies using chiral solvating agents ⟨87JOC5320⟩.

Phosphorus-31 NMR spectroscopy has been used to follow the stereochemical course of the reaction of bis(dimethylamino)phenylphosphine with (*S*)-prolinol to give oxazaphospholidine (**41**) (see Section 8.03.9.2). The (1*S*,3a*S*) stereoisomer was formed first and subsequently converted completely into the thermodynamic (1*R*,3a*S*) product ⟨89CC805⟩.



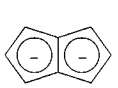
(**41**)

8.03.4 THERMODYNAMIC ASPECTS

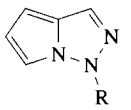
Very little has been reported on the thermodynamic aspects of ring systems (**1**)–(**26**). Melting points, boiling points, and chromatographic behavior have been reported for many compounds, but there appears to have been no attempt to correlate these properties with intermolecular forces. Information on the basicity of these systems is also very scarce.

However, the conformations of (5,5) systems with a bridgehead nitrogen have been investigated extensively. These systems are reported to exist predominantly in a low-energy *cis* fused configuration ⟨71CRV109, 81TL477⟩ and on the basis of a comparison of strain energies of bicyclo[3,3,0]octanes, the *cis* fused system is estimated to be 27 kJ mol^{-1} less strained than the *trans* ⟨70JA3109⟩.

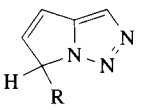
The question of aromaticity in bicyclic (5,5) systems has been discussed in a previous review ⟨78AHC(22)183⟩, which readers should consult for a general treatment of the subject. As regards the ring systems covered in this chapter, little has been reported concerning their aromaticity. Although many of these ring systems can theoretically form 10π-electron aromatic structures isoelectronic with the pentalene dianion (**42**), very few such compounds have been prepared. In fact, the only known 10π systems are all derivatives of 1*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**29**) and 1*H*-pyrrolo[2,1-*c*][1,2,4]triazole (**30**). The 1*H*-pyrrolo[1,2-*c*][1,2,3]triazoles (**43**), which have two adjacent heteroatoms each contributing a pair of electrons to the π system, are reported to be energetically unfavorable compared with the isomeric 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles (**44**), which are 8π systems ⟨90JOC571⟩. The only reported 1*H*-pyrrolo[1,2-*c*][1,2,3]triazole is the 1-carboethoxy derivative (**43**; R = CO_2Et), which does possess some aromatic character as shown by its NMR spectrum. In addition, the 14π tricyclic system (**28**) has also been reported ⟨85JCR(S)363⟩.



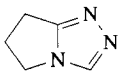
(**42**)



(**43**)



(**44**)



(**45**)

The majority of the compounds under discussion here have pyrrolidine as one of the 5-membered rings. The other ring, containing three heteroatoms, is sometimes a 6π aromatic system as in the tetrahydropyrrolotriazole (**45**), for example, but most of the bicyclic systems covered in this chapter, for example, (**27**), (**31**)–(**33**) have no aromatic character.

8.03.5 REACTIVITY OF FULLY CONJUGATED RINGS

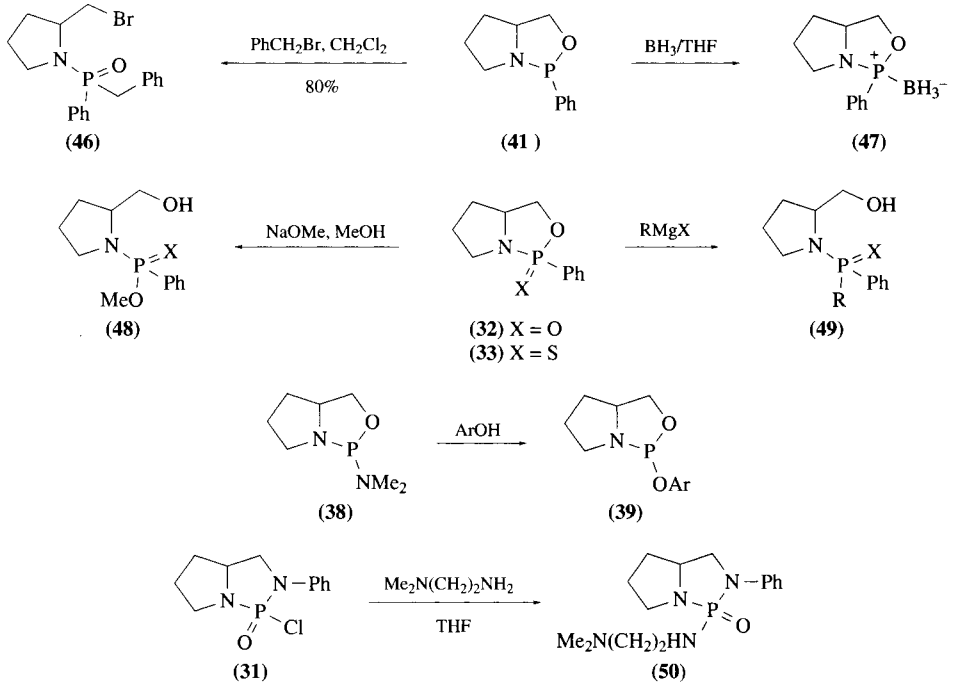
As indicated in the previous section, there are comparatively few known examples of compounds containing fully conjugated rings and very few reactions at a conjugated ring have been reported for any of these compounds. The pyrrolotriazole (**28**) undergoes electrophilic substitution reactions at C-10, as predicted by simple HMO calculations (Section 8.03.2) ⟨85JCR(S)363⟩.

8.03.6 REACTIVITY OF NONCONJUGATED RINGS

The reactions of nonconjugated rings can be divided into those where the bicyclic system is opened up and those where it remains intact. For the purpose of this review, these reactions have been classified according to the atom at which the initial attack takes place.

8.03.6.1 Reactions at Phosphorus

The oxazaphospholidine (**41**) undergoes a Michaelis–Arbuzov reaction to give the phosphine oxide (**46**). This reaction was completely stereospecific with retention of configuration ⟨89CC805⟩. Reaction of (**41**) with borane-THF gave a stable complex (**47**) which has been used as a catalyst in enantioselective borane reductions of ketones ⟨92CC287⟩. Base-catalyzed methanolysis of oxazaphospholidine oxides and sulfides (**32**) and (**33**) gave the corresponding ring-opened products (**48**) resulting from P—O bond fission. This reaction proceeds with inversion of configuration at phosphorus ⟨81TL477⟩. Similarly, (**32**) and (**33**) react with Grignard reagents to give (**49**;R = alkyl, aryl) in almost quantitative yield ⟨81TL571⟩ (Scheme 1).



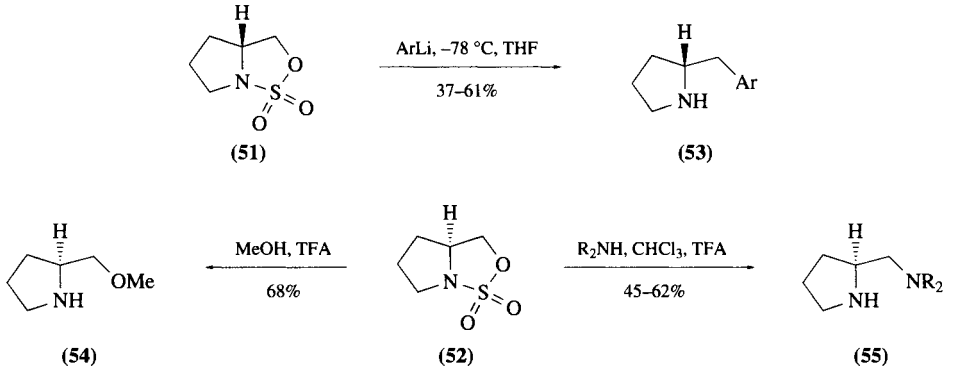
Scheme 1

The dimethylamino group of (**38**) can be displaced by phenols to give mixtures of diastereomeric products (**39**). By controlling the reaction conditions, mixtures containing predominantly the kinetic or the thermodynamic diastereomer can be obtained ⟨88OM59⟩. The chlorodiazaphosphole oxide (**31**) on treatment with *N,N*-dimethylethylenediamine gave the phosphoramide (**50**) in good yield. Again, this reaction occurs with inversion of configuration at phosphorus (Scheme 1) ⟨87JOC5320⟩.

8.03.6.2 Reactions at Carbon

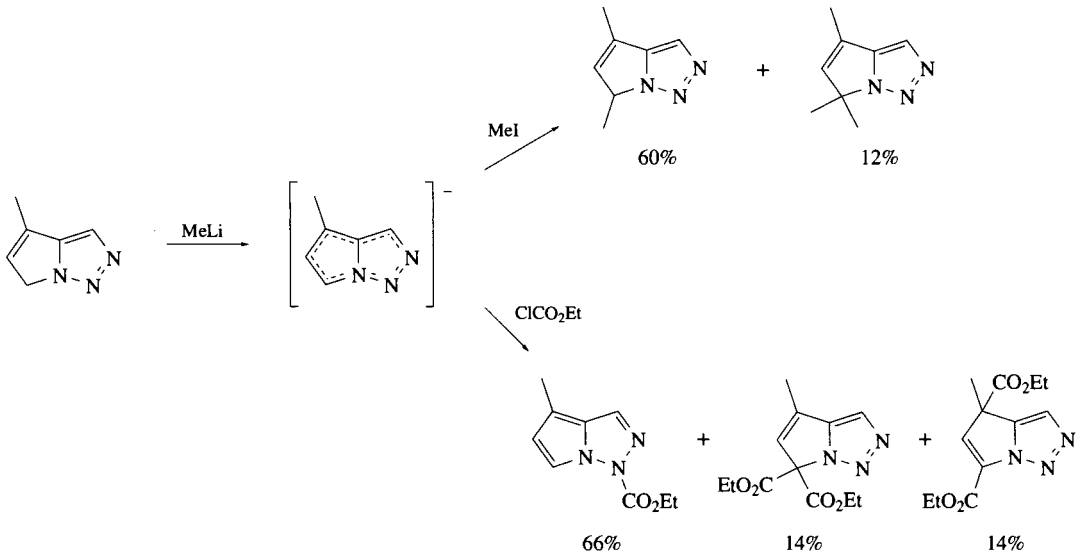
The chemistry of the enantiomeric sulfamidates (**51**) and (**52**) provides a useful route to chiral 2-alkylpyrrolidines (**53**)–(**55**). They react with aryllithiums ⟨92TL5895⟩, amines, and alcohols ⟨90TA877⟩ to give ring-opened products by nucleophilic attack at C-3 (Scheme 2).

Aromatic anions were formed when 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles were treated with methyl



Scheme 2

lithium at −20 °C ⟨90JOC571⟩. Alkylation of these anions with methyl iodide occurred exclusively at the 6-position, whereas acylation with ethyl chloroformate was less regioselective and took place at the 1-, 4-, and 6-positions (Scheme 3).



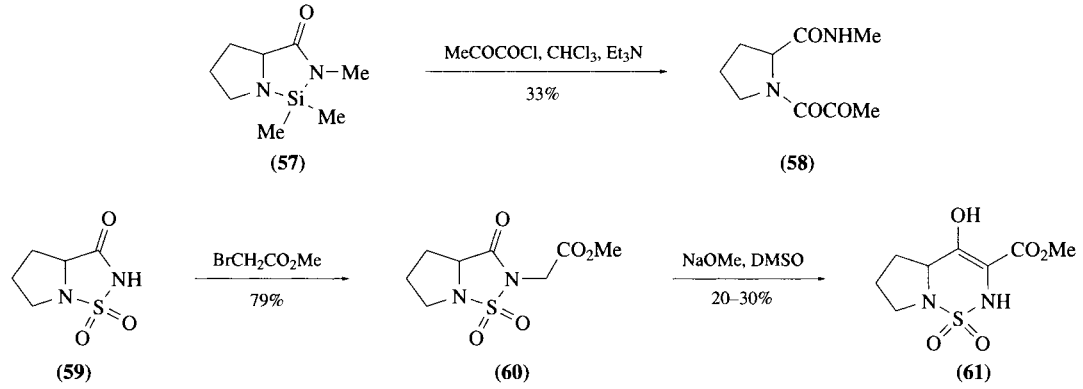
Scheme 3

8.03.6.3 Reaction at Sulfur

The sulfamidite (**56**) was oxidized to the corresponding sulfamidate (**52**) by treatment with ruthenium oxide and sodium periodate ⟨90TA885⟩ (see Scheme 8).

8.03.6.4 Reactions at Nitrogen

The pyrrolodiazasilole (**57**) reacted with pyruvoyl chloride to give (**58**) by acylation of the bridgehead nitrogen atom ⟨74CB2804⟩, whereas the pyrrolothiadiazolidine (**59**) alkylated on the nitrogen in the 2-position to give (**60**), which rearranged to the ring enlarged compound (**61**) on treatment with base (Scheme 4) ⟨93GEP(O)4141218⟩.

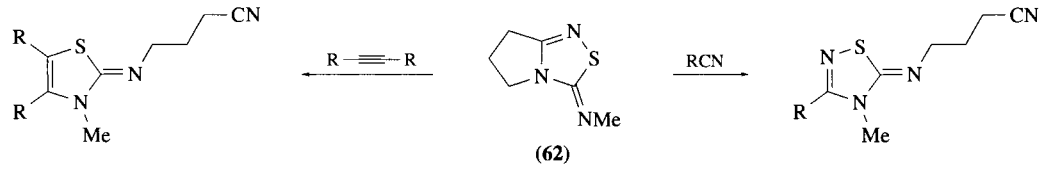


(57) (58) (59) (60) (61)

Scheme 4

8.03.6.5 Miscellaneous Reactions

The pyrrolothiadiazole (**62**) reacted with electrophilic alkynes or nitriles to give monocyclic products by cycloaddition with simultaneous ring opening (Scheme 5) ⟨92T7505⟩.

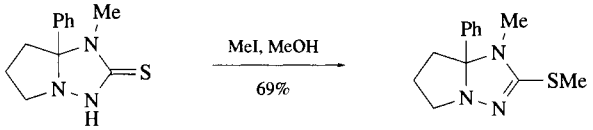


(62)

Scheme 5

8.03.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

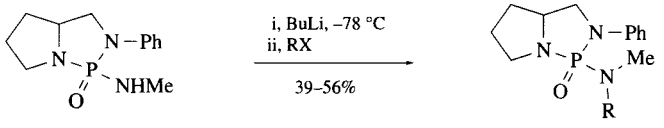
Very few reactions of substituents attached to bicyclic systems (**1**)–(**26**) have been reported. The only examples of reactions of a substituent attached to a ring carbon atom appear to be the methylation of (**63**), which occurs on sulfur yielding (**64**) (Equation (1)) ⟨84JHC889⟩, and simple functionalizations of hydroxymethyl groups attached to the pyrrolo[1,2-*c*][1,2,3]triazole ring system ⟨90S156⟩.



(63) (64) (1)

8.03.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

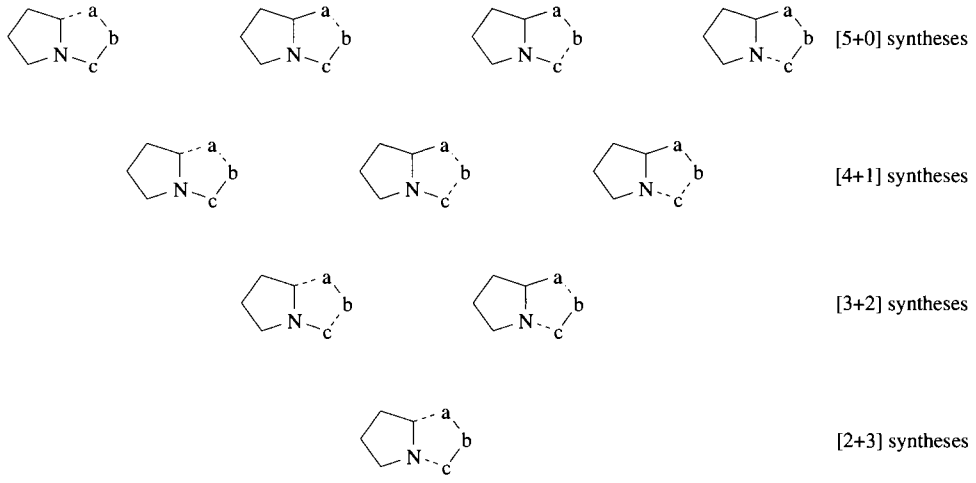
The diazaphosphole (**65**) has been alkylated on the exocyclic nitrogen ⟨87JOC5320⟩ to give (**66**) (Equation (2)), and this appears to be the only report of a reaction of a substituent attached to a ring heteroatom.



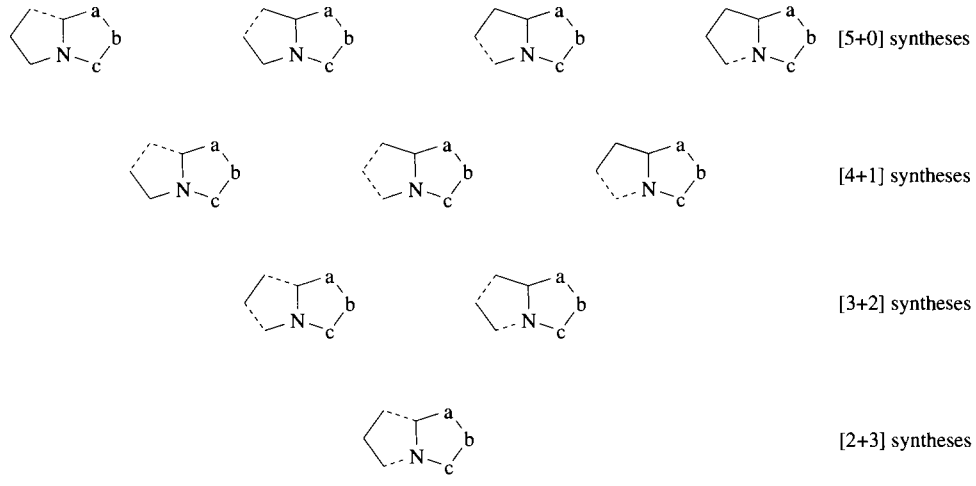
(65) (66) (2)

8.03.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

The majority of syntheses of pyrrolo-fused bicyclic (5,5) systems start from pyrrole derivatives and involve the formation of the ring containing the three heteroatoms. These syntheses can conveniently be classified according to the number of atoms in the pyrrole derivative and the number of additional atoms required to form the second ring. This classification is summarized in Scheme 6, which shows all the possible ring closure routes (represented by dotted lines), some of which have as yet no examples reported in the literature. A second, less common type of synthetic route involves the formation of the pyrrole ring. Scheme 7 shows all the possibilities but, once again, some of these have not been reported. In addition, there are a number of syntheses where both rings are formed simultaneously.



Scheme 6

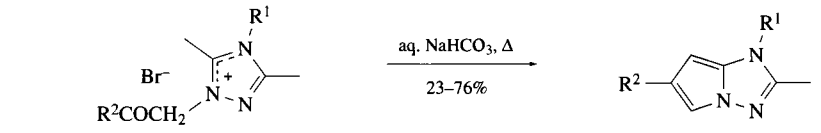


Scheme 7

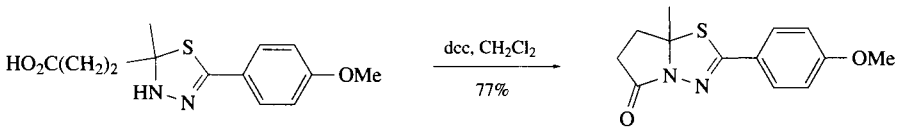
8.03.9.1 [5 + 0] Syntheses

Syntheses in this category involve intramolecular cyclizations of suitable precursors, usually with elimination of water or a hydrogen halide. These precursors are often not isolated as they are

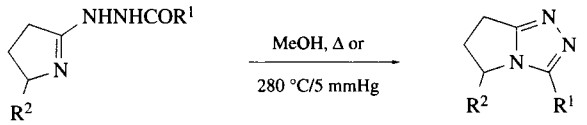
prepared *in situ* and cyclize spontaneously under the reaction conditions. Examples of the formation of the pyrrole ring (Equations (3) and (4)) and the ring containing three heteroatoms (Equations (5) and (6)) are both known.



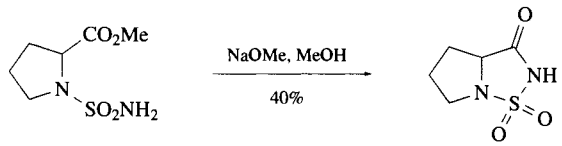
(3)



(4)



(5)

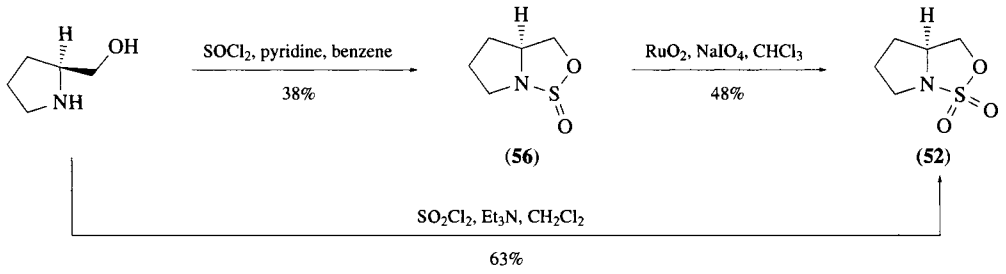


(6)

Suitably substituted triazolium salts cyclize on heating with dilute aqueous $NaHCO_3$ solution to give pyrrolo[1,2-*b*][1,2,4]triazoles (Equation (3)) ⟨73S414, 75UKZ1053⟩. Other syntheses in this category include cyclizations of substituted thiadiazoles ⟨86JCS(P1)1499⟩, amidrazone derivatives ⟨57CB909, 84T2703⟩, and *N*-sulfamoylpyrrolidine-2-carboxylates ⟨93GEP(O)4141218⟩ to give pyrrolothiadiazoles, pyrrolotriazoles, and pyrrolothiadiazolidinones, respectively (Equations (4)–(6)).

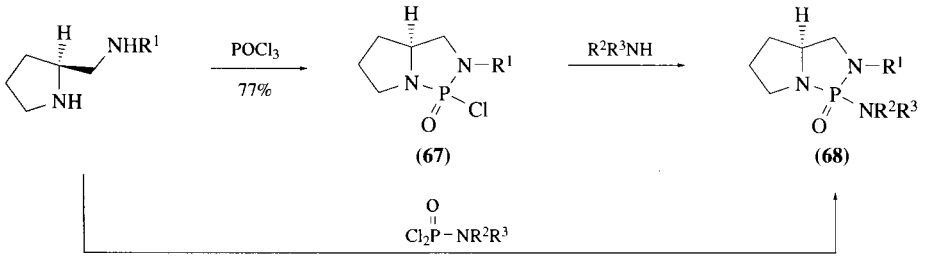
8.03.9.2 [4 + 1] Syntheses

The most common syntheses in this category consist of cyclizations of prolinol and its derivatives. A selection of syntheses of this type are shown in Schemes 8–10.

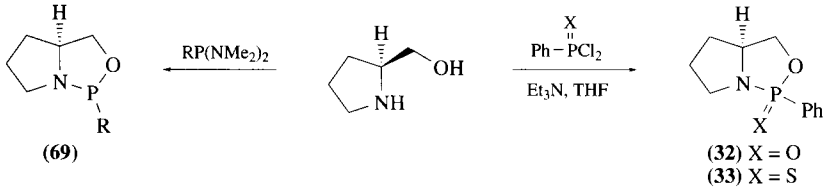


Scheme 8

The sulfamidate (**52**) has been prepared from (*S*)-prolinol either directly by treatment with sulfuryl chloride ⟨90TA877⟩ or in two lower-yielding steps by treatment with thionyl chloride followed by oxidation of the sulfamidite (**56**) (Scheme 8) ⟨90TA885⟩. Cyclizations using a phosphorus compound as the source of the single atom fragment in [4 + 1] annulations have received a great deal of attention. Phosphoramides (**68**) may be prepared either directly from aminomethylpyrrolidines or indirectly via an intermediate chloro compound (**67**) (Scheme 9) ⟨87JOC5320⟩. A series of oxazaphospholidines (**69**) have been prepared from the reaction between dimethylaminophosphines and (*S*)-prolinol (Scheme 10) ⟨84CB2328, 88OM59⟩. The products were shown to be diastereomerically pure and were assigned the (1*R*,3a*S*) configuration. The related P-oxides (**32**) and sulfides (**33**) were



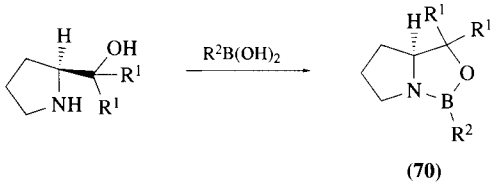
Scheme 9



Scheme 10

obtained as diastereomeric mixtures by treating (*S*)-prolinol with phenylphosphonic or phenylthiophosphonic dichloride, respectively ⟨81TL477⟩. The individual diastereomers were separated by flash column chromatography. Reactions of alkyl or aryl phosphorus dichlorides with (*S*)-prolinol gave mixtures of oxazaphospholidines (**69**) and the corresponding P-oxides. The expected oxazaphospholidine (**69**) could only be isolated in the case of the reaction with *t*-butylphosphorus dichloride ⟨84CB2328⟩.

Oxazaborolidines (**70**) have been used extensively in organic synthesis and their preparation from substituted prolinol derivatives and alkyl boronic acids is well documented (Equation (7)) ⟨88JOC2861, 91JOC751⟩. Earlier workers prepared related compounds starting from bis(dimethylamino) phenylborane ⟨85JOM(294)1⟩ but the boronic acid route has now superseded this.



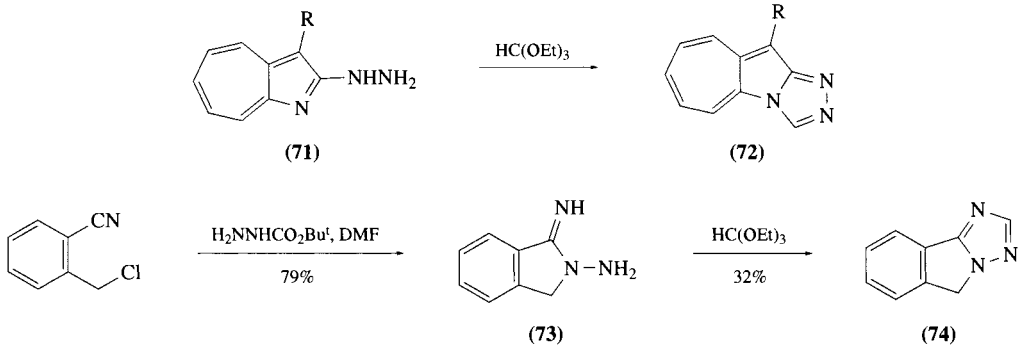
(7)

Cyclohepta[*b*]pyrrol-2-ylhydrazines (**71**) react with triethylorthoformate to give triazoles (**72**), and the 3-oxo, 3-thioxo, and 3-amino derivatives were similarly prepared by treating (**71**) with carbonyldiimidazole, carbon disulfide, or cyanogen bromide, respectively ⟨85JCR(S)363⟩. A similar cyclization of the cyclic amidrazone (**73**) with triethylorthoformate gave the triazoloisoindole (**74**) (Scheme 11) ⟨85UKZ94⟩.

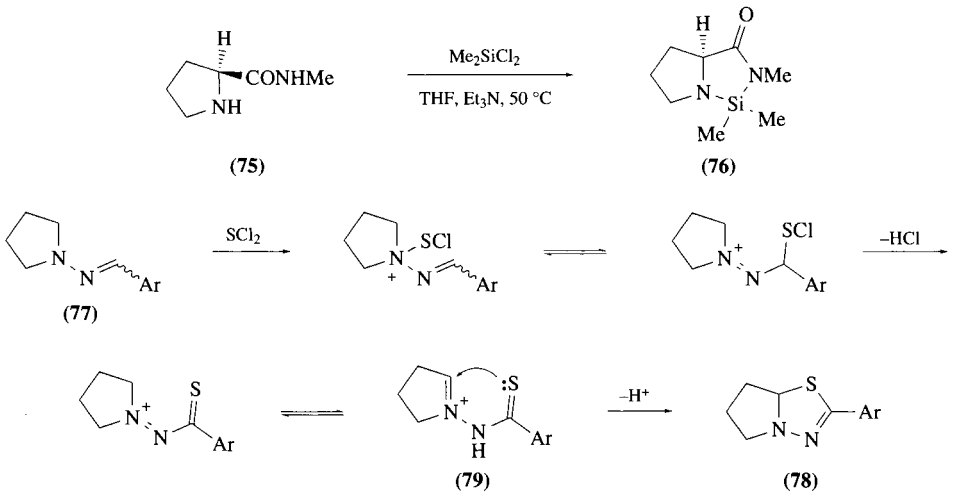
The diazasilole (**76**) was obtained by treating the pyrrolidinecarboxamide (**75**) with dichlorodimethylsilane ⟨74CB2804⟩. Aryl *N*,*N*-tetramethylenehydrazones (**77**) react with sulfur dichloride to give novel pyrrolo[2,1-*b*][1,3,4]thiadiazoles (**78**). The overall reaction can be considered as a [4 + 1] cyclization, although the final step in the proposed mechanism involves a [5 + 0] cyclization of the intermediate (**79**) (Scheme 12) ⟨88JCS(P2)821⟩.

8.03.9.3 [3 + 2] Syntheses

Synthesis of (5,5) systems via a (3 + 2) approach is essentially based on 1,3-dipolar cycloaddition chemistry. Cyclic nitrones (e.g., (**80**)) react with phenyl isocyanates ⟨74H(2)297, 76JA1478⟩ and phenyl isothiocyanates ⟨72TL4191, 73AJC2473⟩ to form oxadiazolidines (**81**) by addition of the dipole exclusively to the C=N bond. However, with substituted phenyl isothiocyanates, dipolar cycloaddition



Scheme 11



Scheme 12

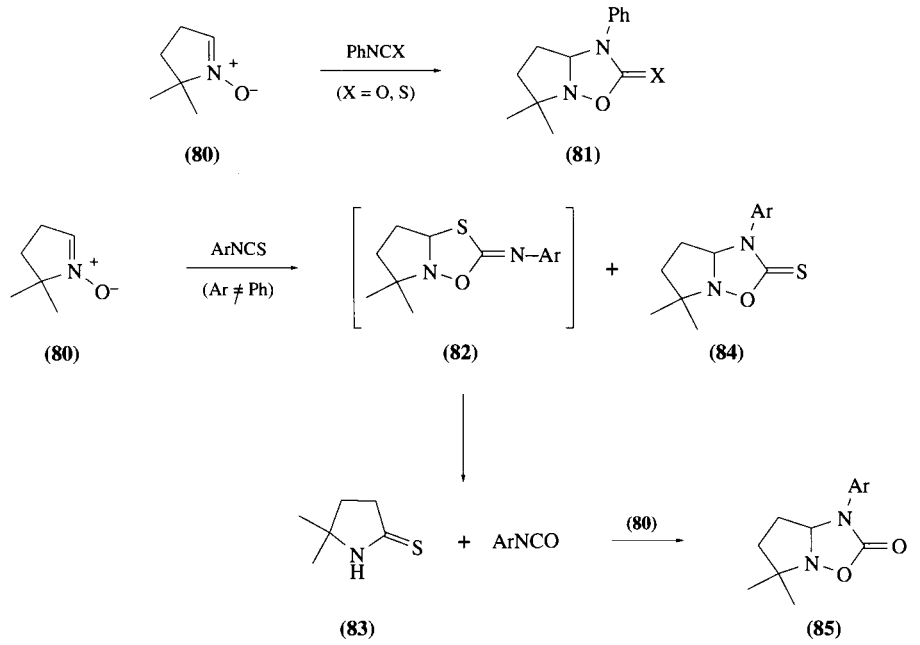
can take place at both of the heterocumulene double bonds. The products (**82**), derived from addition to the C=S bond, are unstable and rearrange to thiolactams (**83**) and aryl isocyanates, which can react with the starting nitrone to give oxadiazolidines (**85**). Consequently, mixtures of products (**83**)–(**85**) are obtained, the relative proportions of which are dependent on the nature of the aryl group and the substituents on the nitrone (Scheme 13).

8.03.9.4 [2 + 3] Syntheses

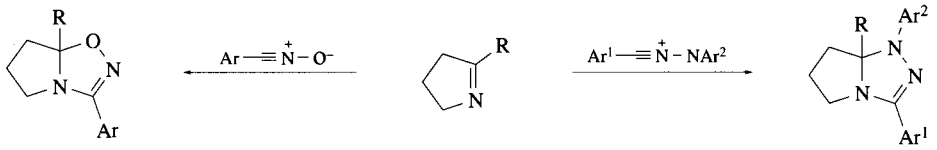
Cyclic imines react with nitrile oxides ⟨84MI 803-01⟩ and nitrilimines ⟨85AP(318)556⟩ to give oxadiazolines and triazolines, respectively (Scheme 14). Analogous reactions have also been reported for cyclic imidates ⟨94T5159⟩.

8.03.9.5 Simultaneous Formation of Both Rings

Reactions involving the formation of both rings simultaneously have been applied mainly to the synthesis of pyrrolotriazoles. Early work showed that intramolecular 1,3-dipolar cycloaddition of azidoalkenes occurs readily to give the isomeric pyrrolotriazolines in quantitative yield (Equation (8)) ⟨65JA749⟩. A similar more recent example is the cyclization of ω-azidobutylidenemalonate ⟨92JCR(S)52⟩. Similar cycloadditions of azido alkynes ⟨90S156⟩, azido enynes (Equation (9))

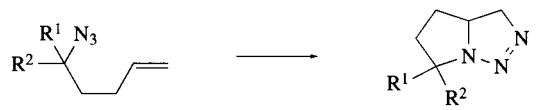


Scheme 13

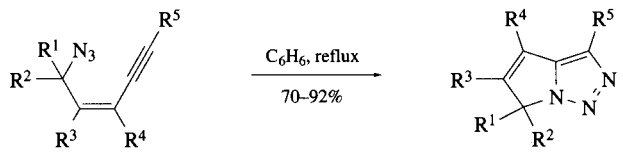


Scheme 14

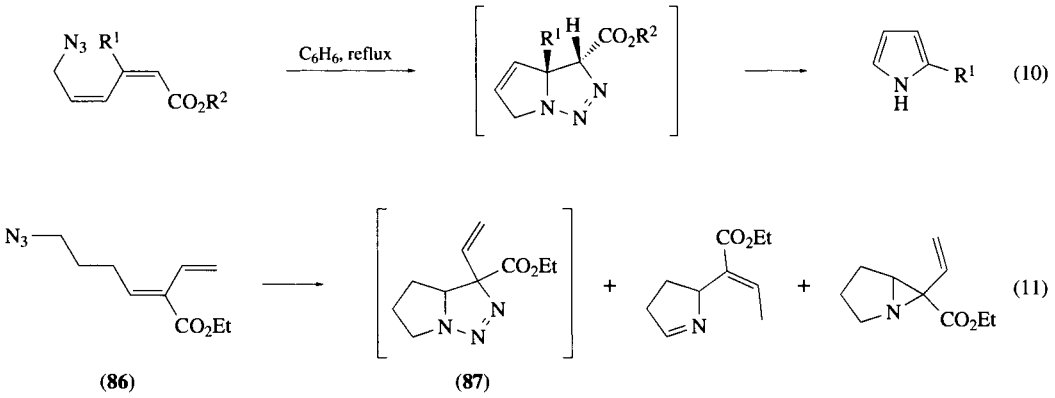
⟨90JOC571⟩, and azido dienoate esters (Equation (10)) ⟨82JOC725⟩ gave the corresponding triazoles or triazolines, respectively. In the latter case, the products are unstable under the reaction conditions, decomposing to 2-substituted pyrroles. Dienoates with "*cis–cis*" geometry were found to undergo cycloaddition at least 15 times more rapidly than the corresponding "*cis–trans*" dienes. The proposed rationalization for this observation was that the transition state in the cycloaddition of the "*cis–cis*" diene is stabilized by secondary orbital interactions between the azido and carbonyl groups. A triazoline (**87**) has also been reported as one of several products formed from the intramolecular cycloaddition of (**86**) (Equation (11)) ⟨85TL3523, 85TL3527⟩. This triazoline is also too unstable to be isolated and evidence for its formation was obtained by ^{1}H NMR spectroscopy. Further unstable triazolines have been prepared from azido dienes by similar methods ⟨90JOC5719⟩.



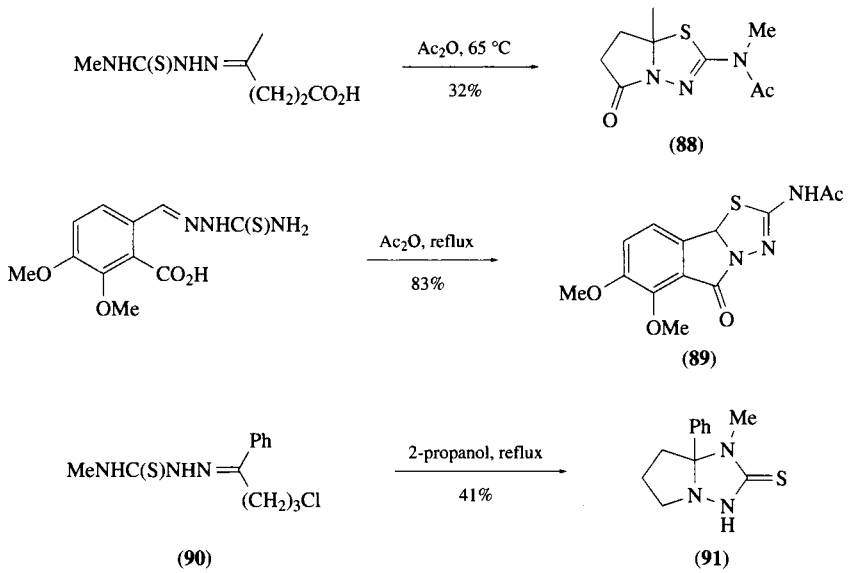
(8)



(9)



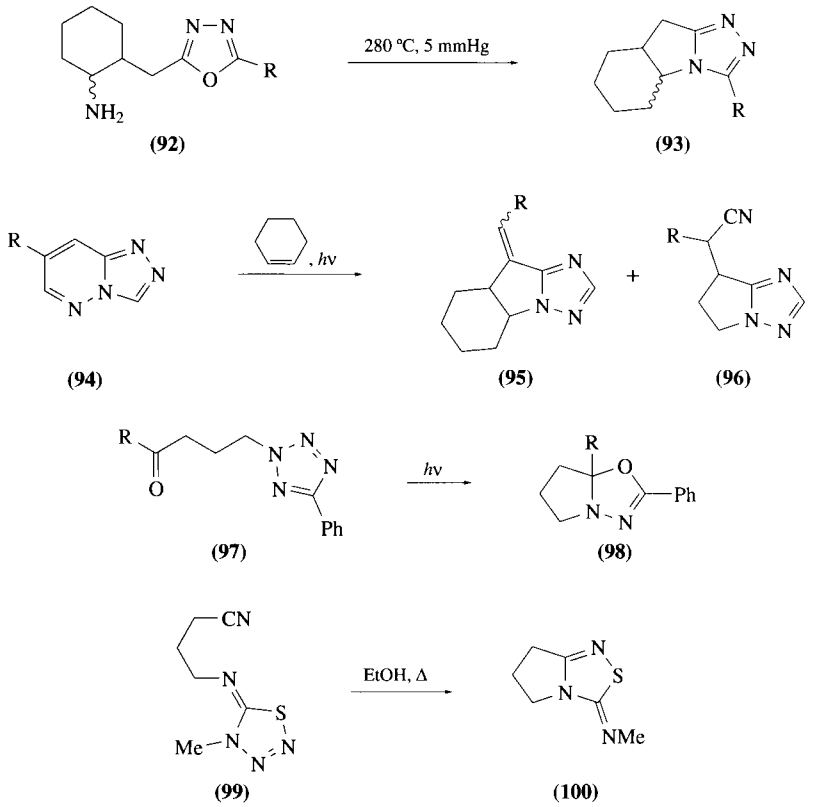
A number of other ring systems have been prepared by intramolecular bis-annulation procedures (Scheme 15). The pyrrolothiadiazole (**88**) ⟨89H(29)133⟩ and the benz fused analogue (**89**) ⟨85LA1679⟩ were prepared by treatment of thiosemicarbazone derivatives with acetic anhydride. Thiosemicarbazone (**90**) similarly underwent a double cyclization to give the pyrrolotriazoline (**91**) ⟨84JHC889⟩.



Scheme 15

8.03.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Few syntheses of this type have been reported, but representative examples are given in Scheme 16. Triazoloindoles (**93**) were obtained by thermolytic cyclodehydration of aminoalkyl oxadiazoles (**92**) ⟨84T2703⟩. A series of pyrrolotriazoles have been prepared by photochemical addition of alkenes to triazolo[4,3-*b*]pyridazines (**94**) ⟨73JHC801, 77JHC411⟩. For example, cyclohexene reacts to give a mixture of products (**95**) and (**96**). Photolysis of tetrazoles (**97**) gave pyrrolo[2,1-*b*][1,3,4]oxadiazoles (**98**), the only reported synthesis of this novel ring system ⟨81JAP(K)81125390⟩. Thermolysis of the thiatriazolinimine (**99**) gave the pyrrolothiadiazole (**100**) via intramolecular cyclization with concurrent loss of nitrogen ⟨92JCS(P1)181⟩.



Scheme 16

8.03.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

Of the ring systems under discussion in this chapter, only the pyrrolotriazoles (**2**) and (**3**) and the pyrrolothiadiazoles (**7**) have been prepared by more than one route. For example, pyrrolo[1,2-*b*][1,2,4]triazoles (**2**) have been prepared: (i) by cyclization of substituted triazolium salts (Equation (1)), a [5 + 0] synthesis; (ii) from cyclic amidrazone (**73**, Scheme 11), a [4 + 1] synthesis; (iii) from thiosemicarbazides (**90**, Scheme 15), a synthesis involving simultaneous formation of both rings; and (iv) from triazolo[4,3-*b*]pyridazines (**94**, Scheme 16) by photochemical addition of an alkene. However, as each of these routes yields different groups of products and no individual compound has been prepared by more than one of these routes, it is not possible to compare them in a meaningful manner. The same is true for ring systems (**3**) and (**7**).

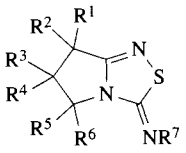
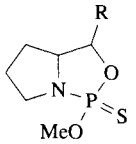
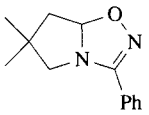
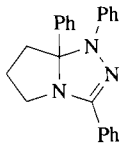
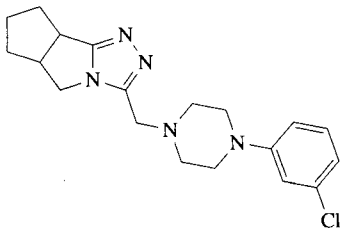
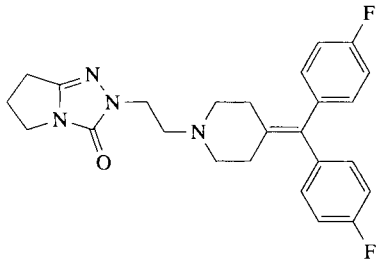
8.03.12 IMPORTANT COMPOUNDS AND APPLICATIONS

None of the compounds described in this chapter has any reported commercial applications, although a number of papers and patents claim various types of biological activity as summarized in Table 3.

The oxazaborolidine (**27**) has found widespread use as a catalyst for the enantioselective reduction of prochiral ketones to provide alcohols of predictable absolute stereochemistry and high enantiomeric excess. Important uses of this method have been in the syntheses of natural products such as ginkgolides A and B ⟨88CSR111, 88TL3201⟩ and the enantiomers of pharmaceuticals such as fluoxetine (Prozac) ⟨89TL5207⟩, isoproterenol ⟨90TL601⟩, and denopamine ⟨91JOC442⟩. The oxazaphospholidine–borane complex (**47**) has also found limited use in the enantioselective reduction of ketones ⟨92CC287⟩.

A number of oxazaphospholidines (**69**) have found use as ligands in the preparation of chiral catalyst systems which promote a variety of enantioselective reactions. Examples include the use of palladium complexes for the asymmetric carbonylation of α-methylbenzyl bromide ⟨88OM59⟩,

Table 3 Biologically active compounds.

Structure	*Activity*	*Ref.*
	Herbicide	86GEP(O)3528583
	Herbicide	81NKK705
	Antiinflammatory	84MI 803-01
	Antiinflammatory	85AP(318)556
	Analgesic	86EUP199641
	5-HT_2 antagonist	92JMC189

cobalt–zinc systems for the homo Diels–Alder reaction between norbornadiene and various alkynes ⟨93TA1977⟩, nickel complexes for the cyclodimerization of butadiene to 4-vinylcyclohex-1-ene ⟨87NJC573⟩, and copper complexes for asymmetric conjugate additions to enones ⟨91JA6332⟩.

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8.04
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 1 : 1

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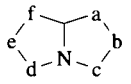
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8.04.1 INTRODUCTION

This chapter reviews bicyclic systems containing two fused five-membered rings with one bridgehead nitrogen and one further heteroatom in each ring. A large number of such systems are theoretically possible. For example, there are six possible (N,N) systems, having one nitrogen (besides the bridgehead nitrogen) in each ring, as well as six (O,O), six (S,S), nine (N,O), nine (N,S), and nine (O,S) systems, making a total of 45 possible ring systems containing just these three heteroatoms. Introducing further heteroatoms causes a dramatic increase in the number of systems possible. However, only 33 systems of this type have been reported in the literature and these are listed in Table 1 together with a selection of references. Some of these bicyclic systems (e.g., (**1**)–(**3**), (**7**)–(**10**), and (**15**)) have also been reported with benz rings fused to one or both of the five-membered rings. The amount of literature on each of these systems varies enormously, some being mentioned in only one or two references, whereas others have been extensively investigated. By far the greatest amount of work has been carried out on the imidazo[2,1-*b*]thiazole system (**15**) and a vast literature exists around the most important compounds of this type, the anthelmintic drug tetramisole (**34**) and its analogues.

As with the 2-0 systems described in the previous chapter (see 8.03), no reviews have been

Table 1 Ring systems (**1**)–(**33**).

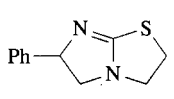


Ring system name and number	*Heteroatom location*	*Ref.*
Imidazo[1,2-*b*]pyrazole (**1**)	a=d=N	73JHC411, 80CHE634, 80JHC1413
Imidazo[1,5-*a*]imidazole (**2**)	a=e=N	70CHE486, 84JHC753, 91S157
Imidazo[1,2-*a*]imidazole (**3**)	a=f=N	72JMC923, 86JHC541
Imidazo[1,5-*b*]pyrazole (**4**)	b=d=N	78JOC4841
Imidazo[1,5-*c*]imidazole (**5**)	b=e=N	82BCJ3586, 83JHC1103
Pyrazolo[1,5-*b*]pyrazole (**6**)	c=d=N	76CPB2267
Imidazo[1,2-*b*]isoxazole (**7**)	a=N, d=O	84BAP195
Imidazo[2,1-*b*]oxazole (**8**)	a=N, f=O	81JPR516, 86JMC386
Imidazo[1,5-*c*]oxazole (**9**)	b=N, e=O	51JCS3479, 70CHE406, 75JOC1521, 89PHA817
Imidazo[5,1-*b*]oxazole (**10**)	b=N, f=O	75JOC1521
Pyrazolo[1,5-*b*]isoxazole (**11**)	c=N, d=O	71JOC19, 94JCS(P2)1337
Pyrazolo[5,1-*b*]oxazole (**12**)	c=N, f=O	93JHC1529
Imidazo[1,2-*b*]isothiazole (**13**)	a=N, d=S	77T1057
Imidazo[1,2-*c*]thiazole (**14**)	a=N, e=S	71CC1100, 82CL1491
Imidazo[2,1-*b*]thiazole (**15**)	a=N, f=S	37JPJ308, 55CB1109, 71JPR977, 72JPJ51
Imidazo[1,5-*c*]thiazole (**16**)	b=N, e=S	79BSB233, 83JHC483
Imidazo[5,1-*b*]thiazole (**17**)	b=N, f=S	83JHC419, 85AJC1873
Pyrazolo[1,5-*b*]isothiazole (**18**)	c=N, d=S	82ZOR2626
Pyrazolo[1,5-*c*]thiazole (**19**)	c=N, e=S	92SUL91
Pyrazolo[5,1-*b*]thiazole (**20**)	c=N, f=S	82JPR639
Imidazo[2,1-*b*]selenazole (**21**)	a=N, f=Se	78JMC496
Oxazolo[3,2-*b*]isoxazole (**22**)	a=d=O	84JOC3127
Oxazolo[2,3-*b*]oxazole (**23**)	a=f=O	80JPR902, 82JFC(21)359
Oxazolo[3,4-*c*]oxazole (**24**)	b=e=O	45JA1515, 81OPP126
Isoxazolo[2,3-*b*]isoxazole (**25**)	c=d=O	66ZOR2225
Thiazolo[4,3-*b*]oxazole (**26**)	a=O, e=S	87TL6077
Thiazolo[2,3-*b*]oxazole (**27**)	a=O, f=S	85CC454
Thiazolo[3,2-*b*]isothiazole (**28**)	a=d=S	82PIA463
Thiazolo[4,3-*b*]thiazole (**29**)	a=e=S	61HC(15-1)63
Thiazolo[2,3-*b*]thiazole (**30**)	a=f=S	69JHC729
Thiazolo[3,4-*c*]thiazole (**31**)	b=e=S	84HCA1827
[1,3]Azaphospholo[5,1-*b*]thiazole (**32**)	a=S, e=P	92HAC351
[1,2]Azasilolo[5,1-*e*][1,2]azasilole (**33**)	c=d=Si	78CC80

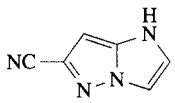
published dealing specifically with 1-1 bicyclic systems, although a number of such systems have been covered by more general reviews. An early review of ring systems containing bridgehead nitrogen atoms covered work reported up to mid-1958 ⟨61HC(15-1)63⟩ and a review of 5-5 systems with a bridgehead nitrogen atom covered literature prior to 1973 ⟨77HC(30)1⟩. The chemistry of aromatic azapentalenes has been reviewed up to the end of 1975 and included work on several 1-1 systems with a bridgehead nitrogen ⟨78AHC(22)183⟩. Syntheses of compounds containing some of the ring systems in Table 1 have been reviewed up to 1991 ⟨87HC(47)1, 92HC(47-2)661⟩. In addition, 19 1-1 systems were discussed in *Comprehensive Heterocyclic Chemistry, First Edition* (CHEC-1), mainly in the chapter on classical heteropentalenes ⟨84CHEC-I(6)973⟩. In view of the large number of known ring systems of this type and the enormous amount of literature on some of these systems, this chapter will concentrate on work which has appeared since the publication of the above-mentioned reviews.

8.04.2 THEORETICAL METHODS

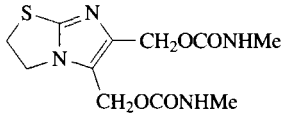
As with the 2-0 ring systems discussed in the previous chapter, there have been very few reports of the application of theoretical methods to the systems under discussion here. Hückel molecular orbital calculations have been carried out on the imidazo[1,2-*b*]pyrazole (**35**). This model predicted the 1H tautomer to be more stable than the 5H and this is in agreement with the observation that the N-1 glycoside (**38**) is thermodynamically more stable than the N-5 isomer (**39**) (see Table 2 for structures) ⟨84JOC3534⟩. The same model also predicted a π electron density of greater than 1.1 on C-7, which is in agreement with the upfield chemical shifts (δ ca. 65 ppm) observed for this carbon in the ^{13}C NMR spectra of (**35**), (**38**), and (**39**).



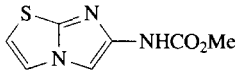
(**34**)



(**35**)



(**36**)



(**37**)

Optimized structures calculated using MNDO predicted the dihydroimidazo[2,1-*b*]thiazole (**36**) to be nearly planar, whereas the analogous 2*H*-3,4-dihydroimidazo[2,1-*b*]thiazine, a 5-6 system, was expected to be nonplanar. The major consequence of this predicted difference in planarity is a modification of the electronic interactions between the lone pair on the sulfur atom and the imidazole π system. MNDO and AM1 (using some MNDO sulfur parameters) were used to compare ground state energies of cations derived from (**36**). These calculations predicted (**36**) to be less reactive as an alkylating agent than the comparable 5-6 system and this was confirmed by experiment ⟨93JMC3618⟩.

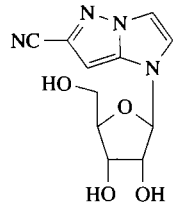
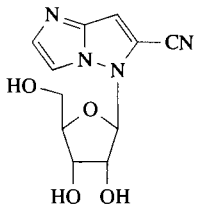
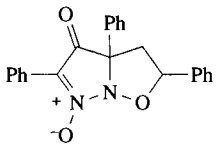
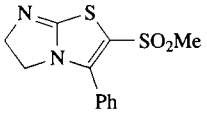
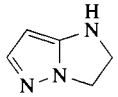
Molecular electrostatic potentials have been calculated for various analogues of the anthelmintic drug mebendazole, including the imidazo[2,1-*b*]thiazole (**37**). These were used to derive relationships between structure and anthelmintic activity ⟨89FES671⟩.

8.04.3 EXPERIMENTAL STRUCTURAL METHODS

8.04.3.1 X-Ray Crystallography

The structures of a number of compounds containing some of the ring systems under discussion here have been determined by x-ray diffraction (Table 2). In general, the observed molecular dimensions were similar to predicted values. For the two nucleosides (**38**) and (**39**), the glycosidic bond in the less stable isomer (**39**) is considerably longer (15.05 nm) than that in the more stable isomer (**38**) (14.51 nm). In the pyrazolo[1,5-*b*]isoxazole (**40**), hydrogen bonds link the carbonyl and nitrone oxygens with the ortho hydrogens in the 5-phenyl ring, causing the molecule to adopt a planar resonance structure. In the dihydroimidazo[1,2-*b*]pyrazole (**42**), the N(4)—C(7a) and N(1)—C(7a) bonds are reported to have substantial double bond character.

Table 2 Compounds investigated by x-ray diffraction.

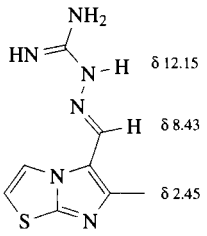
Structure	*Ref.*
 **(38)**	84JOC3534
 **(39)**	84JOC3534
 **(40)**	94JCS(P2)1337
 **(41)**	81JMC604
 **(42)**	83AX(C)353

8.04.3.2 Proton NMR Spectroscopy

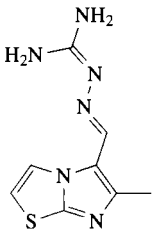
Other than providing basic structural information, ^{1}H NMR spectroscopy has not been extensively used to investigate the systems discussed in this chapter. However, some NMR studies on these systems are worthy of mention here.

Nuclear Overhauser enhancement (NOE) difference spectroscopy has been used to investigate the *E*–*Z* configurations and the conformations of the imidazo[2,1-*b*]thiazole guanylhydrazone (**43**) ⟨92JMC4634⟩. Irradiation of the 6-methyl (δ 2.45 ppm) and NH (δ 12.15 ppm) groups resulted in an enhancement of the alkene proton signal (δ 8.43 ppm). Similarly, irradiation of the alkene proton resulted in enhancement of both the NH and the 6-methyl signals, showing that the hydrazone moiety exists in the *E* configuration. Proton NMR spectroscopy also showed that the hydrochloride of (**43**) exists in DMSO solution as the tautomer shown rather than the enediamine tautomer (**44**).

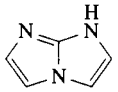
The spectrum of imidazo[1,2-*a*]imidazole (**45**) in D_6-DMSO shows two doublets, indicating the presence of two pairs of equivalent protons (i.e., H-2,H-6 and H-3,H-5) and implying that the molecule is symmetrical due to fast proton exchange between N-1 and N-7. Deuterium exchange occurs at the nucleophilic 3 and 5 positions. In trifluoroacetic acid, the H-2 and H-6 protons couple to the N—H protons ⟨86JHC541⟩.



(43)



(44)



(45)

8.04.3.3 Carbon-13 NMR Spectroscopy

The ^{13}C NMR spectrum of (**45**) shows only three signals, corresponding to the bridgehead carbon C-7a and the atom pairs C-2,C-6 and C-3,C-5, as a result of tautomeric equilibrium. Deuteration occurs at C-3 and C-5, causing the signals corresponding to C-2,C-6 and C-3,C-5 to shift upfield due to an isotope effect and the C-3,C-5 signal to appear as a triplet ($^1J_{C-D} = 31.5$ Hz) ⟨86JHC541⟩.

8.04.3.4 Nitrogen-15 NMR Spectroscopy

This technique has rarely been applied to the systems covered in this chapter. In the imidazo[2,1-*b*]thiazole and imidazo[1,2-*a*]imidazole ring systems, the bridgehead nitrogen is more shielded than the other ring nitrogens ⟨89MI 804-01, 86JHC541⟩.

8.04.4 THERMODYNAMIC ASPECTS

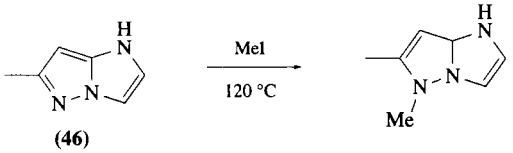
The lipophilic character of a series of nitroimidazo[2,1-*b*]thiazoles has been determined by means of both TLC and HPLC. The relationship between TLC R_m values, HPLC retention times, and the hydrophobic bonding constant π was studied to investigate structure–mutagenicity relationships for this series of compounds. Best correlations were obtained between R_m and $\Sigma\pi$ values ⟨85JC281⟩.

8.04.5 REACTIVITY OF FULLY CONJUGATED RINGS

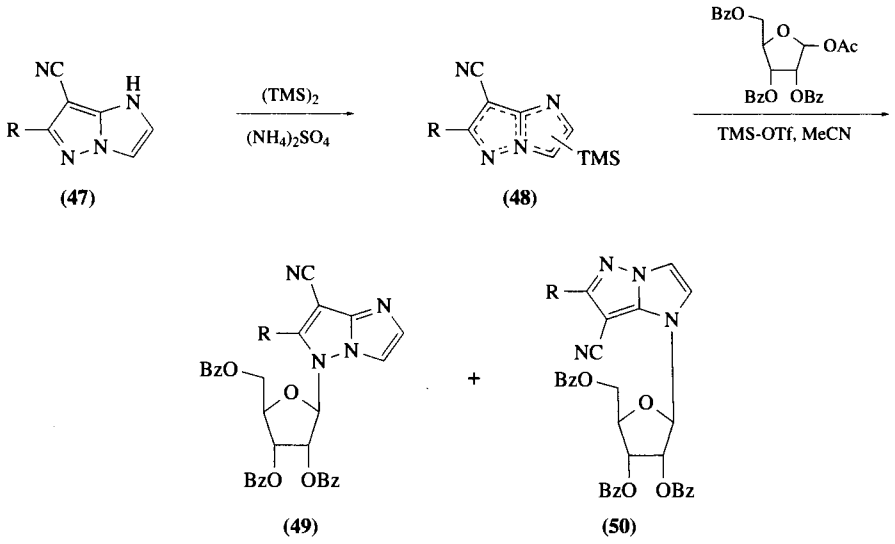
The majority of the reactions reported at fully conjugated rings have been electrophilic substitutions, although displacements of halogen by a range of nucleophiles are also known. Earlier reviews gave comprehensive treatments of the reactivity of several of the ring systems under discussion here ⟨77HC(30)1, 78AHC(22)183⟩ and most of the reactions since the late 1970s at fully conjugated rings have been on imidazo[2,1-*b*]thiazole derivatives.

8.04.5.1 Electrophilic Attack at Nitrogen

Methylation of the imidazo[1,2-*b*]pyrazole (**46**) occurred exclusively at N-5 (Equation (1)), whereas acylation took place on N-1 (see Section 8.04.6.1). Imidazo[1,2-*b*]pyrazoles (**47**) reacted with hexamethyldisilazane to give the corresponding trimethylsilyl derivatives (**48**) which were glycosylated both on the conjugated (pyrazole) and nonconjugated (imidazole) rings to give mixtures of isomeric nucleosides (**49**) and (**50**) (Equation (1), Scheme 1) ⟨84JOC3534⟩.



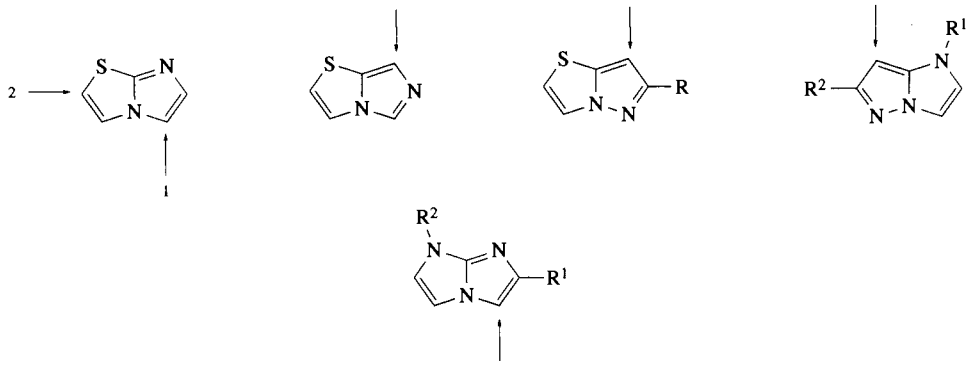
(46) (1)



Scheme 1

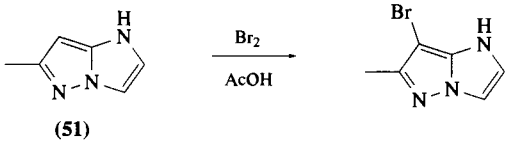
8.04.5.2 Electrophilic Attack at Carbon

Scheme 2 indicates the positions of electrophilic substitution for some of the more common bicyclic systems under consideration in this chapter. For the imidazo[2,1-*b*]thiazole system, the numbers 1 and 2 refer to the preferential order for the two centers of attack. Occasionally, mixtures of products are obtained in which the product resulting from attack at center 1 predominates but more usually, attack at center 2 only occurs when center 1 is blocked by a substituent.

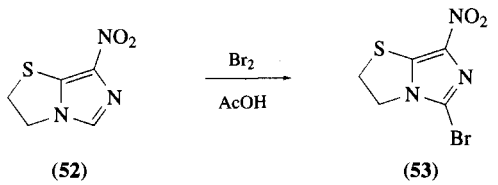


Scheme 2

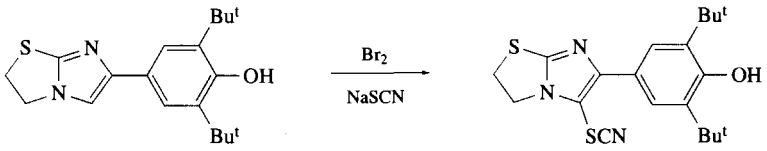
Examples of brominations are shown in Equations (2) and (3). Bromination is usually performed using bromine in acetic acid. The imidazo[1,2-*b*]pyrazole (**51**) brominated in the 7 position ⟨78AQ795⟩ and the imidazo[5,1-*b*]thiazole (**52**), in spite of the strongly electron withdrawing nitro substituent on the imidazole ring, brominated at the vacant imidazole ring position to give a moderate yield of (**53**) ⟨85AJC1873⟩. Thiocyanations have been carried out either with bromine and sodium thiocyanate ⟨83CPB3179⟩ or with bromine and thiourea ⟨72YZ927⟩ (Equations (4) and (5)). A large number of imidazo[2,1-*b*]thiazoles have been formylated using Vilsmeier conditions (Equations (6) and (7)). Both dihydroimidazo[2,1-*b*]thiazoles (**54**) and the fully unsaturated analogues (**55**) formylate at the 5 position ⟨83CPB3179, 87EJM19, 89JHC525⟩.



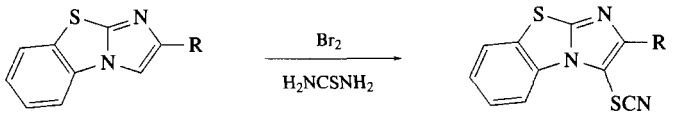
(2)



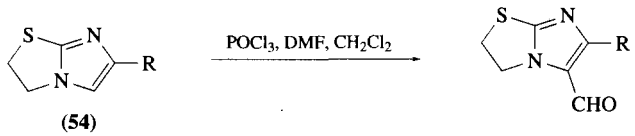
(52) (53) (3)



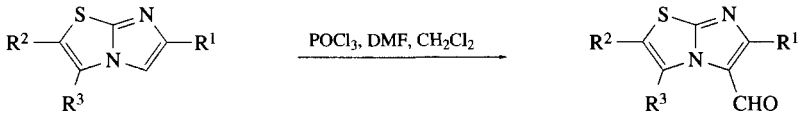
(4)



(5)

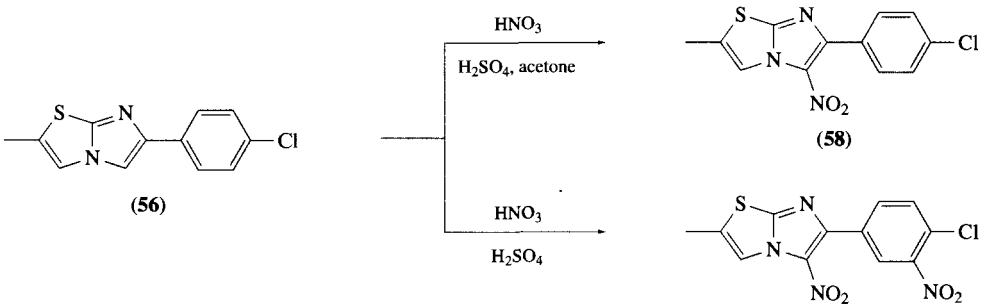


(54) (6)



(55) (7)

Other electrophilic substitution reactions of imidazo[2,1-*b*]thiazoles are shown in Schemes 3 and 4, and in Equations (8), (9), and (10). Nitration of 6-arylimidazo[2,1-*b*]thiazoles, e.g. (**56**) and (**57**) under standard conditions occurs both in the 5 position of the imidazothiazole ring and on the phenyl substituent. The mononitro products (**58**) and (**59**) can be obtained by performing the reaction in an organic solvent. The 5-nitroso analogues were similarly prepared by treating (**56**) and (**57**) with sodium nitrite in aqueous acetic acid ⟨87MI 804-01⟩. Sulfonations ⟨93MI 804-01⟩, trifluoroacetylations ⟨93JCR(S)201⟩, and Mannich reactions ⟨83CPB3179, 88EJM385⟩ have also been reported for this ring system.

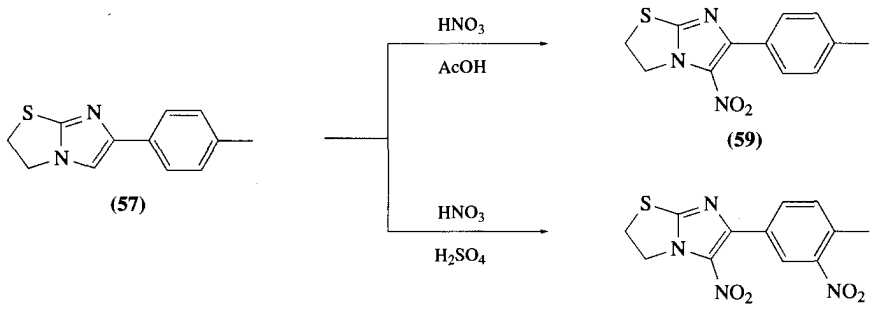


(56) (58)

Scheme 3

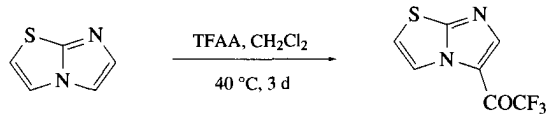


(8)

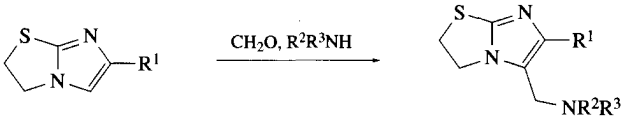


(57) (59)

Scheme 4



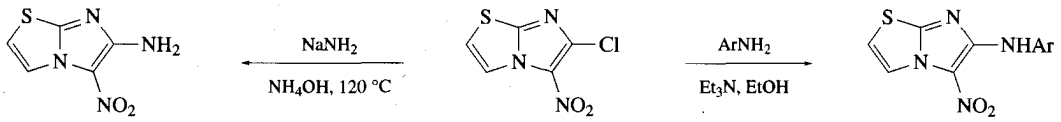
(9)



(10)

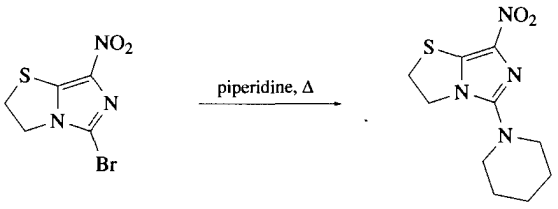
8.04.5.3 Nucleophilic Attack at Carbon

There have been comparatively few reports of nucleophilic substitution reactions at carbon and all have involved displacement of halogen (Scheme 5, Equations (11) and (12)). Usually, electron withdrawing substituents are necessary to activate the ring system towards nucleophilic attack. The 6-chloro substituent in (**60**) is readily displaced by a range of amines and similar reactions were also reported for the corresponding 2,3-dihydro analogues ⟨93MI 804-02⟩. The imidazo[5,1-*b*]thiazole (**61**) reacted with a five fold excess of piperidine to give a low yield of (**62**) ⟨85AJC1873⟩. An example of nucleophilic attack by sulfur is the reaction of (**63**) with sodium sulfide to give the corresponding thiol (**64**) ⟨91JHC41⟩.



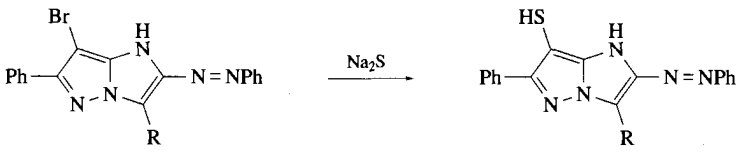
(60)

Scheme 5



(11)

(61) (62)



(12)

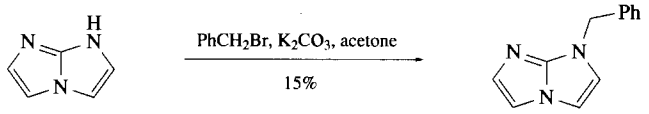
(63) (64)

8.04.6 REACTIVITY OF NONCONJUGATED RINGS

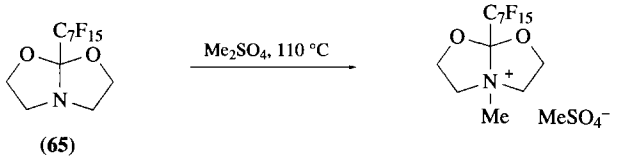
Reactions of nonconjugated rings can be divided into two types, those in which the ring system remains intact and those where one or both rings of the bicyclic system are cleaved.

8.04.6.1 Reactions where the Ring System is Preserved

The most common reactions in this category are N-alkylations and acylations, oxidations and reductions. Alkylations and acylations have been reviewed previously ⟨78AHC(22)183⟩ and more recent examples are shown in Equations (13)–(18). Reaction of imidazo[1,2-*a*]imidazole with benzyl bromide gave a low yield of the 1-benzyl derivative ⟨86JHC541⟩. The bicyclic amide acetal (**65**) was methylated on the bridgehead nitrogen on heating with dimethyl sulfate. Bicyclic amide acetals such as (**65**), which have a 7a-perfluoroalkyl substituent, are reported to be relatively unreactive towards a variety of electrophiles and nucleophiles ⟨82JFC(21)359⟩ compared with the more reactive 7a-alkyl analogues, which readily undergo ring opening reactions (see Section 8.04.6.2). The imidazo[1,5-*c*]thiazole (**66**) reacted with the fluoroquinolone (**67**) by nucleophilic displacement of the fluorine atom in the 7 position to give (**68**) ⟨93MI 804-03⟩. Acylation of (**69**) and (**46**) has been reported to occur at N-1 ⟨78AQ795, 82S689⟩. Debenzylation of (**71**) failed using palladium on charcoal but a low yield of (**72**) was obtained using palladium hydroxide catalyst ⟨83S1033⟩.

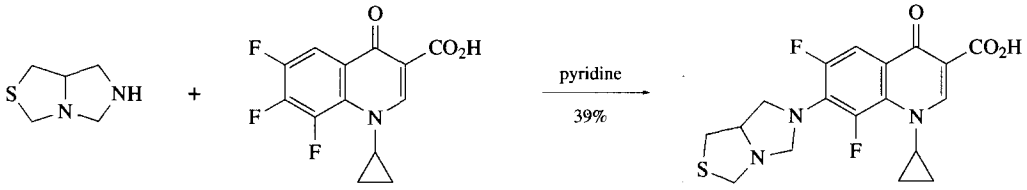


(13)



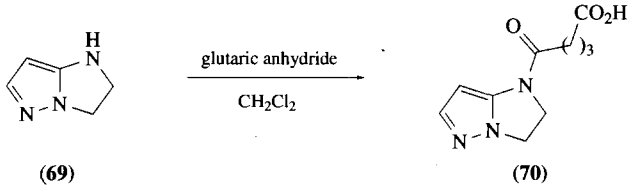
(65)

(14)



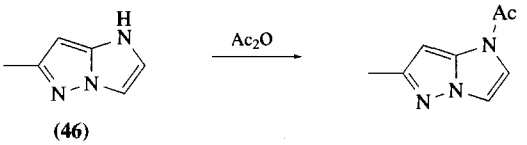
(66) (67) (68)

(15)



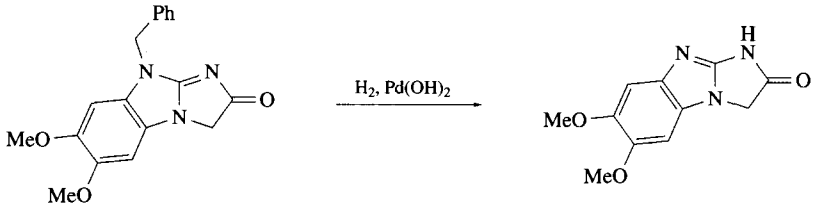
(69) (70)

(16)



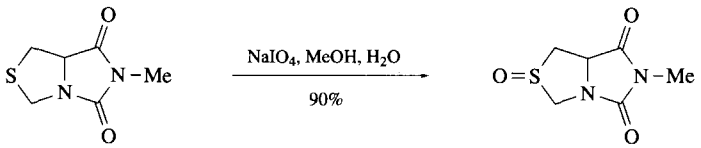
(46)

(17)

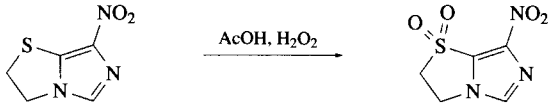


(71) (72) (18)

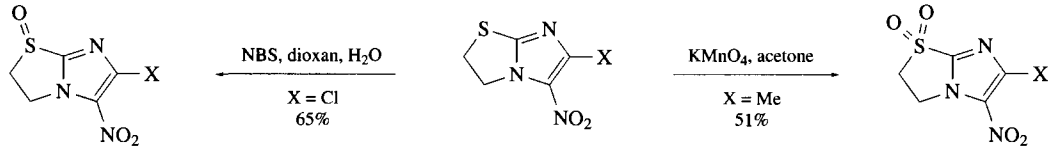
Scheme 6 and Equations (19)–(22) summarize various oxidations and reductions which were not reported in previous reviews. The cyclic thioethers (**73**) and (**74**) have been oxidized to the corresponding sulfoxide and sulfone, respectively ⟨79BSB233, 85AJC1873⟩. Similar oxidations of imidazo[2,1-*b*]thiazoles (**75**; X = Cl, Me) have also been reported ⟨87MI 804-01, 93MI 804-02⟩. The dihydropyrazolo[2,3-*b*]indazole (**76**) was oxidized with lead tetraacetate to give (**77**) in low yield ⟨76CPB2267⟩. The cyclic lactams (**78**; X = O, H_2) were reduced with LAH to give (**79**) ⟨87EJM11, 93MI 804-03⟩.



(73) (19)

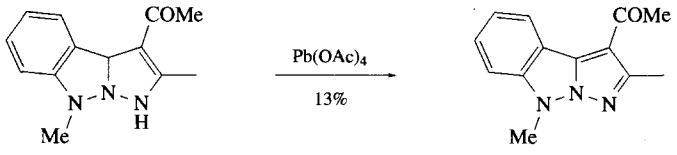


(74) (20)



(75)

Scheme 6



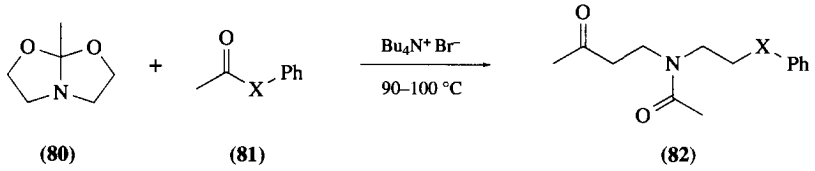
(76) (77) (21)



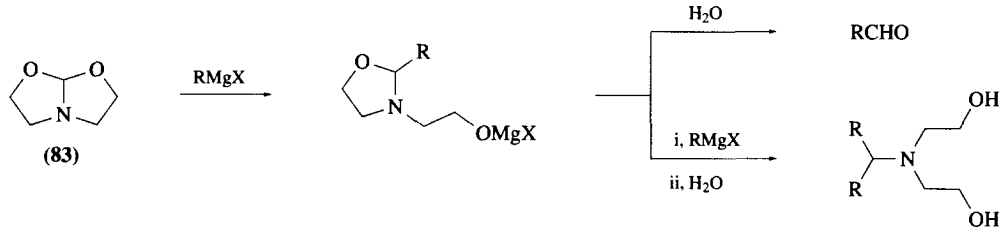
(78) (79) (22)

8.04.6.2 Ring Cleavage Reactions

Nonconjugated rings tend to be less stable with respect to ring cleavage than conjugated rings and benz-fused rings are more stable than rings without a fused benz ring. Many examples of ring-opening reactions of nonconjugated rings have been reported ⟨77HC(30)1, 78AHC(22)183⟩ and a selection of mainly more recent examples is shown in Schemes 7 and 8, and in Equations (23)–(29).

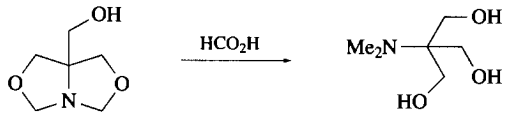


(80) (81) (82) (23)

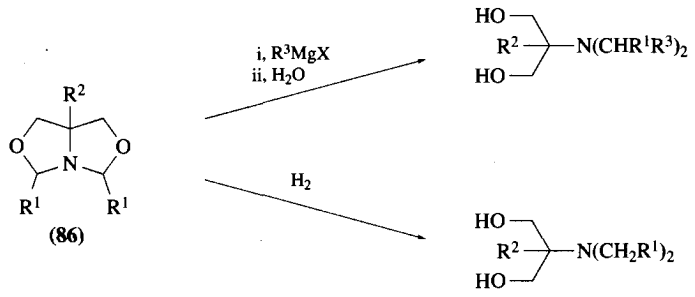


(83)

Scheme 7

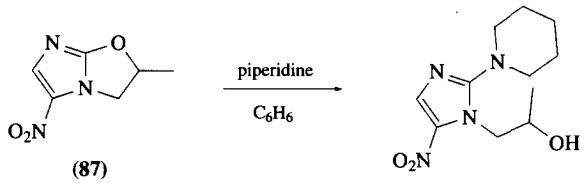


(84) (85) (24)

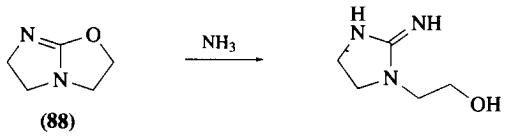


(86)

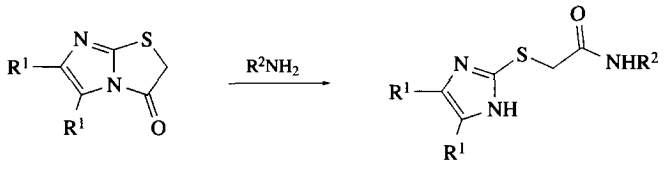
Scheme 8



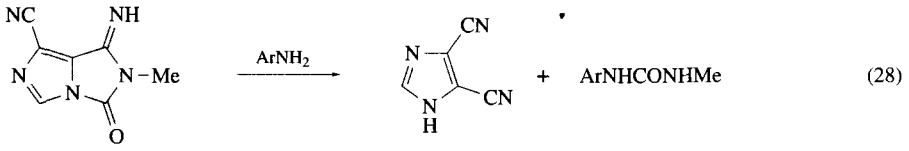
(87) (25)



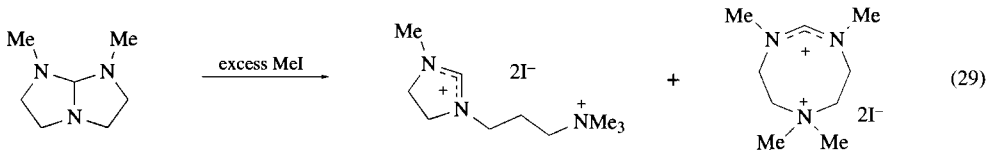
(88) (26)



(89) (90) (27)



(91) (92) (28)



(93) (94) (95) (29)

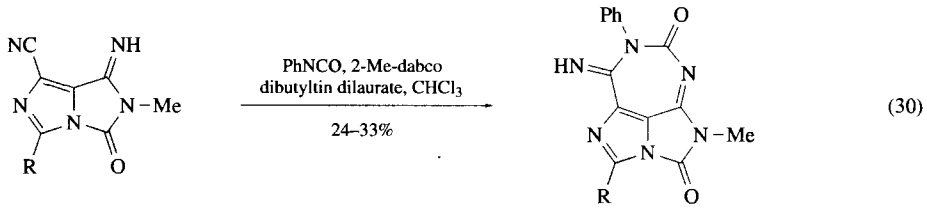
Addition reactions of the bicyclic amide acetal (**80**) with esters and thioesters (**81**; X = O, S) gave ring opened products (**82**) ⟨91CL697⟩. Alkyl and aryl Grignard reagents react with (**83**) to give products arising from C—O bond fission. With one mole of Grignard reagent, the products are aldehydes, whereas with two moles, bis(hydroxyethyl)alkylamines are obtained ⟨80JPR902⟩. Reduction of the oxazolo[3,4-*c*]oxazole (**84**) with formic acid results in ring cleavage to give (**85**) ⟨81OPP126⟩ and similar products were obtained from (**86**) both by hydrogenation and by addition of Grignard reagents ⟨45JA1515⟩.

The imidazo[2,1-*b*]oxazoles (**87**) and (**88**) ring opened on treating with amines to give products resulting from C—O bond fission ⟨57JA5276, 84IJC(8)363⟩, whereas the imidazo[2,1-*b*]thiazolone (**89**) gave acetamide derivatives (**90**) by nucleophilic attack at the carbonyl group followed by C—N bond fission ⟨72JPR785⟩. A similar type of behavior has been reported for the imidazo[1,5-*c*]-imidazole (**91**). In this case, the initial product resulting from attack of the amine at the carbonyl group reacts further to give the urea (**92**) and 4,5-dicyanoimidazole ⟨82BCJ3586⟩. Methylation of the imidazo[1,2-*a*]imidazole (**93**) using an excess of methyl iodide gave ring opened quaternary salts (**94**) and (**95**) ⟨80JA6365⟩.

8.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

There have been numerous reports of reactions of substituents attached to ring carbon atoms and it is not possible to list them all here. Instead, the major types of reaction are shown in Table 3 together with representative examples. As will be obvious from this table, the vast majority of reactions of this type have been reported for the imidazo[2,1-*b*]thiazole ring system (**15**).

One miscellaneous reaction is also worthy of mention here. The imidazo[1,5-*c*]imidazole (**96**) reacted with phenyl isocyanate to give the tricyclic compound (**97**) (Equation (30)) ⟨82BCJ3586⟩.



(96) (97) (30)

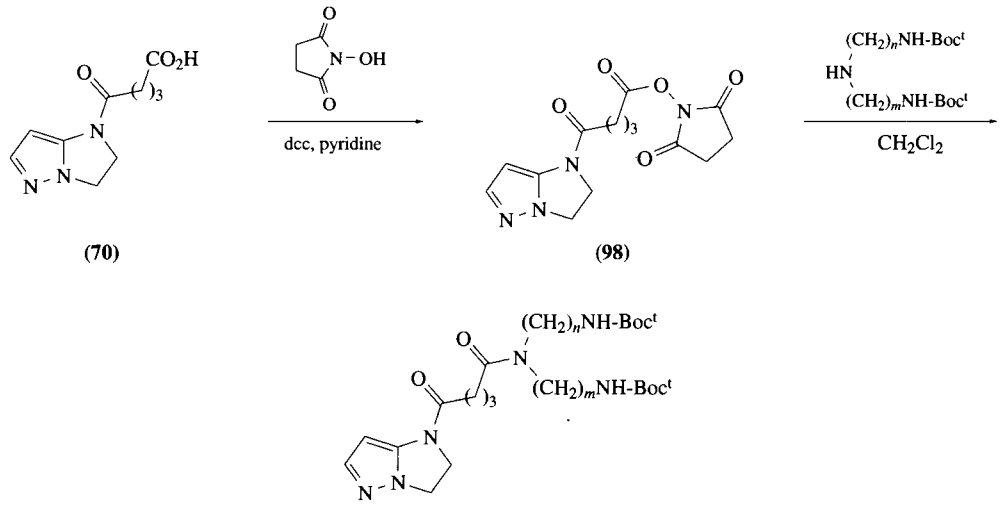
8.04.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Very few reactions of this type have been reported. The glutaric acid derivative (**70**) was esterified with *N*-hydroxysuccinimide and the resulting product (**98**) was used to selectively acylate the secondary nitrogen of various spermidine derivatives (Scheme 9) ⟨82S689⟩.

Table 3 Reactions of substituents attached to carbon atoms in ring systems (**1**)–(**33**).

Reaction	*Ring System*[a]	*Reagents*	*Ref.*
$CO_2H \rightarrow CO_2R$	(**15**)	RX, Et_3N, THF	83AP(316)141, 86EJM451
$CO_2H \rightarrow CONHR$	(**15**)	(i) $SOCl_2$; (ii) RNH_2	86EJM451, 92MI 804-01
$CO_2R \rightarrow CO_2H$	(**15**)	NaOH; EtOH	81FES893, 83FES533
	(**15**)	aq.HCl	81FES893
$CO_2R \rightarrow CHO$	(**15**)	[b]	88EJM385
$CO_2R \rightarrow CH_2OH$	(**15**)	LAH, CH_2Cl_2, THF	93JMC3618
$CO_2R \rightarrow CONHNH_2$	(**9**)	$NH_2NH_2 \cdot H_2O$, EtOH	70CHE406
	(**15**)	$NH_2NH_2 \cdot H_2O$, EtOH	88EJM385
$CHO \rightarrow CO_2H$	(**15**)	$KMnO_4$, acetone, H_2O[c]	88EJM385
$CHO \rightarrow CH_2OH$	(**15**)	$NaBH_4$, ROH	80FES896, 83CPB3179, 89JHC525
$CHO \rightarrow CH{=}NOH$	(**9**)	NH_2OH, EtOH, H_2O	70CHE406
	(**15**)	NH_2OH, EtOH, H_2O	82EJM271, 91CCC2436
$CHO \rightarrow CH{=}NNHR$	(**15**)	$RNHNH_2$, R^1OH, H_2O	80FES573, 87EJM19, 92JMC4634
$CHO \rightarrow CH{=}CHNO_2$	(**15**)	$MeNO_2$, NH_4OAc	88EJM385
$CH{=}NOH \rightarrow CN$	(**9**)	Ac_2O, NaOAc	70CHE406
	(**15**)	$SOCl_2$	82EJM271
	(**15**)	SeO_2, $CHCl_3$, DMF	82EJM271
$CH_2OH \rightarrow CH_2OAc$	(**15**)	Ac_2O, pyridine	80FES896
$CH_2OH \rightarrow CH_2OCONHR$	(**15**)	RNCO, Et_3N, THF	80FES896, 88EJM385, 89JHC525
	(**15**)	RNCO, $Bu_2Sn(OAc)_2$, CH_2Cl_2	93JMC3618
$CH_2Cl \rightarrow CH{=}CMe_2$	(**15**)	$NaC(Me_2)NO_2$, CH_2Cl_2, H_2O	91H(32)2083
$CH_2COAr \rightarrow CH_2CH(OH)Ar$	(**15**)	$NaBH_4$	86EJM499, 94EJM309
$Me \rightarrow CHO$	(**15**)	SeO_2, dioxan	80FES573
$CN \rightarrow CONH_2$	(**1**)	ppa	84JOC3534
	(**1**)	NH_4OH, H_2O_2	84JOC3534
	(**15**)	H_2SO_4	82EJM271
$CN \rightarrow CSNH_2$	(**9**)	H_2S, Et_3N, EtOH	70CHE406
$CN \rightarrow C(=NOH)NH_2$	(**9**)	NH_2OH, EtOH, H_2O	70CHE406
	(**15**)	NH_2OH, EtOH, H_2O	88EJM385
$CO_2CH_2CN \rightarrow CO_2CH_2CONH_2$	(**15**)	H_2SO_4	86EJM451
$SR \rightarrow SOR$	(**15**)	MCPBA, acetone	93MI 804-01
$SR \rightarrow SO_2R$	(**1**)	MCPBA, CH_2Cl_2	84JOC3534
	(**15**)	MCPBA, DMF	93MI 804-01
$SO_3H \rightarrow SO_2NH_2$	(**15**)	(i) $POCl_3$, Et_3N; (ii) NH_4OH	93MI 804-01
$SCN \rightarrow SMe$	(**15**)	MeI, KOH, MeOH	83CPB3179
$COCF_3 \rightarrow H$	(**17**)	(i) aq.NaOH; (ii) aq.HCl	83JHC419

Notes: [a]Ring systems (**1**)–(**33**) are shown in Table 1. [b]Multistep reaction. [c]Simultaneous oxidation of thiazole sulfur may occur.

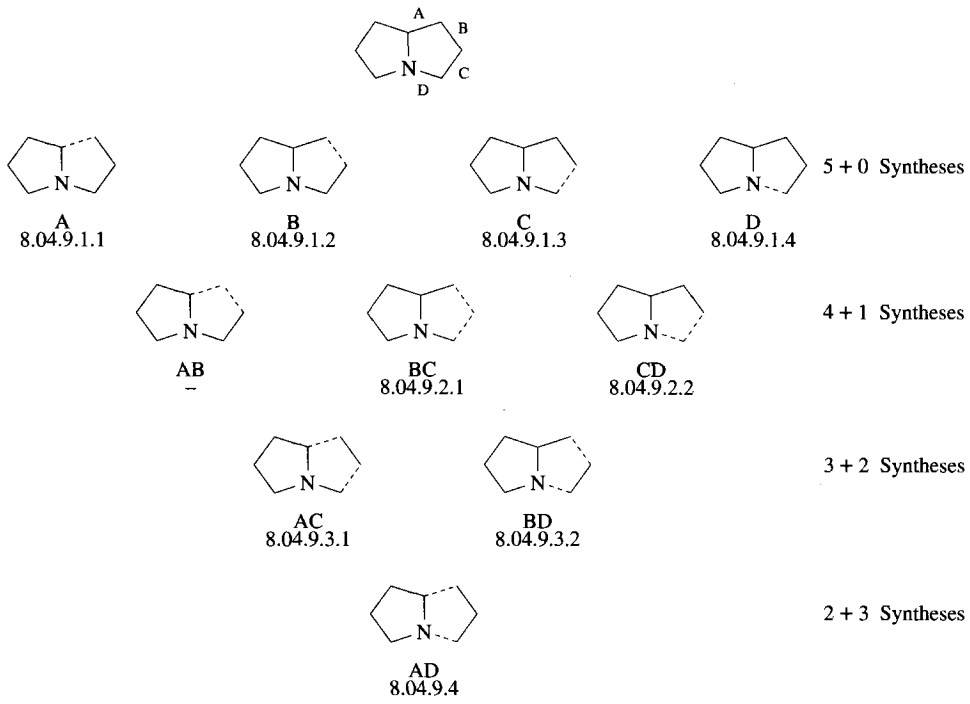


Scheme 9

8.04.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Many routes have been used to prepare the various ring systems described in this chapter and some of these were described in previous reviews ⟨61HC(15-1)63, 77HC(30)1, 78AHC(22)183, 87HC(47-1)1,

92HC(47-2)661〉. This review will concentrate mainly on more recent syntheses. Most of these involve the formation of a second ring by cyclization of, or cycloaddition to, suitably substituted monocyclic heterocycles and, for the purpose of this review, these routes have been divided into (5 + 0), (4 + 1), (3 + 2), and (2 + 3) syntheses, where the numbers refer to the number of atoms in the heterocyclic component and the number of additional atoms required to form the second ring, respectively. These syntheses have been further subdivided according to which bond(s) are formed in the overall reaction. For example, there are four different possible types of (5 + 0) syntheses, where ring closure occurs via the formation of bond A, B, C, or D. This classification is summarized in Scheme 10, where bond formation is indicated by dotted lines.



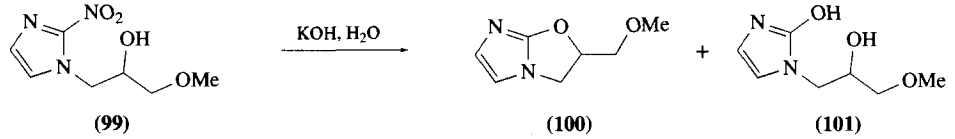
Scheme 10

In addition to these, there have been a number of reports of syntheses involving simultaneous formation of both rings from acyclic precursors (Section 8.04.9.5) and others involving rearrangements of different ring systems (Section 8.04.10).

8.04.9.1 (5 + 0) Syntheses

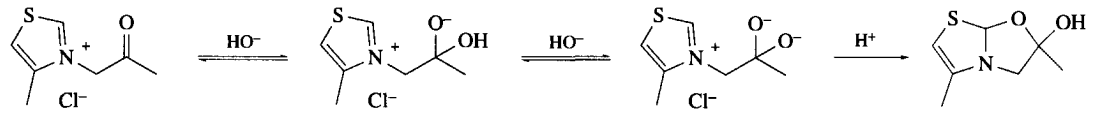
8.04.9.1.1 Type A syntheses

Very few (5 + 0) syntheses have been reported where ring closure occurs by formation of bond A (Equation (31), Scheme 11). In dilute aqueous potassium hydroxide solution, misonidazole (**99**) reacts to give two products (**100**) and (**101**), both involving loss of the nitro group. The imidazo[2,1-*b*]oxazole (**100**) is formed by intramolecular cyclization, whereas (**101**) is produced by nucleophilic substitution by hydroxide. This reaction does not appear to have been carried out on a preparative scale 〈86JCS(P2)689〉. Similar intramolecular cyclizations involving displacements of a nitro group from dinitroimidazoles are discussed in Section 8.04.9.4.



(31)

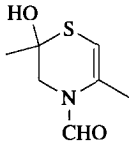
(**99**) (**100**) (**101**)



(102) (103) (104)

Scheme 11

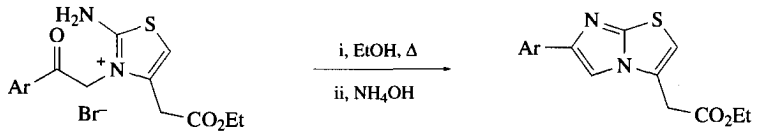
The thiazolo[2,3-*b*]oxazole (**104**) has also been prepared by a base-catalyzed type A cyclization ⟨85CC454⟩. In this case, the cyclization of thiazolium salt (**102**) is believed to occur by intramolecular nucleophilic attack of a hydrate dianion intermediate (**103**) on the positively charged ring. However, other workers have cast doubt on the structure of the product from this reaction claiming, on the basis of x-ray analysis, that it exists as (**105**) in the solid phase ⟨85CC1113⟩.



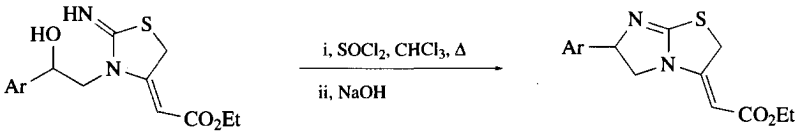
(105)

8.04.9.1.2 Type B syntheses

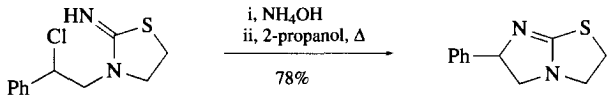
Most syntheses of this type involve cyclization of amino substituted heterocycles (or their tautomers), having a suitable substituent on an adjacent ring position. This method provides a convenient route to imidazo[2,1-*b*]thiazoles (Equations (32)–(35)), imidazo[1,2-*a*]imidazoles (Equations (36)–(39)), imidazo[1,2-*b*]pyrazoles (Equation (40) and Scheme 12), imidazo[1,5-*a*]imidazoles (Equation (41)) and imidazo[1,5-*c*]thiazoles (Equation (42)).



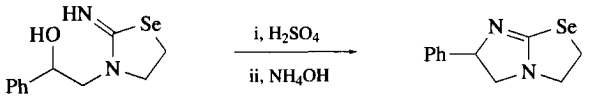
(106) (107) (32)



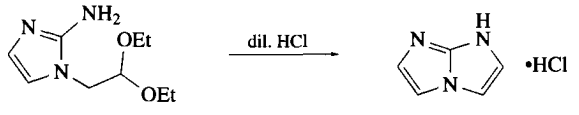
(108) (109) (33)



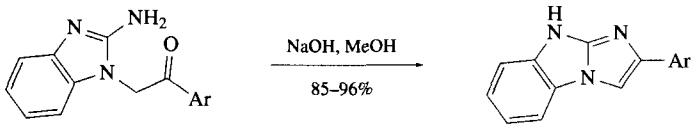
(110) (34) (34)



(111) (112) (35)

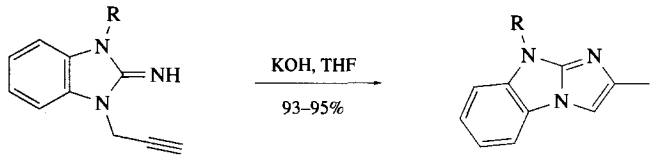


(113) (45) (36)



(37)

(114)



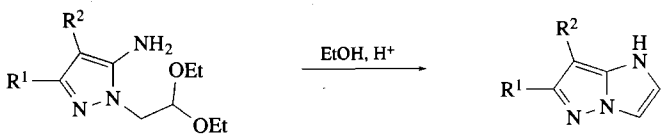
(38)

(115)



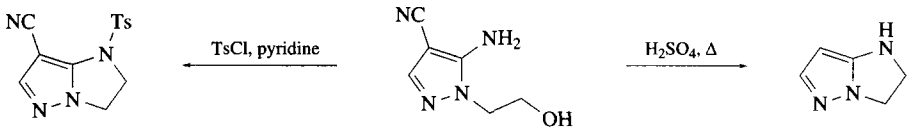
(39)

(116)



(40)

(117)



(118) (119)

Scheme 12



(41)

(120) (121)



(42)

(122) (123)

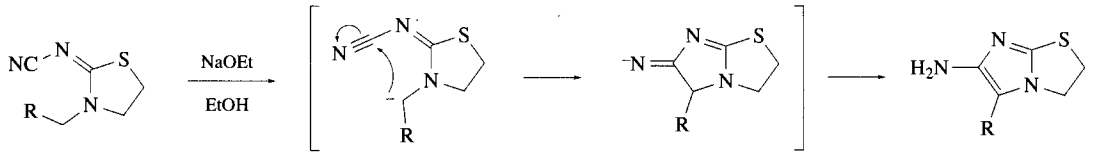
A selection of cyclizations of 2-amino-3-substituted thiazoles, leading to the formation of imidazo[2,1-*b*]thiazoles, is shown in Equations (32)–(35). Cyclization of the phenacylthiazolium salt (**106**) or the alcohol (**108**), obtained from (**106**) by sodium borohydride reduction, afforded (**107**) or (**109**), respectively ⟨94EJM309⟩. The cyclization of (**110**) provided one of the earliest syntheses of the anthelmintic drug tetramisole (**34**) ⟨68JOC1350⟩ and the corresponding imidazo[2,1-*b*]selenazole (**112**) was prepared from (**111**) in a similar manner ⟨78JMC496⟩.

Syntheses of imidazo[1,2-*a*]imidazoles have also been widely reported in the literature (Equations (36)–(39)). For example, the parent ring system (**45**) was prepared by acid-catalyzed cyclization of

the acetal (**113**) ⟨86JHC541⟩ and the benz fused analogue, imidazo[1,2-*a*]benzimidazole, was obtained similarly ⟨72JMC923⟩. Other syntheses of imidazo[1,2-*a*]benzimidazoles (**114**)–(**116**) involve cyclization of benzimidazoles having ketonic or alkynic substituents in the 3 position ⟨71KGS1243, 72JMC923, 76CHE1151⟩. Similar cyclizations of 5-aminopyrazoles yielded imidazo[1,2-*b*]pyrazoles (Equation (40), Scheme 12). Acetals (**117**) ⟨73JHC411, 78AQ795, 84JOC3534⟩ and the alcohol (**118**) ⟨87MI 804-02⟩ have both been used as starting materials for this type of reaction. In the case of the alcohol (**118**), cyclization occurs under both acidic and basic conditions and under the acidic conditions, the nitrile group is hydrolyzed and spontaneous decarboxylation occurs to give (**119**). Similar cyclizations of 5-aminoimidazoles (**120**) occur under basic conditions to give imidazo[1,5-*a*]imidazoles (**121**) ⟨91S157⟩. Imidazo[1,5-*c*]thiazoles (**123**) were prepared by acid-catalyzed cyclization of suitably substituted thiazole derivatives (**122**) (Equations (41) and (42)) ⟨87EJM11⟩.

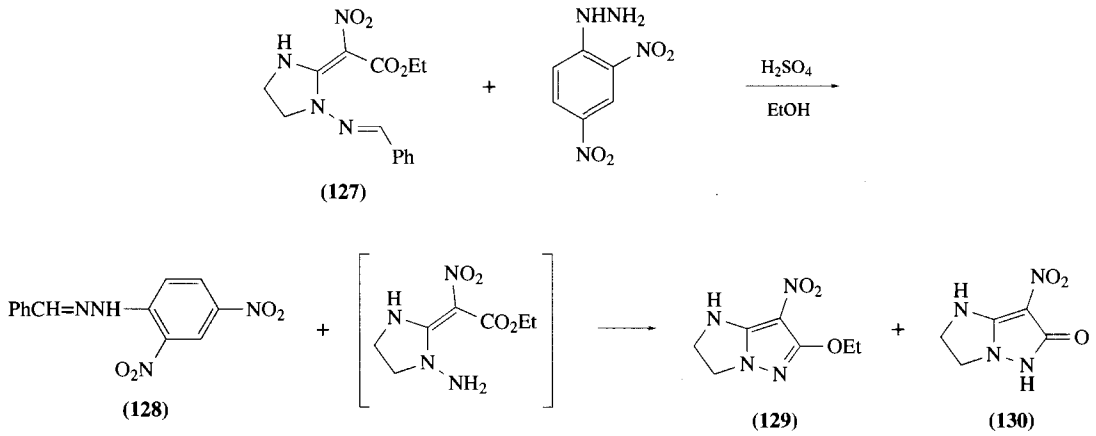
8.04.9.1.3 Type C syntheses

This type of cyclization has been used mainly to prepare imidazo[2,1-*b*]thiazoles and imidazo[1,2-*b*]pyrazoles (Schemes 13 and 14). Base-catalyzed cyclizations of 2-(cyanoimino)thiazolidines (**124**) afforded imidazo[2,1-*b*]thiazoles (**126**) via intermediates (**125**). Cyclization of (**124**) only occurs when R is an electron withdrawing group ⟨88S261⟩. Imidazo[1,2-*b*]pyrazoles have been prepared from suitably substituted imidazolidine derivatives ⟨80JHC1413⟩. The imidazolidine (**127**), prepared in 5 stages from 2-imidazolidine thione, was subjected to a hydrazinolysis reaction initiated by 2,4-dinitrophenylhydrazine to give a mixture of imidazo[1,2-*b*]pyrazoles (**129**) and (**130**) and the hydrazone (**128**).



(124) (125) (126)

Scheme 13



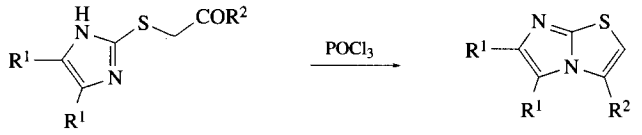
(127) (128) (129) (130)

Scheme 14

8.04.9.1.4 Type D syntheses

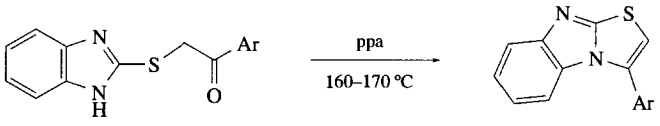
This type of ring closure has been reported mainly for the synthesis of imidazo[2,1-*b*]thiazoles and imidazo[1,5-*b*]pyrazoles. Imidazo[2,1-*b*]thiazoles (**131**) and thiazolo[3,2-*a*]benzimidazoles (**132**) are obtained by cyclizing β-oxoethylthioimidazoles using strong dehydrating agents such as phosphorus oxychloride or ppa ⟨70IJC230, 83JHC419⟩. In some closely related work, tetrahydro and dihydro analogues (**134**) and (**136**) were prepared from β-oxoethylthioimidazolinium salts (**133**) and (**135**), respectively ⟨71KGS1128, 86EJM499, 94EJM309⟩ (Equations (43) and (44), Scheme 15, Equation

(45)). The chloroethylaminothiazoles (**137**) can be cyclized directly to imidazo[2,1-*b*]thiazole (**139**) albeit in low yield. Heating (**137**) in 2-propanol gives the bis(thiazolylamino)ethyl chloride (**138**) which cyclizes to give a better yield of (**139**) (Scheme 16). The mechanism proposed for the cyclization of (**138**) involves the initial formation of a dihydroimidazole ring and subsequent elimination of 2-aminothiazole ⟨93JCR(S)201⟩.



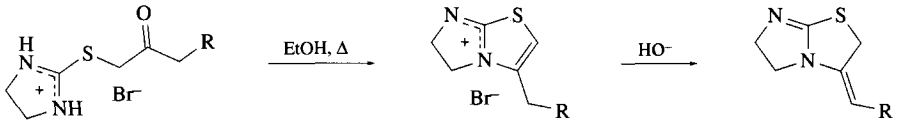
(43)

(**131**)



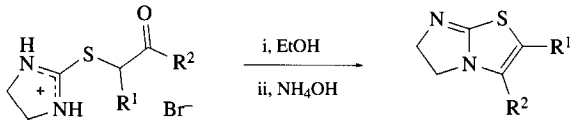
(44)

(**132**)



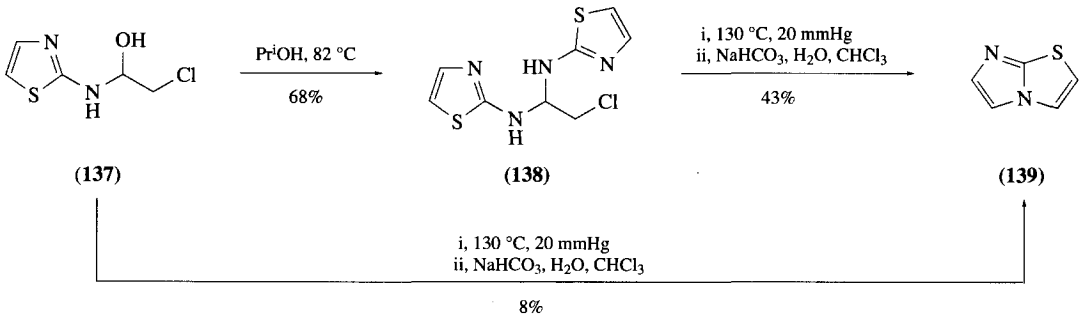
(**133**) (**134**)

Scheme 15



(45)

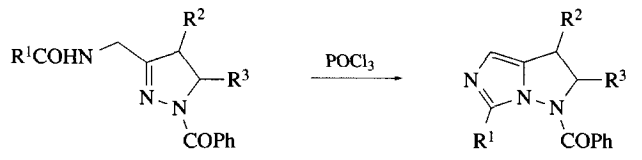
(**135**) (**136**)



(**137**) (**138**) (**139**)

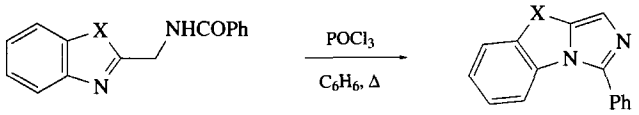
Scheme 16

Imidazo[1,5-*b*]pyrazoles (**141**) have been prepared by cyclodehydration of suitably substituted *N*-pyrazolylmethylamides (**140**) ⟨78JOC4841⟩ and similar dehydration reactions have been reported for substituted benzimidazoles and benzoxazoles (**142**) to give imidazo[5,1-*b*]benzimidazoles, e.g. (**143**; X = NMe), and imidazo[5,1-*b*]benzoxazoles, e.g. (**143**; X = O), respectively (Equations (46) and (47)) ⟨70CHE406, 70CHE486⟩.



(46)

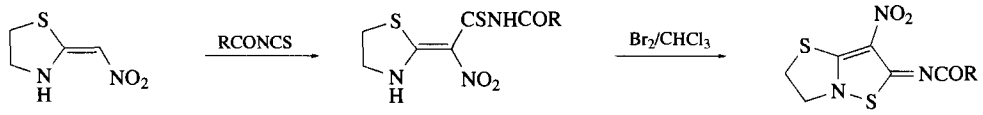
(**140**) (**141**)



(47)

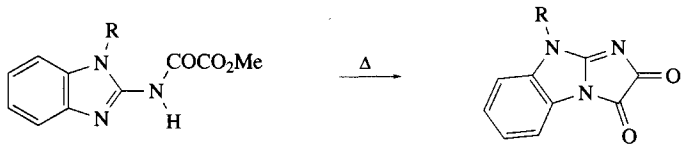
(142) (143)

Several other ring systems have also been prepared by this type of ring closure (Scheme 17, Equations (48) and (49)). Thiazolidines (**145**), prepared by reaction of the nitroalkene (**144**) with acylisothiocyanates, undergo oxidative cyclization to thiazolo[3,2-*b*]isothiazoles (**146**) ⟨82PIA463⟩. When 2-methoxalylaminobenzimidazoles (**147**) are heated to 240–250 °C they cyclize to imidazo[1,2-*a*]benzimidazoles (**148**). However, yields are low and these compounds are better prepared by the alternative cyclization described in 8.04.9.3.2 ⟨76CHE1151⟩. Cyclizations of 2-(chloroacetamido)-benzimidazoles to give 2-oxoimidazo[1,2-*a*]benzimidazoles have also been reported ⟨83S1033⟩. Intramolecular cyclization of 2-thiocyanatoalkylbenzimidazoles (**149**) occurs under mild conditions to give thiazolo[3,4-*a*]benzimidazoles (**150**) ⟨71CC1100⟩.



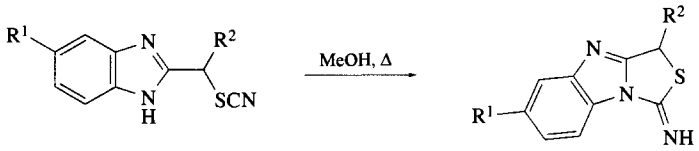
(144) (145) (146)

Scheme 17



(48)

(147) (148)



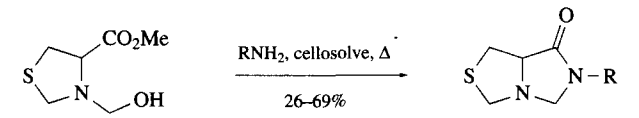
(49)

(149) (150)

8.04.9.2 (4 + 1) Syntheses

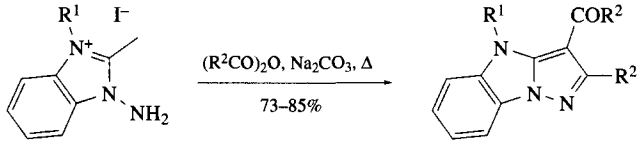
8.04.9.2.1 Type BC syntheses

Reaction of the tetrahydrothiazole (**151**) with primary amines gives imidazo[1,5-*c*]thiazoles (**152**) in moderate yields ⟨87EJM11⟩. Quaternary salts (**153**), obtained by alkylation of 1-amino-benzimidazoles, cyclize on heating with an anhydride and sodium carbonate to give pyrazolo[1,5-*a*]benzimidazoles (**154**) (Equations (50) and (51)) ⟨80CHE634⟩.



(50)

(151) (152)

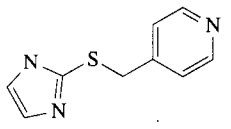


(51)

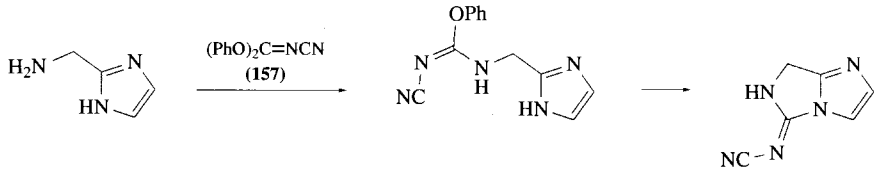
(153) (154)

8.04.9.2.2 Type CD syntheses

The imidazo[2,1-*b*]thiazole (**156**) was prepared by cyclization of the methylthioimidazole (**155**) with TFAA (Equation (52)) ⟨83JHC419⟩. The imidazo[1,5-*a*]imidazole (**159**) was obtained by reaction of 2-aminomethylimidazole with the 1-carbon synthon (**157**) ⟨84JHC753⟩. The overall reaction can be considered as a (4 + 1) synthesis, although it proceeds via the isolable intermediate (**158**), which undergoes a Type D (5 + 0) ring closure (Scheme 18).



(155) (156) (52)



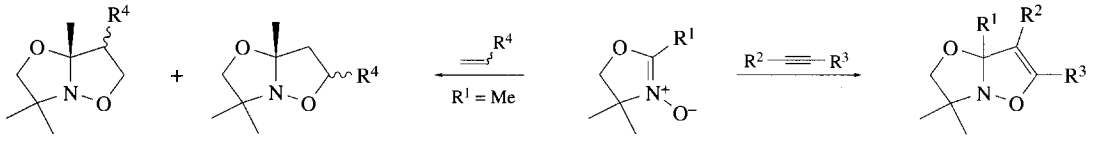
(158) (159)

Scheme 18

8.04.9.3 (3 + 2) Syntheses

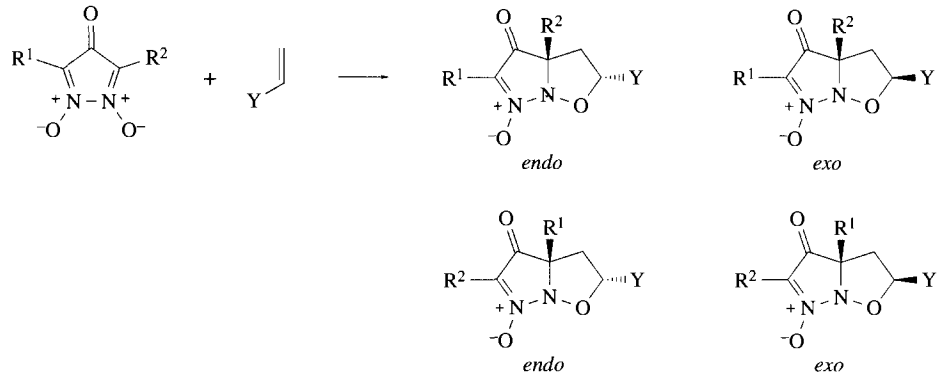
8.04.9.3.1 Type AC syntheses

Syntheses of this type are much less common than their type BD counterparts but a number have been reported and these are summarized in Schemes 19–21.

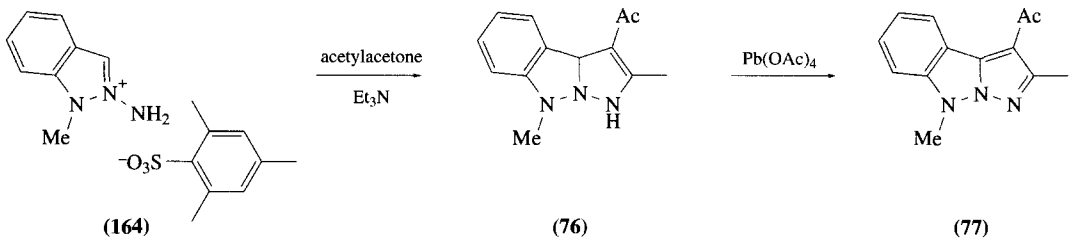


(163) (162) (160) (161)

Scheme 19



Scheme 20



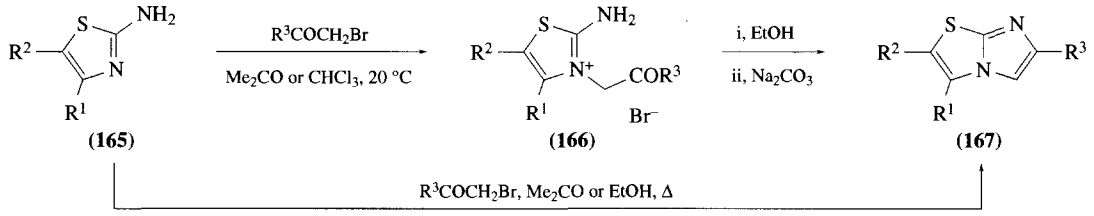
Scheme 21

Oxazoline *N*-oxides (**160**) react with a range of dipolarophiles to give oxazolo[3,2-*b*]isoxazoles. For example, (**160**) reacts with DMAD to give (**161**; $R^2 = R^3 = CO_2Me$) and with alkenes to give complex mixtures of diastereomeric regioisomers (**162**) and (**163**) ⟨84JOC3127⟩. Similar dipolar cycloaddition reactions of imidazoline-1-oxides with alkenes gave imidazo[1,2-*b*]isoxazole derivatives ⟨84BAP195⟩.

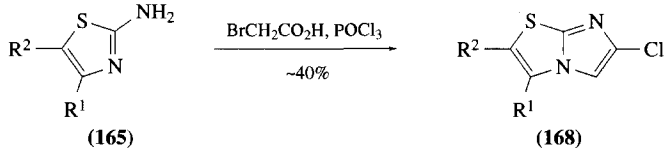
Pyrazolo[1,5-*b*]isoxazoles were prepared by cycloaddition of pyrazolone *N*,*N*-dioxides with electron-rich alkenes ⟨94JCS(P2)1337⟩. In general, mixtures of diastereomeric regioisomers are obtained, with the predominant formation of *exo* cycloadducts. The 1-methyl-2-aminoindazolium salt (**164**) reacted with acetylacetone in the presence of triethylamine to give the pyrazolo[2,3-*b*]indazole derivative (**76**), which was oxidized with lead tetraacetate to give (**77**) (Section 8.04.6.1) ⟨76CPB2267⟩.

8.04.9.3.2 Type BD syntheses

The main application of this type of ring closure is in the synthesis of the imidazo[2,1-*b*]thiazole skeleton. This ring system is generally prepared by reaction of 2-aminothiazoles (**165**) with α-halocarbonyl compounds (Scheme 22, Equation (53)). Although the reaction is formally a (3 + 2) type synthesis, intermediate thiazolium salts (**166**) can be isolated and their cyclization can be considered to be a type B (5 + 0) synthesis. Indeed, these reactions have been carried out both as one- or two-step processes. Imidazo[2,1-*b*]thiazoles (**167**; R = for example, alkyl, aryl, CO_2Et, CF_3) were prepared in a single step simply by heating the appropriate α-haloketone with a 2-aminothiazole in a suitable solvent ⟨86JHC1031, 87MI 804-01, 91EJM335⟩. Other workers have investigated the course of this reaction and isolated the intermediate thiazolium salts (**166**) ⟨89JCS(P1)643⟩. These studies showed that alkylation of the 2-aminothiazole by α-bromoketones occurs on the ring nitrogen rather than the amino group to give salts (**166**) which cyclize to give imidazo[2,1-*b*]thiazoles (**167**) having the R^3 substituent at position 6. A related synthesis of 6-chloro derivatives (**168**) involves treating (**165**) with bromoacetic acid and phosphoryl chloride ⟨91EJM335⟩.



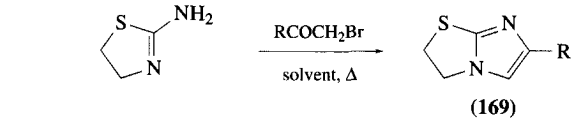
Scheme 22



(53)

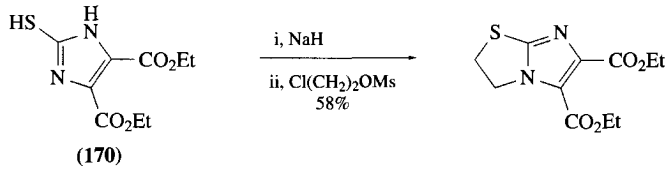
2,3-Dihydroimidazo[2,1-*b*]thiazoles (**169**) can be prepared from 2-amino-2-thiazoline and α-bromoketones in a similar manner to the corresponding fully unsaturated analogues ⟨80FES573, 89JHC525⟩. An alternative synthesis of this ring system involves cyclization of imidazole-2-thiols (**170**) with bifunctional reagents ⟨93JMC3618⟩. 5,6-Dihydroimidazo[2,1-*b*]thiazoles (**171**) may be

prepared by reaction of imidazoline-2-thiol with an α-halocarbonyl compound ⟨81JMC604⟩. Mixtures of diastereomeric imidazo[2,1-*b*]thiazoles (**172**) and (**173**) have been synthesized from benzimidazole-2-thiol and α,β-epoxy cyanoesters (Equations (54)–(57)) ⟨91EJM51⟩.



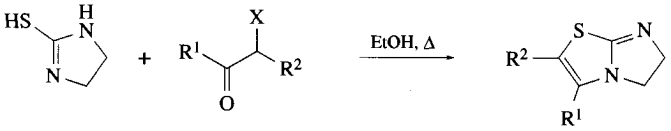
(54)

(169)



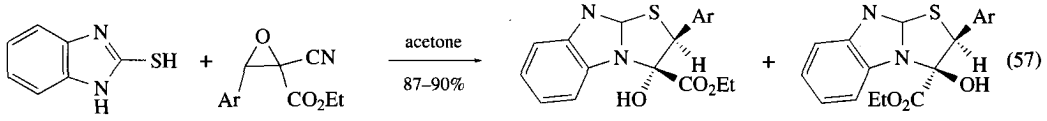
(55)

(170)



(56)

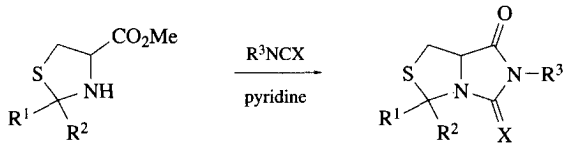
(171)



(57)

(172) (173)

Imidazo[1,5-*c*]thiazoles have also been prepared by this type of ring closure reaction. The amino acid derivative (**174**), prepared from cysteine, was shown to undergo cyclization reactions with both isocyanates and isothiocyanates to give (**175**; X = O,S) ⟨86EJM355, 94CPB1076⟩. In a similar type of reaction, imidazo[1,5-*c*]imidazoles (**177**) were obtained by treating dicyanoimidazoles (**176**) with methyl isocyanate ⟨82BCJ3586, 83JHC1103⟩ (Equations (58) and (59)).



(58)

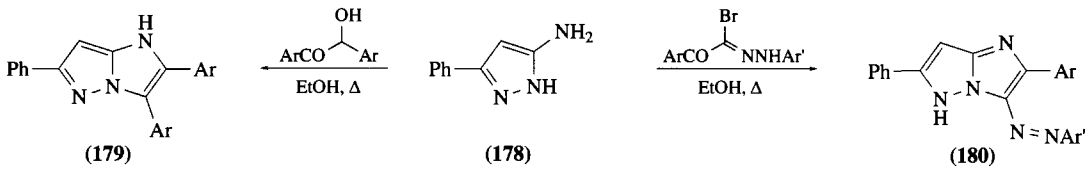
(174) (175)



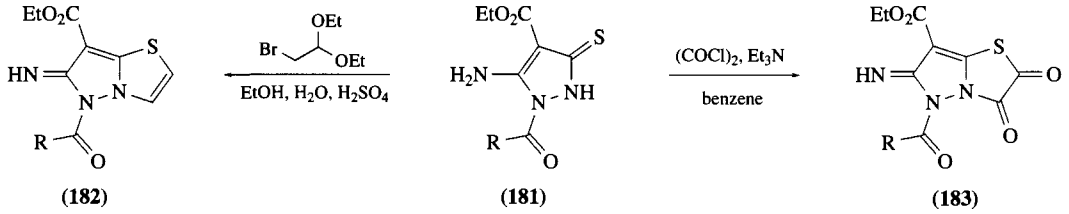
(59)

(176) (177)

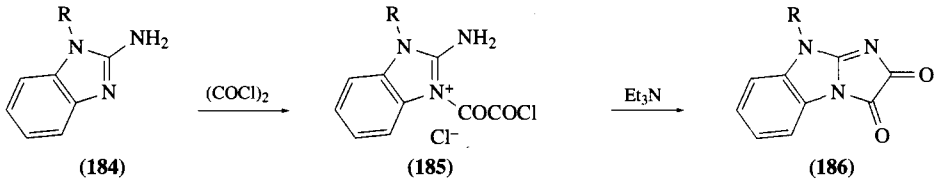
Various imidazo[1,2-*b*]pyrazoles have been prepared from 5-aminopyrazoles by this type of ring closure (Scheme 23). The aminopyrazole (**178**) reacts with α-hydroxyketones to give (**179**) ⟨84JHC945⟩ and with α-aroyl-*N*-arylhydrazidoyl bromides to yield 3-arylazo compounds (**180**) ⟨80JHC877, 83JHC639⟩. Pyrazolo[5,1-*b*]thiazoles (**182**) and (**183**) were obtained by treating 5-thioxopyrazolines (**181**) with bromoacetaldehyde diethyl acetal and oxalyl chloride, respectively (Scheme 24) ⟨82JPR(324)639⟩. Reaction of 2-aminobenzimidazoles (**184**) with oxalyl chloride gives isolable benzimidazolium salts (**185**) which cyclize on heating with base to give imidazo[1,2-*a*]benzimidazoles (**186**) (Scheme 25) ⟨76CHE1151⟩. Reaction of aminothiazole (**187**) with phenacyl bromide gave (**188**), which cyclized on heating to give the novel imidazo[1,2-*c*]thia^{IV}zole (**189**) (Scheme 26) ⟨82CL1491⟩.



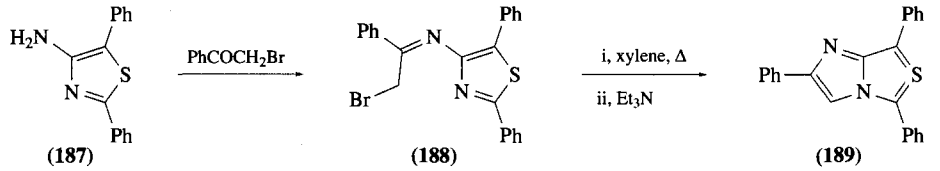
Scheme 23



Scheme 24



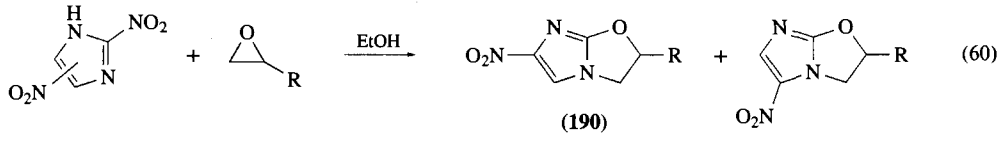
Scheme 25



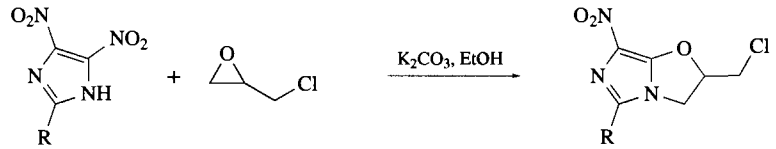
Scheme 26

8.04.9.4 (2 + 3) Syntheses

Syntheses of this type, involving the formation of bonds A and D, are comparatively rare and only two ring systems have been prepared by this route. Reactions of oxiranes with 2,4(5)- or 4,5-dinitroimidazoles afforded 2,3-dihydroimidazo[2,1-*b*]oxazoles or 2,3-dihydroimidazo[5,1-*b*]oxazoles respectively (Equations (60) and (61)) ⟨81JMC601, 89EJM631, 89PHA817⟩. With 2,4(5)-dinitroimidazoles, mixtures of regioisomeric products result, generally with the 6-nitro isomer (**190**) predominating. In the reaction of 4,5-dinitroimidazoles with epichlorohydrin, omission of the base resulted in the isolation of intermediate 1-(3-chloro-2-hydroxypropyl)imidazoles which could then be cyclized by heating with potassium carbonate in ethanol.



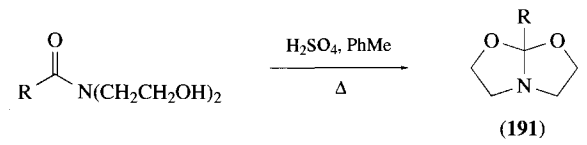
(60)



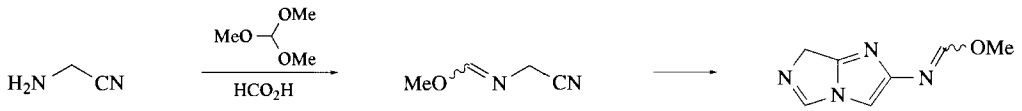
(61)

8.04.9.5 Simultaneous Formation of Both Rings

A number of bicyclic 5-5 systems have been prepared from acyclic precursors in reactions involving simultaneous formation of both rings and readers are directed to previous reviews for a discussion of the early literature. Recent reports of this type of synthesis are summarized in Equation (62), Schemes 27 and 28, and Equation (63).

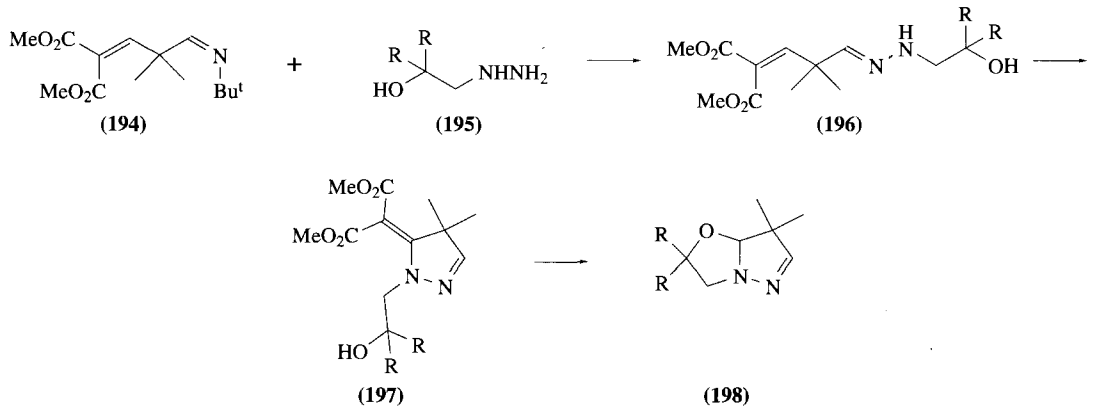


(191) (62)



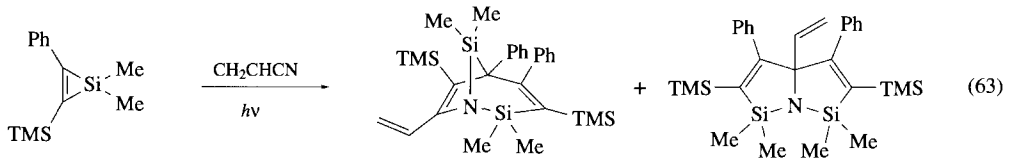
(192) (193)

Scheme 27



(194) (195) (196) (197) (198)

Scheme 28



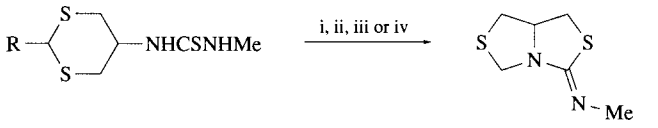
(199) (200) (201) (63)

Oxazolo[2,3-*b*]oxazoles (**191**; R = CF_3, *n*-C_7F_{15}) have been prepared by acid-catalyzed dehydration of *N*,*N*-bis(hydroxyalkyl)amides ⟨82JFC(21)359⟩. The imidazo[1,5-*a*]imidazole (**193**) was prepared by reaction of aminoacetonitrile with excess trimethylorthoformate in the presence of catalytic amounts of formic acid ⟨84JOC1212⟩. The reaction is believed to involve the initial formation of the imidate (**192**) which reacts successively with aminoacetonitrile and the *ortho*-ester to give the observed product. Pyrazolo[5,1-*b*]oxazoles (**198**) have been synthesized by reaction of hydrazino alcohols (**195**) with the Michael adduct (**194**), prepared from *N*-isobutylidene-*t*-butylamine and dimethyl-methoxymethylene malonate ⟨93JHC1529⟩. The reaction is believed to involve cyclization of the intermediate hydrazones (**196**) to give pyrazoles (**197**), which subsequently cyclize to the bicyclic system with loss of dimethyl malonate.

The 1,2-azasilolo[5,1-*e*]-1,2-azasilole (**201**) was obtained along with (**200**) by photochemical addition of the silacyclopropene (**199**) to acrylonitrile ⟨78CC80⟩. The mechanism for the formation of (**201**) is believed to involve two successive (2 + 2) cycloaddition processes.

8.04.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

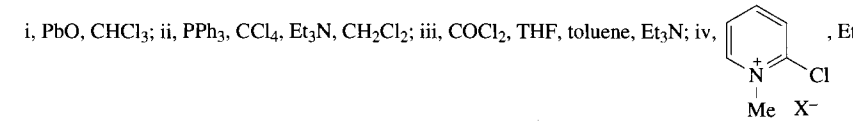
Under conditions normally applied to convert thioureas into the corresponding carbodiimides, 2-aryldithian-5-ylthioureas (**202**) rearrange to thiazolo[3,4-*c*]thiazoles (**203**) and (Equation (64)). The stereochemistry of the products is strongly dependent on the nature of the substituent R and the reagents used to effect the transformation. In some cases, the reaction conditions can be controlled to give mainly *cis*- or *trans*-fused products. The 1,3-dithian-5-amine (**204**) reacts with phosgene or trichloromethyl chloroformate to give the corresponding isocyanate which rearranges on heating to the thiazolothiazolone (**205**) (Scheme 29) ⟨84HCA1827⟩.



(64)

(202) (203)

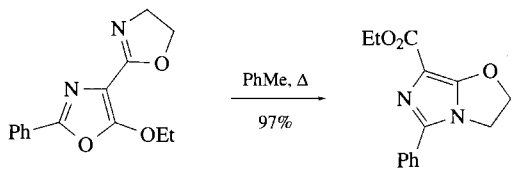
i, PbO, $CHCl_3$; ii, PPh_3, CCl_4, Et_3N, CH_2Cl_2; iii, $COCl_2$, THF, toluene, Et_3N; iv, , Et_3N, MeCN



(204) (205)

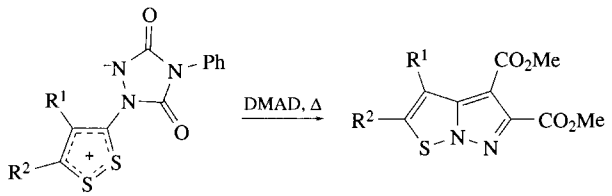
Scheme 29

The oxazolyloxazoline (**206**) rearranged on heating in toluene to give the imidazo[5,1-*b*]oxazole (**207**) ⟨75JOC1521⟩. Treatment of (**208**) with DMAD at 110 °C gave pyrazolo[1,5-*b*]isothiazole derivatives (**209**) ⟨82ZOR2626⟩.



(65)

(206) (207)



(66)

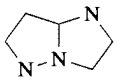
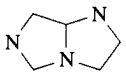
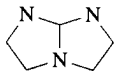
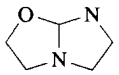
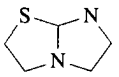
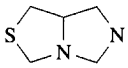
(208) (209)

8.04.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

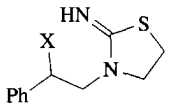
The imidazo[1,2-*b*]pyrazole, imidazo[1,5-*a*]imidazole, imidazo[1,2-*a*]imidazole, imidazo[2,1-*b*]oxazole, imidazol[2,1-*b*]thiazole, and imidazo[1,5-*c*]thiazole ring systems have all been prepared by more than one of the different types of synthetic route described in Sections 8.04.9 and 8.04.10. The various routes to each of these heterocycles are summarized in Table 4. For example, the imidazo[2,1-*b*]thiazole skeleton has been synthesized by (5 + 0) routes (types B, C, and D), (4 + 1) routes (types BC and CD), and by (3 + 2) routes (type BD) (for a summary of this classification see Scheme 10). By far the most common route to this system is the (3 + 2) ring closure discussed in Section 8.04.9.3.2. Tetramisole (**34**), the most important compound of this type in terms of commercial

application, has been synthesized via (5 + 0) type B chemistry involving intramolecular cyclizations of compounds (**210**; X = Cl, OH) and (**211**) ⟨66JMC545, 68JOC1350⟩ and also by (3 + 2) type BD chemistry by cyclization of (**212**) with bifunctional reagents. The latter approach provided an unambiguous stereospecific synthesis of the two optical isomers of tetramisole ⟨67TL1467⟩.

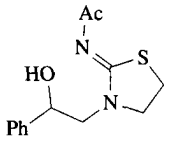
Table 4 Preparative routes to the most important bicyclic systems.

Ring system	*Name and number*[a]	*Route*[b]	*Ref.*
	Imidazo[1,2-*b*]pyrazole (**1**)	(5 + 0) B (5 + 0) C (3 + 2) BD	73JHC411, 78AQ795, 84JOC3534, 87MI 804-02 80JHC1413 80JHC877, 83JHC639, 84JHC945
	Imidazo[1,5-*a*]imidazole (**2**)	(5 + 0) B (5 + 0) D (4 + 1) CD	91S157 70CHE406, 70CHE486 84JHC753
	Imidazo[1,2-*a*]imidazole (**3**)	(5 + 0) B (5 + 0) D (3 + 2) BD	72JMC923, 86JHC541 76CHE1151, 83S1033 73CPB981, 76CHE1151
	Imidazo[2,1-*b*]oxazole (**8**)	(5 + 0) A (2 + 3) AD	86JCS(P2)689 81JMC601, 89EJM631
	Imidazo[2,1-*b*]thiazole (**15**)	(5 + 0) B (5 + 0) C (5 + 0) D (4 + 1) BC (4 + 1) CD (3 + 2) BD	68JOC1350, 94EJM309 88S261 83JHC419, 86EJM499, 93JCR(S)201, 94EJM309 79JHC1201 83JHC419 83JHC639, 86JHC1031, 87MI 804-01, 91EJM335
	Imidazo[1,5-*c*]thiazole (**16**)	(5 + 0) B (4 + 1) BC (3 + 2) BD	87EJM11 87EJM11 86EJM355, 94CPB1076

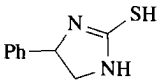
[a]Numbers refer to Table 1. [b]Synthetic routes are summarized in Scheme 10.



(**210**)



(**211**)



(**212**)

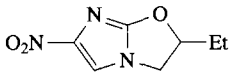
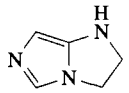
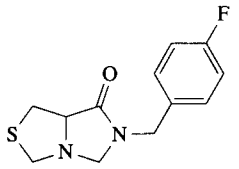
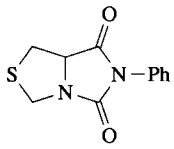
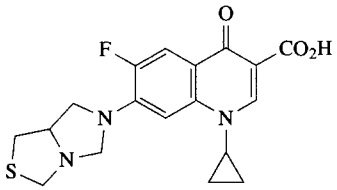
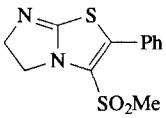
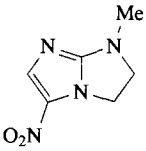
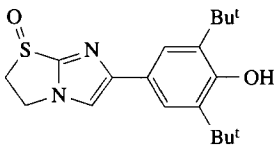
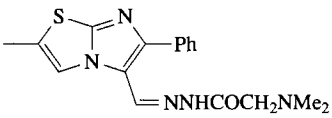
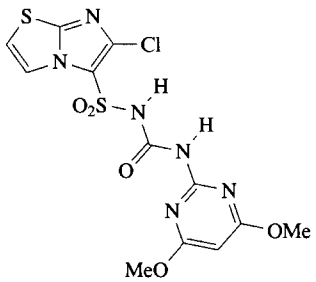
Of the reported routes to imidazo[1,5-*c*]thiazoles, the (4 + 1) type BC and (3 + 2) type BD routes are more generally applicable and involve milder reaction conditions. Imidazo[1,2-*b*]pyrazoles can be obtained by both (5 + 0) syntheses (types B and C) and (3 + 2) syntheses (type BD). The (3 + 2) synthesis allows access to a range of 2,3-disubstituted heterocycles whereas the (5 + 0) type B route allows simple analogues to be synthesized from already functionalized aminopyrazoles. The (5 + 0) type C synthesis is limited in scope due to the multistep route to the required precursors.

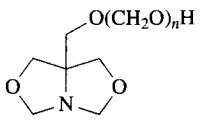
8.04.12 IMPORTANT COMPOUNDS AND APPLICATIONS

There have been numerous reports in the chemical, medical, and agrochemical literature of potential uses for compounds containing the type of 5-5 bicyclic ring system under discussion here. Many of these applications have also been patented. A number of compounds with biological activity were discussed in CHEC-1 ⟨84CHEC-I(6)973⟩ and a selection of more recently reported compounds is shown in Table 5. Compounds with other potential applications include oxazolo[3,4-*c*]oxazoles (**213**) as microbiocides, fungicides, and fuel additives ⟨76GEP(O)2617680, 77USP4022906, 88USP4725612⟩, pyrazolo[1,5-*b*]pyrazoles (**214**) as photographic couplers ⟨84MI 804-01⟩, and imidazo[2,1-*b*]thiazoles (**215**) as dyestuffs ⟨69BRP1159691⟩.

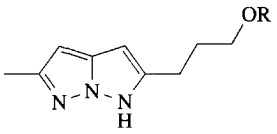
Undoubtedly, the imidazo[2,1-*b*]thiazole ring system has found the greatest number of claimed applications, and compounds containing this heterocyclic skeleton have been reported to possess a wide variety of biological activities. Work has shown imidazo[2,1-*b*]thiazole derivatives to have

Table 5 Compounds with biological activity.

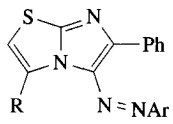
Compound	*Activity*	*Ref.*
	Antitubercular	89EJM631
	Antitumor	83AX(C)353, 87MI 804-02
	Immunomodulatory	87EJM11
	Antiepileptic	86EJM355
	Antibacterial	93MI 804-03
	Antiinflammatory	81JMC604
	Antiamoebic	84IJC(B)342
	Antiinflammatory	83CPB3179
	Diuretic	87EJM19
	Herbicidal	93MI 804-01



(213)

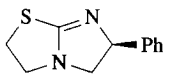


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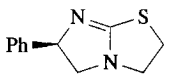


(215)

activity as anthelmintic agents ⟨91EJM51⟩, antihypertensives ⟨92MI 804-01⟩, antiinflammatories ⟨81JMC604, 82EJM271, 83CPB3179, 83FES533⟩, antitumor agents ⟨80FES896, 92JMC4634, 93MI 804-02⟩, diuretics ⟨87EJM19⟩, immunosuppressive agents ⟨86JMC386⟩, fungicides ⟨86EJM499⟩, and herbicides ⟨91CCC2436, 93MI 807-01⟩ in various *in vitro* and *in vivo* disease models. The most important compound containing this ring system, however, is DL-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (tetramisole) (**34**) which was first introduced in veterinary practice as an anthelmintic agent in 1965 and in human medicine in 1966. It was subsequently found to also possess immunoregulating properties. Both these activities reside mainly in the (*S*)-enantiomer, levamisole (**216**), which was first marketed in 1968. The (*R*)-enantiomer, dexamisole (**217**), is many times less potent ⟨B-79MI 804-01⟩. Although first introduced as a broad spectrum anthelmintic active against nematodal infections, levamisole is now recognized as an immunotherapeutic compound with antianergic properties. The pharmacological profile of levamisole is such that it has potential uses in such diverse disease areas as recurring infections, immune deficiency states, allergic and gastrointestinal disorders, and rheumatic diseases.



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8.05
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 2 : 1

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Universität Innsbruck, Austria

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8.05.1 INTRODUCTION

The (5,5)-fused bicyclic ring system with one fusion nitrogen atom and three additional heteroatoms in a 2 : 1 distribution over both five-membered rings (2N1) allows for a large variety of conceivable structures. The additional heteroatoms are mainly nitrogen, oxygen, and sulfur; a few representatives of (5,5)-fused ring system also contain phosphorus, selenium or silicon atoms.

The various types of (5,5) (2N1)-ring systems as retrieved are listed in Table 1. The topology (first column) refers to the positions of the heteroatoms, the position of the fusion nitrogen atom is given in parentheses. The heteroatoms are quoted in the order of their position (second column), a slash indicating the fusion nitrogen atom in either 4 or 7 position. Numbering of heteroatom positions and naming of the parent fused heterocycles follow Rule FR-5.4 of the "Recommendations for the Nomenclature of Fused and Bridged Fused Ring Systems" ⟨94MI1⟩. Application of the priority rules for heteroatom locations can result in different numbering but unequivocal naming for topologically equivalent structures, for example 13{4}7 and 134{7} (cf. last two rows in Table 1). The last two columns in Table 1 survey the (5,5) (2N1) systems covered in CHEC-I and CHEC-II.

A major review (2 parts) reports on syntheses of fused heterocycles ⟨87HC(47), 92HC(47)⟩ focusing on the type(s) of functional group(s) and/or ring atom(s) of the first ring involved in the formation of the second ring.

8.05.2 THEORETICAL METHODS

The π-electron density distribution of the tautomeric forms of 1*H*-, 3*H*-, and 4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**1**), (**2**), (**3**) has been determined by quantum mechanical methods. The result was compared with physical properties (chromatographic mobility, melting points, IR spectra, ^{1}H NMR spectra) of the unsubstituted compound (**1**) and the 3- and 4-methylsubstituted derivatives (**2**; R = Me), (**3**; R = Me). In addition, the basicity constants of these compounds have been used to estimate the tautomeric equilibrium of the 1*H*-, 3*H*-, and 4*H*-forms. By all methods applied (except

Table 1 (5,5) Fused ring systems (2N1): one fusion nitrogen atom, two heteroatoms in one fused ring, and one in the other ring.

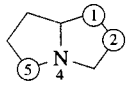
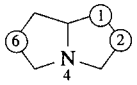
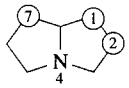
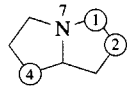
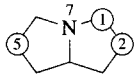
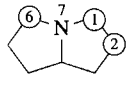
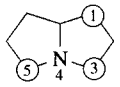
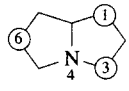
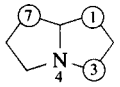
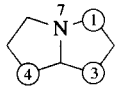
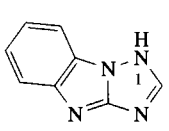
Topology of Heteroatom positions	*Heteroatoms in positional order*	*Name of (5,5) (2N1) system*	*CHEC-I*	*CHEC-II*
	ON/O	Isoxazolo[2,3-*d*][1,2,4]oxadiazole	+	
	ON/N	Pyrazolo[1,5-*d*][1,2,4]oxadiazole	+	
	NS/O	Isoxazolo[3,2-*c*][1,2,4]thiadiazole	+	
	NN/N	Pyrazolo[5,1-*c*][1,2,4]triazole	+	+
12{4}5	PS/N	Imidazo[1,2-*c*][1,3,2]thiazaphosphole	–	–
		[1,3,2]Thiazaphospholo[3,4-*a*]benzimidazole	?	+
	NN/S	Thiazolo[4,3-*c*][1,2,4]triazole	+	+
	NN/N	Imidazo[5,1-*c*][1,2,4]triazole		
12{4}6				
	ON/O	Oxazolo[3,2-*d*][1,2,4]oxadiazole	+	+
	ON/S	Thiazolo[3,2-*d*][1,2,4]oxadiazole		+
	ON/N	Imidazo[1,2-*d*][1,2,4]oxadiazole		+
	SSi/N	Imidazo[1,2-*d*][1,4,2]thiazasilole	+	
12{4}7	SS/N	Imidazo[2,1-*c*][1,2,4]dithiazole	+	+
		[1,2,4]Dithiazolo[4,3-*a*]benzimidazole	?	
	SN/N	Imidazo[1,2-*d*][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[4,3-*a*]benzimidazole	?	+
	NO/O	Oxazolo[2,3-*c*][1,2,4]oxadiazole		–
		[1,2,4]Oxadiazolo[3,4-*b*]benzoxazole	?	+
	NO/S	Thiazolo[2,3-*c*][1,2,4]oxadiazole		–
		[1,2,4]Oxadiazolo[3,4-*b*]benzothiazole		+
		Imidazo[2,1-*c*][1,2,4]oxadiazole	–	+
	NS/O	Oxazolo[2,3-*c*][1,2,4]thiadiazole		+
		[1,2,4]Thiadiazolo[3,4-*b*]benzoxazole		
	NS/S	Thiazolo[2,3-*c*][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[3,4-*b*]benzothiazole	?	+
		Imidazo[2,1-*c*][1,2,4]thiadiazole	–	+
		[1,2,4]Thiadiazolo[4,3-*a*]benzimidazole	?	+
	NN/O	Oxazolo[2,3-*c*][1,2,4]triazole	+	–
		[1,2,4]Triazolo[3,4-*b*]benzoxazole	?	+
	NN/S	Thiazolo[2,3-*c*][1,2,4]triazole	+	+
		[1,2,4]Triazolo[3,4-*b*]benzothiazole	?	+
	NN/Se	Selenazolo[2,3-*c*][1,2,4]triazole		+
	NN/N	Imidazo[2,1-*c*][1,2,4]triazole	+	+
		[1,2,4]Triazolo[4,3-*a*]benzimidazole	?	+
	NP/S	Thiazolo[3,2-*d*][1,4,2]diazaphosphole		+
		[1,4,2]Diazaphospholo[5,1-*b*]indazole	?	+
	SOS/	Thiazolo[3,2-*c*][1,2,3]oxathiazole		+
	NNS/	Thiazolo[3,2-*c*][1,2,3]triazole	+	+
	NNN/	[1,2,3]Triazolo[4,3-*b*]benzothiazole	?	+
		Imidazo[1,2-*c*][1,2,3]triazole	+	+
124{7}	PSN/	Imidazo[1,2-*c*][1,3,2]thiazaphosphole		+
		[1,4,2]Diazaphospholo[5,4-*b*]benzothiazole	?	+
	NNO/	Oxazolo[3,4-*c*][1,2,3]triazole		+
	NNN/	Imidazo[1,5-*c*][1,2,3]triazole	+	
125{7}				
	ONO/	Isoxazolo[2,3-*b*][1,2,5]oxadiazole	+	
	NNN/	Pyrazolo[1,5-*c*][1,2,3]triazole	+	
126{7}				
	NN/N	Pyrazolo[1,5-*b*][1,2,4]triazole		+
		[1,2,4]Triazolo[1,5-*b*]indazole	?	+
13{4}5				
	ON/S	Thiazolo[4,3-*b*][1,3,4]oxadiazole		+
	SN/S	Thiazolo[4,3-*b*][1,3,4]thiadiazole		+
	SN/N	Imidazo[5,1-*b*][1,3,4]thiadiazole		+
	NO/N	Imidazo[1,5-*b*][1,2,4]oxadiazole		+
13{4}6	NN/S	Thiazolo[3,4-*b*][1,2,4]triazole	+	+
	NN/N	Imidazo[1,5-*b*][1,2,4]triazole		+

Table 1 (continued)

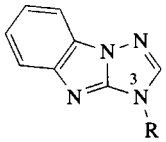
Topology of Heteroatom positions	*Heteroatoms in positional order*	*Name of (5,5) (2N1) system*	*CHEC-I*	*CHEC-II*
 13{4}7	ON/S	Thiazolo[4,3-*b*][1,3,4]oxadiazole		+
	ON/N	Imidazo[2,1-*b*][1,3,4]oxadiazole	+	+
	SN/S	Thiazolo[2,3-*b*][1,3,4]thiadiazole	+	+
	SN/N	Imidazo[2,1-*b*][1,3,4]thiadiazole	+	+
	SSi/O	[1,3,4]thiadiazolo[3,2-*a*]benzimidazole	?	+
		[1,3,4]thiazasilo[2,3-*b*]benzoxazole		+
	SSi/S	[1,3,4]thiazasilo[2,3-*b*]benzthiazole		+
	SeN/N	Imidazo[2,1-*b*][1,3,4]selenadiazole	+	
	NP/S	Thiazolo[2,3-*b*][1,3,4]diazaphosphole		+
 134{7}	ONO/	Oxazolo[3,2-*b*][1,2,4]oxadiazole		+
	ONN/	Imidazo[1,2-*b*][1,2,4]oxadiazole	+	+
	SSN/	Imidazo[1,2-*d*][1,4,2]dithiazole	+	
	SNS/	Thiazolo[3,2-*b*][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[3,2-*b*]benzothiazole	?	+
	SNN/	Imidazo[1,2-*b*][1,2,4]thiadiazole		+
		[1,2,4]Thiadiazolo[2,3-*a*]benzimidazole	?	+
	NNO/	Oxazolo[3,2-*b*][1,2,4]triazole	+	+
		[1,2,4]Triazolo[5,1-*b*]benzoxazole	?	+
	NNS/	Thiazolo[3,2-*b*][1,2,4]triazole	+	+
		[1,2,4]Triazolo[3,2-*b*]benzothiazole	?	+
	NNN/	Imidazo[1,2-*b*][1,2,4]triazole	+	+
		[1,2,4]Triazolo[1,5-*a*]benzimidazole	?	+

UV spectra which give inconclusive results) the 4*H*-tautomer (**3**; R = H) appears to predominate over the 3*H*-form (**2**; R = H) (by 2–3 orders of magnitude) while no signs were obtained indicating the existence of the 1*H*-form (**1**) ⟨89KGS209⟩.

In an application oriented study the molecular electrostatic potential of 6-(methoxycarbonylamino)imidazo[2,1-*b*][1,3,4]thiadiazole (**4**) (among other heterocyclic compounds) has been calculated, and based on this a structure–activity relationship was established ⟨89FES671⟩.

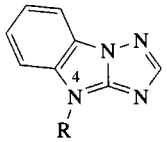


(1)

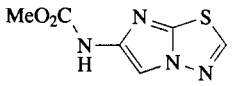


(2)

R = H, Me



(3)



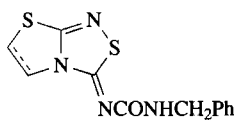
(4)

8.05.3 STRUCTURE

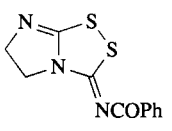
8.05.3.1 X-ray

The following structures have been assigned or confirmed by x-ray crystal analysis.

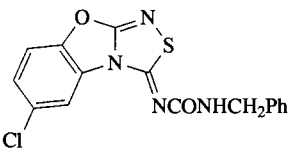
12{4}7: *NS/S* 3-(Benzylcarbamoylimino)-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (**5**) and its 5,6-dihydro derivative ⟨94T7019⟩; *SS/N* 3-(benzoylimino)-5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**6**) ⟨89MI 805-03⟩; *NS/O* 3-(benzylcarbamoylimino)-6-chloro-3*H*-[1,2,4]thiadiazolo[3,4-*b*]benzoxazole (**7**) ⟨94T7019⟩.



(5)

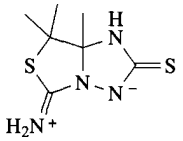


(6)

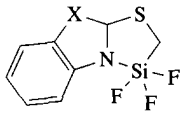


(7)

13{4}6: *NN/S* Anhydro 5-iminium-7,7,7a-trimethyl-2,3,5,6,7,7a-hexahydrothiazolo[3,4-*b*][1,2,4]-triazole-2-thione hydroxide (**8**) ⟨93TH 805-01, 95FES379⟩.



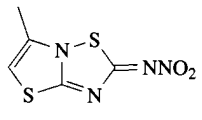
(**8**)



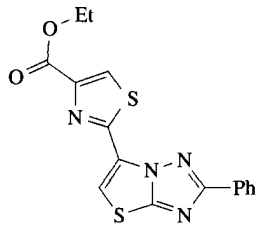
(**9**) X = O
(**10**) X = S

13{4}7: *SSi/O* 3,3,3-Trifluoro-3,9a-dihydro-2*H*-[1,3,4]thiazasilano[2,3-*b*]benzoxazole (**9**) and *SSi/S* 3,3,3-trifluoro-3,9a-dihydro-2*H*-[1,3,4]thiazasilano[2,3-*b*]benzthiazole (**10**) ⟨93JOM(461)27⟩.

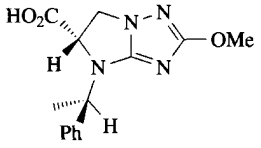
134{7}: *SNS/* 6-Methyl-2-nitroimino2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazole (**11**) ⟨84CPB3483⟩; *NNS/* 2-phenyl-5-[(4-ethoxycarbonyl)thiazol-2-yl]thiazolo[3,2-*b*][1,2,4]triazole (**12**) ⟨85AX(C)1238⟩; and *NNN/*5,6-dihydroxy-2-methoxy-4-[(1*R*)-phenylethyl]-4*H*-imidazo[1,2-*b*][1,2,4]triazole-(5*S*)-carboxylic acid (**13**) ⟨92TA51⟩.



(**11**)



(**12**)



(**13**)

8.05.3.2 NMR Data

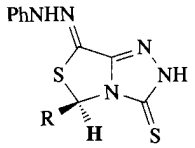
8.05.3.2.1 Proton NMR

The (5,5) (2N1)-fused heterocyclic system contains four ring-carbon atoms, the fusion carbon atom and two and one carbon atoms in the respective five-membered rings.

(i) Saturated rings with CH_2 and CH groups

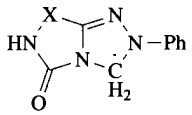
The ^{1}H NMR data refer to at least one saturated five-membered ring moiety.

12{4}6: *NN/S* 7-Phenylhydrazono-2,3,5,7-tetrahydrothiazolo[4,3-*c*][1,2,4]triazole-3-thione (**14**) ⟨90AP(323)57⟩ and *NN/N* 2-phenyl-3,5,6,7-tetrahydro-2*H*-imidazo[5,1-*c*][1,2,4]triazoles (**15**) ⟨83JHC189⟩.



(**14**)

R = H δ 5-C**H** 5.5–5.6
R = Ph δ 5-C**H** 5.2
(DMSO-d_6)



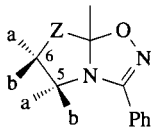
(**15**)

X = CH_2 δ 7-C**H** 6(d); δ 3-C**H** 6.2 (d)
X = C=CH_2 δ 3-C**H** 3.6–3.8(s)
($CDCl_3$)

12{4}7: *ON/O* 7a-Methyl-3-phenyl-5,6-dihydro-7a*H*-oxazolo[3,2-*d*][1,2,4]oxadiazoles (**16**) and *ON/S*-thiazolo[3,2-*d*][1,2,4]oxadiazoles (**17**) (Table 2) ⟨92T7703⟩; *ON/N* 3-phenyl-7,7a-dihydro-4*H*-imidazo[1,2-*d*][1,2,4]oxadiazoles (**18**) (Table 3) ⟨83JCR(S)230⟩; *SS/N* 3-benzoylimino-5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**19**) ⟨86S751⟩; *NO/O* 3*H*-[1,2,4]oxadiazolo[3,4-*b*]benzoxazole

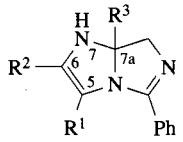
(**20**); *NO/S* 3*H*-[1,2,4]oxadiazolo[3,4-*b*]benzothiazole (**21**) ⟨93PS(85)183⟩; *NS/S* 3-(benzylcarbamoylimino)-5,6-dihydro-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (**22**) ⟨94T7019⟩; *NN/O* 2,3-dihydro[1,2,4]-triazolo[3,4-*b*]benzoxazoles (**23**); *NN/S* 2,3-dihydro[1,2,4]triazolo[3,4-*b*]benzothiazoles (**24**) (Table 4) ⟨93PS(85)183⟩; *NN/S* 3-aryl-5,6-dihydrothiazolo[1,2-*c*][1,2,4]triazoles (**25**) (Table 5); *NN/S* 3-aryl-5,6-dihydrothiazolo[1,2-*c*][1,2,4]triazol-5-one (**26**) ⟨90JIC226⟩; *NN/N* 5,6-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazo [2,1-*c*][1,2,4]triazol-2-one and -3-thione (**27**), 3-methylthio-5,6-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*c*][1,2,4]triazole (**28**) ⟨86SUL51⟩; and *NP/S* 3-alkoxycarbonyl-5,6-dihydrothiazolo[3,2-*d*][1,2,4]diazaphosphole (**29**) ⟨92S267⟩.

Table 2 Proton NMR signals for compounds (**16**) and (**17**).

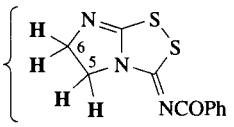
	Z	*δ*[a] *5-CH*	*δ*[a] *6-CH*	*J* (Hz)
	O	a = Me b = Me	a 3.58 b 3.78	$^4J_{6a,5Me}$ 0.8; $^2J_{6a,6b}$ 8.5
	O	a 3.37 b 3.65	a 3.91 b 3.53	$^2J_{5a,5b}$ 11.0; $^3J_{5a,6a}$ 6; $^3J_{5a,6b}$ 11.5; $^3J_{5b,6a}$ 1; $^3J_{5b,6b}$ 5; $^2J_{6a,6b}$ 8
(16) Z = O **(17)** Z = S	S	a 2.66 b 2.81	a 4.19 b 3.26	$^2J_{5a,5b}$ 10.5; $^3J_{5a,6a}$ 5.7; $^3J_{5a,6b}$ 12.2; $^3J_{5b,6a}$ 0; $^3J_{5b,6b}$ 5.8; $^2J_{6a,6b}$ 12.9

[a]The assignment of chemical shifts can be reversed.

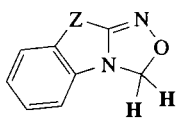
Table 3 Proton NMR shifts and coupling constants for compounds (**18**).

	R[1], *δ 5-CH*	*R*[2], *δ 6-CH*	*δ 7-NH*	*R*[3], *δ 7a-CH*	*J* (Hz)
	H 7.30	H 7.14	12.21	H 7.93	$^3J_{5,6}$ 1; $^4J_{5,7a}$ 0.7; $^4J_{6,7a}$ 0.7
	H 7.09	H 6.98	12.48	Me	$^3J_{5,6}$ 1.5
	Ph	Ph	12,27	H 7.94	
	H 6.84	Me	12.30	H 7.59	$^3J_{5H,6Me}$ 0.8; $^4J_{5,7a}$ <0.5
	Me	H 6.98	12.05	H 7.78	$^3J_{5H,6Me}$ 0.8; $^4J_{6,7a}$ 1.1
	H 7.25	Ph	12.15	H 7.95	
(18)	Ph	H[a]	12.18	H 7.80	$^4J_{6,7a}$ 0.9
	H 6.70	Me	12.34	Et	$^3J_{5H,6Me}$ 0.8
	Me	H 6.68	12.07	Et	$^3J_{5H,6Me}$ 0.8

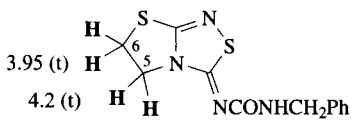
Solvent: DMSO-d_6. [a] Overlapped by aromatic protons.

4.1, m (DMSO-d_6) 

(19)

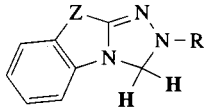


(20) Z = O, δ3-CH_2 = 5.35 (s), $CDCl_3$
(21) Z = S, δ3-CH_2 = 5.50 (s), $CDCl_3$

3.95 (t) 4.2 (t) 

(22)
(DMSO-d_6)

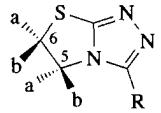
Table 4 Proton NMR shifts for compounds (**23**) and (**24**).

	Compound	*Z*	*R*	*δ 3-CH_2*	*Solv.*[a]
	**(23)**	O	H	5.1–6.0 (br)	D
		O	Ph	6.5 (s)	C
	(24)	S	H	5.5 (s)	D
		S	Ph	6.25 (s)	D

[a]C = $CDCl_3$; D = DMSO-d_6.

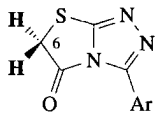
124{**7**}: *NNS/* 3-Aroyl-5,6-dihydrothiazolo[3,2-*c*][1,2,3]triazoles (**30**) ⟨88851⟩ and *NNN/* 3-aroyl-5,6-dihydro-4*H*-imidazo[1,2-*c*][1,2,3]triazoles (**31**) ⟨92JOC184⟩.

Table 5 Proton NMR data for compounds (**25**).

	R	δ^a 5-CH	δ^a 6-CH	J[Hz]	Solv.[a]	*Ref.*
 (**25**)	aryl	5a, 5b, 6b 3.35–4.88	6a = Me (m, m, m)		C, D	83PJC567
	Ph	5a = Me b 4.95 (ddq)	a 4.37 (dd) b 3.53 (dd)	$^3J_{5b,5Me}$ 6.8; $^3J_{5b,6a}$ 7.5; $^3J_{5b,6b}$ 2.5; $^2J_{6a,6b}$ 11.0	C	84T2703
	aryl	4.82 (t) 4.79 (t)	4.49 (t) 4.36 (t)		T T	911JC(B)38 83IJC(B)249
	Ph	3.9–4.6 (m)			C	84CPB5040
	aryl	3.84 (s)	3.75 (s)		C	86JHC1439

[a]The assignment of chemical shifts can be reversed. [b]C = $CDCl_3$; D = DMSO-d_6; T = trifluoroacetic acid.

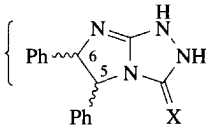
4.15 (s)



(**26**)

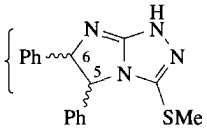
X = S 5.2 (m)
X = O 5.3 (m)

(DMSO-d_6)



(**27**)

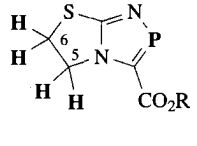
5.2, m
(DMSO-d_6)



(**28**)

δ3.88-3.95 (t)

δ4.59-4.62 (td)



(**29**)

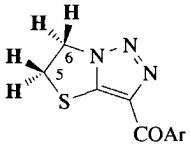
δ(^{31}P)252.7–253.6 ($CDCl_3$)

$^3J_{5h,6H}$ = 7.6–8.0
$^4J_{5h,2P}$ = 2.8–2.9

δ 6-C**H** 4.10–4.20 (t)

δ 5-C**H** 4.60–4.70 (t)

($CDCl_3$)

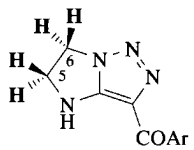


(**30**)

δ 5,6-C**H** 4.25–4.26, 4.44–4.46

7 Hz

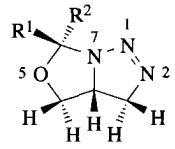
(DMSO-d_6)



(**31**)

125{**7**}: *NNO*/ *cis*- and *trans*-6-isopropyl-3,3a,4,6-tetrahydrooxazolo[3,4-*c*][1,2,3]triazole (**32**) (Table 6) ⟨88JOC27⟩.

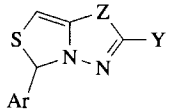
Table 6 Proton NMR signals for compounds (**32**).

Solvent: $CDCl_3$		cis: R^1 = H, R^2 = iPr δ CH	trans: R^1 = H, R^2 = iPr δ CH
 (**32**)	3-CH	3.41 (dd) J 4.0, 7.8	3.11 (dd) J 7.4, 7.4
	3-CH	3.75 (m)	3.99 (dd) J 7.2, 7.4
	3a-CH	3.77 (m)	3.76 (m)
	4-CH	4.47 (dd) J 2.5, 5.5	4.17 (dd) J 8.8, 9.0
	4-CH	4.52 (dd) J 2.3, 5.5	4.52 (dd) J 6.7, 8.8
	6-CH	4.46 (d) J 2.2	4.46 (d) J 7.2

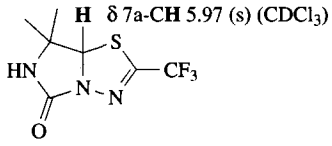
13{**4**}**6**: *ON*/*S* 2-Amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,3,4]oxadiazoles (**33**); *SN*/*S* 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles (**34**); *NN*/*S* 5-aryl-2-sulfonyl-1*H*,5*H*-imidazo[3,4-*b*][1,3,4]-

thiadiazoles (**35**) (Table 7); *SN/N* 5,6,7,7a-tetrahydro-7,7-dimethyl-2-trifluoromethylimidazo-[4,3-*b*][1,3,4]thiadiazol-5-one ⟨90HCA492⟩.

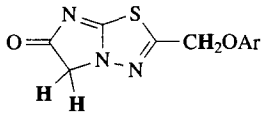
Table 7 Proton NMR signals for compounds (**33**)–(**35**).

	Z	*Y*	*δ 5-CH (s)*	*δ 5-CH*	*Solv.*[4]	*Ref.*
	O	NH_2	6.27–6.30	arom[b]	C/D	94MI 805-01
		NHAr	6.66–7.96		C/D	92MI 805-02
	S	NH_2	2.8	4.5(s)	C	91JIC144
			6.23–6.24	arom[b]	C/D	94MI 805-01
		NHAr	6.70–7.98		C/D	92MI 805-02
(**33**) Z = S	NH	SH	6.24–6.26	arom[b]	C/D	94MI 805-01
(**34**) Z = O	NAr		6.62–7.94		C/D	92MI 805-02
(**35**) Z = N						

[a]C = $CDCl_3$; D = DMSO-d_6. [b]arom: signal overlapping with aromatic proton signals.



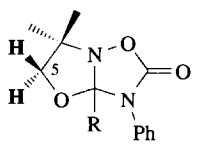
(**36**)



(**37**) δ 4.8–5.4 (DMSO-d_6)

13{**4**}**7**: *SN/N* 2-Aryloxymethyl-5,6-dihydroimidazo[2,1-*b*][1,2,4]thiadiazole (**37**) ⟨89IJC(B)358⟩. **134**{**7**}: *ONO/* 3a-substituted 6,6-dimethyl-2-phenyl-3,3a,5,6-tetrahydro-2*H*-oxazolo[3,2-*b*][1,2,4]oxadiazol-2-ones (**38**) (Table 8); *NNO/* 5,6-dihydrooxazolo[3,2-*b*][1,2,4]triazole (**39**); *NNS/* 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazoles (**40**; *NNN/* 5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]triazoles (**41**) (Table 9); *NNS/* 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-6-ones (**42**); *NNN/* 5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-ones (**43**) (Table 10); and *NNN/* 5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]triazol-5-ones (**44**) ⟨85JHC385⟩.

Table 8 Proton NMR signals for compounds (**38**).

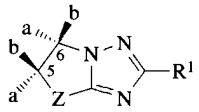
	R	*δ 5-CH*	$^2J_{5,5}$ (Hz)	*Solv.*[a]	*Ref.*
	Me	3.81 (d), 3.88 (d)	9	B	84JOC3127
	Et	3.81 (d), 3.87 (d)	9	C	84JOC3127
(**38**)	Ph	4.09 (s)		C	85JOC3076

[a]B = benzene-d_6; C = $CDCl_3$.

(ii) CH groups in unsaturated rings

12{**4**}**7**: *ON/N* Compounds (**18**) are listed in Table 3 (see Section 8.05.3.2.1 (i)); *NS/S* 3-imino-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles (**45**) (Table 11); *NN/S* thiazolo[2,3-*c*][1,2,4]triazoles (**46**) (Table 12).

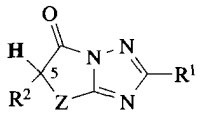
Table 9 Proton NMR signals for compounds (**39**)–(**41**).

	Z	R^1	δ^a *5-CH*	δ^a *6-CH*	*J* (Hz)	*Solv.*[a]	*Ref.*
	O	H	a = Me;	a 4.22 (dd)	9.4, 8.9, 7.4	C, D	90T3211
		δ 7.57 (s)	b 3.88 (dd)	b 5.40–5.75 (m)			
	S	Ph	a 4.51	a = OH;		C	87AP(320)528
			b 3.87	6.32			
	S	NH_2	CH_2CH_2 3.81 (t),	4.18 (t)		C	88S261
	S	aryl	3.70 (s)	3.86 (s)		C	86JHC1439
	S	aryl	4.29 (t)	4.80 (t)		T	83IJC(B)249
	S	aryl	4.49 (t)	4.82 (t)		T	91IJC(B)38
	NH	OMe	a = CO_2H	a 4.02 (dd)	9, 9, 6	C	92TA51
			b 4.18 (dd)	b 4.75 (dd)			
	N-CH_2Ph	OMe	a = CO_2Et	a 4.04 (dd)	9, 9, 6	C	92TA51
			b 4.17 (dd)	b 4.35 (dd)			
	N-CH_2Ph	OMe	a = CO_2H	a 3.93 (dd)	9, 9, 6	C	92TA51
			b 4.27 (dd)	b 4.46 (dd)			
	N-CH(Ph)Me	OMe	a = CO_2H	a 3.92 (dd)	9, 9, 6	C	92TA51
			b 4.28 (dd)	b 4.67 (dd)			

(**39**) Z = S
(**40**) Z = O
(**41**) Z = N

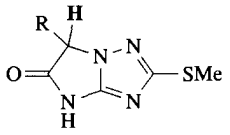
[a] C = $CDCl_3$; D = DMSO-d_6; T = trifluoroacetic acid.

Table 10 Proton NMR signals for compounds (**42**) and (**43**).

	Z	R^1	R^2	δ (ppm) *5-CH*	*Solv.*[a]	*Ref.*
	S	Ph	H	5.27	D	83JPR869
	S	Ph	Me	4.6	D	83JPR869
	S	aryl	H	4.84	T	91IJC(B)38
	NH	NH_2	Et	3.79	D	93T165
	NH	NH_2	CH_2Ph	4.11–4.17	D	93T165
	NH	NH_2	CH_2CO_2Et	4.27–4.46	D	93T165

(**42**) Z = S
(**43**) Z = NH

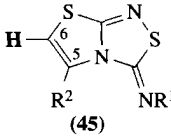
[a] D = DMSO-d_6; T = trifluoroacetic acid.



(**44**)

R =H, δ 6–CH = 4.66 (s), (DMSO-d_6)
R =Me, δ 6–CH = 4.95 (q), (DMSO-d_6)

Table 11 Proton NMR signals for compounds (**45**).

	R^1	R^2 δ *5-CH*	δ *6-CH*	$^3J_{5,6}$ (Hz)	*Solv.*[a]	*Ref.*
	aryl	H 7.33 (d)	6.45 (d)	5	C	86S1027
	aryl	aryl	6.72–6.9 (s)		C/D	88IJC(B)501
	CONHCH$_2$Ph	H 7.52 (d)	7.28 (d)	5	D	94T7019

(**45**)

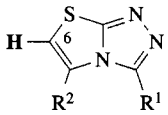
[a] C = $CDCl_3$; D = DMSO-d_6.

A compilation of δ 6-CH data from the isomers of 12{4}7-NN/S and δ 5-CH from 134{7}-NNS/ (see below) permits comparison between both series ⟨87IJC(B)526⟩. With similar substituents and in the same solvent the latter compounds display the 5-CH signal further downfield. The typical range for δ 6-CH of aryl-substituted 12{4}7-NN/S compounds (**46**) is 6.70–7.10 as compared to 7.00–7.90 of 5-CH of 134{7}-NNS/ (**58**) ⟨87IJC(B)526⟩.

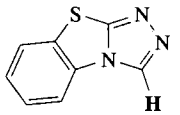
NN/S [1,2,4]Triazolo[3,4-*b*]benzothiazole (**47**) ⟨84KGS40⟩; and *NP/S* 3-ethoxy-

carbonylthiazolo[3,2-*d*][1,4,2]diazaphosphole (**48**) and 3-*e*thoxycarbonyl-1-methylthiazolo[3,2-*d*][1,4,2]diazaphospholium methylsulfate (**49**) ⟨92S267⟩.

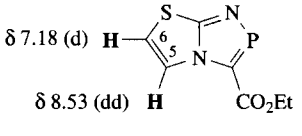
Table 12 Proton NMR signals for compounds (**46**).

	R[1]	*R*[2]	*δ 6-CH*	*Solv.*[a]	*Ref.*
 (**46**)	H; δ 8.64	$CH_2P^+Ph_3\ Cl^-$	6.62 (s)	D	85JHC1185
	Me	Me	6.14	C	87IJC(B)526
	Me, Ph, het	CH_2CO_2Et	7.20–7.67	D	89LA75
	aryl	aryl	7.05	T	83IJC(B)249
			6.70–7.70	C, D, T	87PJC547
			7.45–7.90	D	91EJM929
			6.97	C	92JIC268
			6.90–7.10	C, C/T, T	87IJC(B)526
	Ph	CO_2Et	8.50	T	91KGS537
	Ph	het	7.25	C	94IJC(B)579

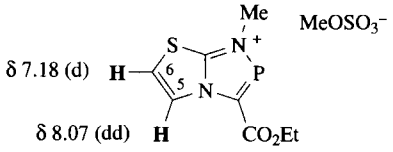
[a]C = $CDCl_3$; D = DMSO-d_6; T = trifluoroacetic acid.



(**47**) δ3-CH 9.55 (pyrinide-d_5)

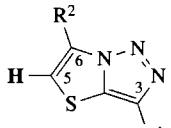


(**48**)

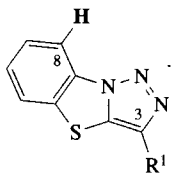


(**49**)

Table 13 Proton NMR signals for compounds (**50**).

	R[1]	*δ 3-CH*	*δ 5-CH*	*R*[2]	*δ 6-CH*	*Solv.*[a]	*Ref.*
 (**50**)	H	7.5	7.15	H	8.0$J_{5,6}$ 4 Hz	C	91T2851
	Me		7.1	H	7.95$J_{5,6}$ 4 Hz	C	
	Ph		8.30	H	8.95	C	
	H	7.65–7.8	6.95–7.25	$SiMe_3$, aryl, het, cycloalkyl		C	
	Me		6.38–7.2	$SiMe_3$, alkyl		C	
	H	7.3	5.7	H	6.9	B	92JHC713
		7.8	7.3		8.1	C	
		7.95	7.75		8.6	D	
	H	7.8	6.82	Me		C	
	CO_2Et		5.4	Me		B	
			6.95			C	
			7.1			A	
			7.5			D	

[a]A = CD_3CN, B = C_6D_6 C = $CDCl_3$;.20 = DMSO-d_6.

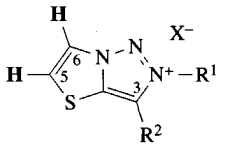


(**51**)

R^1 = H δ3-CH 7.87 (dd); δ8-CH 8.25 (dd) ($CDCl_3$)
R^1 = CO_2Et δ3-CH 7.75 (dd); δ8-CH 8.14 (dd) (CD_2Cl_2)

124{7}: *NNS*/ Thiazolo[3,2-*c*][1,2,3]triazoles (**50**) (Table 13); *NNS*/ [1,2,3]triazolo[4,3-*b*]benzothiazoles (**51**) (see Section 8.05.3.2.1 (iii)) ⟨92JHC713⟩; and *NNS*/ 2,3-disubstituted thiazolo[3,2-*c*][1,2,3]triazolium salts (**52**) (Table 14).

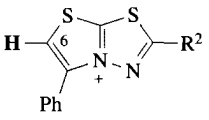
Table 14 Proton NMR signals for compounds (**52**).

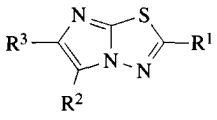
	R^1	R^2	X	δ 5-*CH*	δ 6-*CH*	$J_{5,6}$	*Solv.*[a]	*Ref.*
 (**52**)	Me	H δ 8.96 (d)	I	8.29 (d)	8.94 (d)	4.15 $J_{3,6}$ 0.74	D	91T2851
	Me	Me	I	8.33 (d)	8.91 (d)	4.15	D	91T2851
	CH_2CO_2Me	Me	Br	7.20, 7,90		3	C	94H2017

[a] C = $CDCl_3$; .20 = DMSO-d_6.

13{4}6: *ON/S, SN/S, NN/S* See Section 8.05.3.2.1(i).

13{4}7: *SN/S* 2-Amino-5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazolium salts (**53**) and betaines with the negative charge at the 2-amino nitrogen atom (**54**) and further remote in the side chain at position 2 (**55**): δ 6-CH reflects the charge distribution of the molecules ⟨92T1282⟩; *SN/N* imidazo[2,1-*b*][1,4,4]thiadiazoles (**56**). Only few reports give data for R^1 = H, ⟨85FES34, 85FES190⟩ and R^3 = H ⟨86H(24)379⟩. The majority of reported shift data refer to R^2 = H ⟨83JHC1003, 84FES585, 85FES34, 85FES190, 86CCC2214, 88ZOR192, 89IJC(B)500, 89JIC118, 90IJC(B)88, 91IJC(B)620, 92FES63, 92EJM425, 93H(35)763, 94JCR(S)38⟩; these singlet signals stand out from the bulk of aromatic multiplet signals but in some reports they overlap with aromatic proton signals ⟨88H(27)1935, 88ZOR1306, 90FES1341⟩.





(**56**)

(**53**) R^2 = NR^3R^4 δ8.18–8.50

(**54**) R^2 = N^+–R^1 δ7.42–7.50

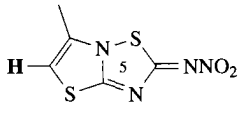
(**55**) R^2 = N–$^+R^1$ δ7.68–7.99

R^1 = H, δ2-CH 7.85

R^2 = H, δ5-CH 7.26–8.76

R^3 = H, δ6-CH 8.54–9.28

134{7}: *SNS/* 6-Methyl-2-nitrimino-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazole (**57**) ⟨84CPB3483⟩; *NNS/* thiazolo[3,2-*b*][1,2,4]triazoles (**58**); except for R^2 = H, δ 5-CH ⟨85IJC(B)1221, 86JHC1531, 87IJC(B)526, 87MI 805-02, 90FES953, 90IJC(B)88, 91EJM929, 92SC2815, 94IJC(B)579⟩ the ranges given for proton resonances of R^1 = H, δ 2-CH ⟨84UKZ1279, 86JHC1531⟩ and of R^3 = H, δ 6-CH ⟨83IJC(B)249, 84UKZ1279, 88CB977, 88H(27)161, 89JCR(S)262, 89SYN843⟩ are somewhat divergent. For a comparison of δ 5-CH of 134{7}-NNS/ (**58**) with δ 6-CH of the isomer 12{4}7-NN/S (**46**) (see Section 8.05.3.2.1(i)).

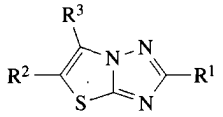


(**57**)

δ 7.44 (d)

$^4J_{5H,6Me}$ 1.0 Hz

(DMSO-d_6)

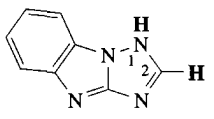


(**58**)

R^1 = H, δ2-CH 7.53, 7.56; 7.90–8.19; 8.42–8.50

R^2 = H, δ5-CH 7.00–7.90

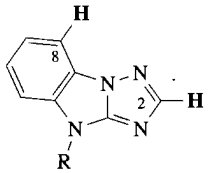
R^3 = H, δ6-CH 6.94; 7.35–7.66;8.95–9.30



(**59**)

δ 1-NH 12.47 (C)
12.43 (D)

δ 2-CH 8.14 (C)
8.15 (D)

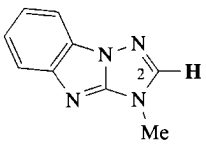


(**60**)

R = Me δ 2-CH 7.70 (C)
8.15 (D)
8.23 (T)

R = $PhCH_2$ δ 2-CH 8.25 (C), δ 8-CH 7.70 (m)(C)

R = MeCO δ 2-CH 8.33 (C), δ 8-CH 8.83 (m)(D)



(**61**)

δ 2-CH 7.70 (C)
8.63 (D)
8.13 (T)

Solvents: C = $CDCl_3$, D = DMSO-D_6, T = TFA

NNN/ Variation of solvents affects to a different extent δ 2-CH of the unsubstituted triazolo[1,5-*a*]benzimidazole (**59**) (quoted as the 1*H* form though proven to be predominantly the 4*H* form, see Section 8.05.2 and 8.05.4.1) some 4-substituted 4*H*-triazolo[1,5-*a*]benzimidazoles (**60**), and 3-methyl-3*H*-triazolo[1,5-*a*]benzimidazoles (**61**) ⟨89KGS209⟩.

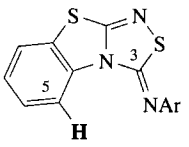
(iii) Peri-*H shifts in benzo-fused rings*

Some benzo derivatives exhibit one signal at distinctly lower field, markedly separated from the other aromatic proton signals. This shift is attributed to the effect of anisotropic deshielding of the fused heterobicyclic rings and/or functional groups attached to them in proximity to the benzene ring. Thus, the signal is assigned to the *peri*-H in the 5- or 8-position of the benzo-fused tricyclic system.

124{**7**}: *NNS*/ See Section 8.05.3.2.1(ii).

12{**4**}**7**: *NS*/*S* 3-Arylimino-3*H*-[1,2,4]thiadiazolo[3,4-*b*]benzothiazoles (**62**) ⟨86S1027, 89JHC1289⟩.

134{**7**}: *NNN*/ See Section 8.05.3.2.1(ii).



(62)

δ5–CH	8.56	$CDCl_3$	86S1027
	8.60–9.01	$CDCl_3$	89JHC1289

8.05.3.2.2 Carbon-13 NMR

No general correlation between ^{13}C NMR data and the structure of fused heterocycles is available. Carbon-13 NMR data have been quoted for a number of (5,5) (2N1) fused compounds mainly in order to complement the spectral structure determination. For compounds of the following systems ^{13}C NMR data have been reported.

124{**7**} : *NNS*/ ⟨91T2851, 91T2861, 92JHC713⟩; *NNN*/ ⟨92JOC184⟩.

125{**7**} : *NNO*/ ⟨88JOC27⟩.

12{**4**}**7** : *ON*/*O* ⟨92T7703⟩; *ON*/*S* ⟨92T7703⟩; *SS*/*N* ⟨86S751, 88JPC338⟩; *SN*/*N* ⟨88JPC338⟩; *NS*/*O* ⟨94T7019⟩; *NS*/*S* ⟨94T7019⟩; *NS*/*N* ⟨94T7019⟩; *NN*/*S* ⟨88LA75⟩; *NP*/*S* ⟨92S267⟩.

13{**4**}**5** : *NN*/*N* ⟨90JOC4724⟩.

13{**4**}**6** : *SN*/*N* ⟨90HCA492⟩.

13{**4**}**7** : *SN*/*S* ⟨88ZOR1306, 92T1282⟩; *SN*/*N* ⟨85FES34, 88ZOR192, 92FES63⟩.

134{**7**} : *ONO*/ ⟨85JOC3076⟩; *NNS*/ ⟨88CB977⟩; *NNN*/ ⟨92TA51⟩.

8.05.3.2.3 Phosphorus-31 NMR

124{**7**} : *PSN* ⟨90PS(51–52)57⟩.

12{**4**}**7** : *NP*/*S* ⟨86PS(28)289⟩ for compound (**29**) see Section 8.05.3.2.1(i) ⟨92S267⟩.

8.05.3.3 Mass Spectra

For numerous (5,5) (2N1)-compounds mass spectra data have been included in their spectral characterization. Mostly the molecular ions are given, and in some cases also fragments have been assigned. Only few reports contain a complete analysis, these include the following systems:

12{**4**}**7** : *NN*/*S* ⟨87IJC(B)526⟩.

13{**4**}**6**: *NN*/*S* ⟨87UKZ1183⟩.

13{**4**}**7** : *SN*/*N* ⟨94IJC(B)585⟩.

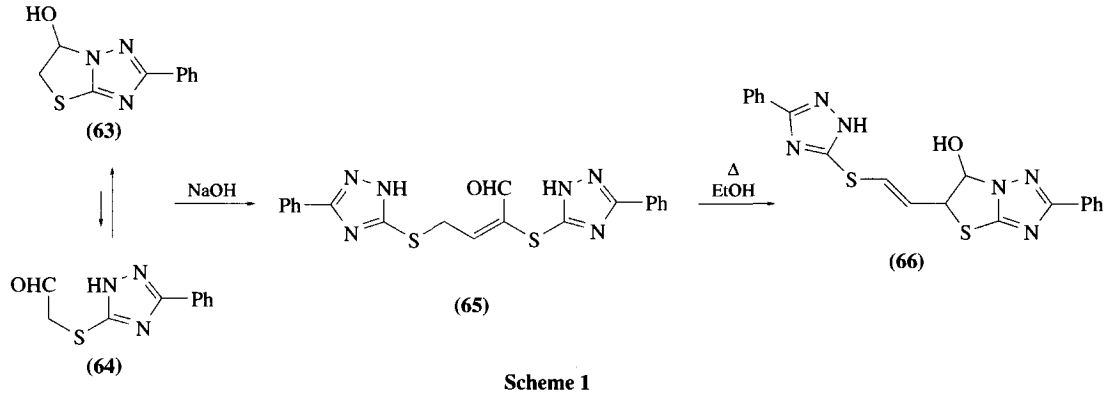
8.05.4 THERMODYNAMIC ASPECTS

8.05.4.1 N—H Tautomerism

By employing theoretical and physical methods (see Section 8.05.2) and spectroscopic data (see Section 8.05.3.2.1 (ii)) the unsubstituted triazolo[1,5-*a*]benzimidazole has been shown to exist predominantly in the 4*H* form (**3**; R = H) in an equilibrium with the 3*H* form (**2**; R = H); the 1*H* form (**1**; R = H) seems to be virtually nonexistent ⟨89KGS209⟩.

8.05.4.2 Ring–Chain Tautomerism

In the solid state 6-hydroxy-2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**63**) is the form present. In solution an equilibrium appears to exist with the chain form (5-phenyl-[1,2,4]triazol-3-yl)thioacetaldehyde (**64**). Reactions of both the bicyclic form (**63**) (see Section 8.05.6.1.3 and 8.05.7.3) and the chain form (**64**) have been observed. When treated with sodium hydroxide, the compound reacts in its chain form (**64**) as an aldehyde undergoing aldol condensation to give compound (**65**) ⟨87AP328⟩. Boiling compound (**65**) in ethanol converts it into its ring tautomer (**66**) (Scheme 1) ⟨87AP328⟩. Both tautomers (**65**) and (**66**) by treatment with sulfuric acid are converted into 2-phenyl-6-(2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-5-yl) thiazolo[3,2-*b*][1,2,4]triazole (**146**) (see Section 8.05.7.4 and 8.05.9.1.9) ⟨87AP328⟩.

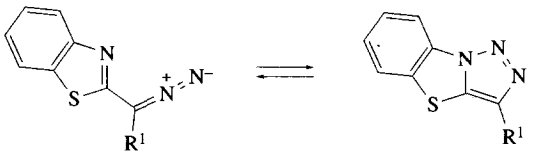


Scheme 1

The 2-diazomethyl thiazoles (**67**; $R^1 = H$, $R^2 = H$, Me) (prepared from the corresponding tosylhydrazones with sodium hydroxide, by the Bamford–Stevens reaction) exist predominantly or exclusively in the ring-tautomer form of thiazolo[3,2-*c*][1,2,3]triazoles (**68**; $R^1 = H$, $R^2 = H$, Me)) (Equation (1)). The same holds for the corresponding benzothiazole derivative (**69**; $R^1 = H$) which is only present as [1,2,3]triazolo[4,3-*b*]benzothiazole (**51**; $R^1 = H$) (Equation (2)) ⟨92JHC713⟩. By contrast, the 2-diazoester substituted thiazole (**67**; $R^1 = CO_2Me$) and the benzothiazole (**68**; $R^1 = CO_2Me$) (prepared from the corresponding 2-ethoxycarbonylmethyl-substituted heterocycles with tosylazide) in the solid state exist in the cyclic forms (**68**; $R^1 = CO_2Et$, $R^2 = Me$) and (**51**; $R^1 = CO_2Me$) respectively (IR evidence). In solution (^1H NMR evidence) these compounds equilibrate with the ring-open diazo forms; the equilibrium is shifted toward the diazo forms by raising the temperature of the solution and by using less polar solvents ⟨92JHC713⟩.



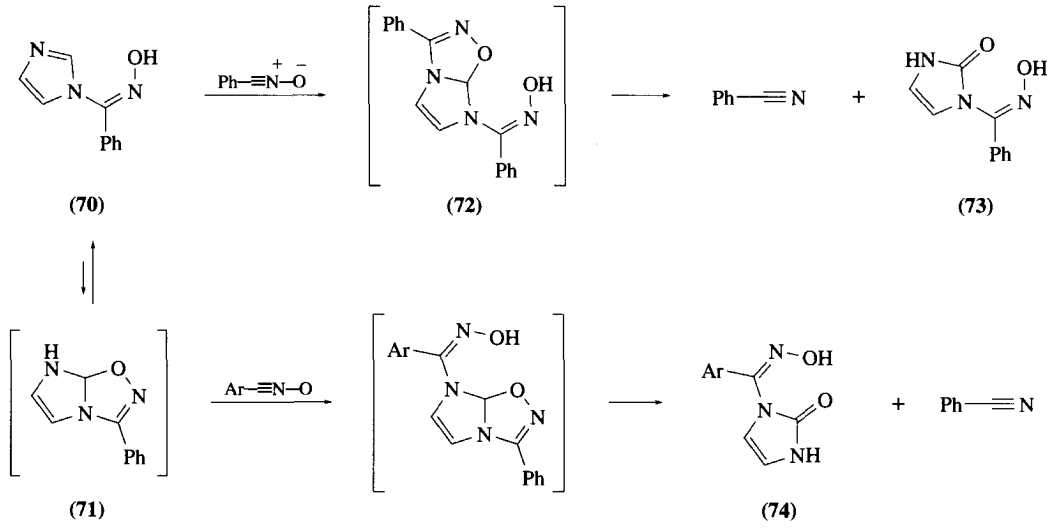
(1)



(2)

The reaction of imidazole with benzonitrile oxide (in excess) gives little (*Z*)-1-benzoylimidazole oxime (**70**) besides (*Z*)-3-benzoyl-2,3-dihydro-1*H*-imidazol-2-one oxime (**73**) and benzonitrile (and in addition some side products). In the solid state only the chain form (**70**) is observed, but the formation of (**72**) indicates a chain-ring tautomerism in solution. The latter tautomer (**71**) is supposed to undergo nucleophilic addition to benzonitrile oxide. The resultant 7-benzoyl-3-phenyl-7, 7a-dihydroimidazo [4,5-*a*][1,2,4]oxadiazole (**72**) is considered the key intermediate suffering a [3 + 2]

cycloreversion reaction leading to the formation of the final products (**73**) and benzonitrile (Scheme 2) ⟨93JCS(P1)2615⟩. The existence of the two tautomers in solution, though not observed directly, is supported by a cross-over trapping experiment, where addition of a second arylnitrile oxide gives (**74**) and another aryl cyanide (see Section 8.05.6.1.3).



(70) (72) (73)

(71) (74)

Scheme 2

8.05.4.3 Ring–Ring Tautomerism

An equilibrium exists between the two forms of 2,3-dihydro [2,1-*b*][1,2,4]thiadiazole-3-thione (**75**) and 3-imino-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**76**) In the solid state the 2-substituent determines the preferred form, *N*-alkyl existing in the former, *N*-aryl in the latter form. In solution (**76**) is predominant (Equation (3)) ⟨88JPC338⟩.

Similarly, the colorless 2-substituted 2,3-dihydro[1,2,4]thiadiazolo[4,5-*a*]benzimidazol-3-thiones (**75**) and the yellow 3-imino-3*H*-[1,2,4]dithiazolo[4,3-*a*]benzimidazoles (**76**) equilibrate in solution with the latter predominating. With R = Bu^n both ring tautomers have been isolated in the crystalline state ⟨83T2311⟩.



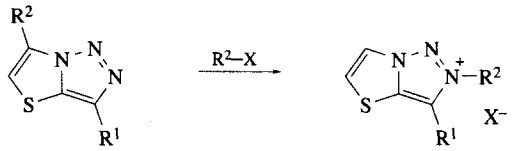
(75) (76) (3)

8.05.5 REACTIVITY OF FULLY CONJUGATED RINGS

8.05.5.1 Electrophilic Attack at Ring Nitrogen

8.05.5.1.1 N-*Alkylation*

3-Substituted thiazolo[3,2-*c*][1,2,3]triazoles (**50**) react with alkyl halides at 2-N affording the corresponding quaternary 2,3-disubstituted thiazolo[3,2-*c*][1,2,3]triazolium salts (**52**) (Equation (4)) ⟨91T2851, ⟨94H2017⟩.



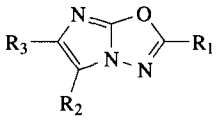
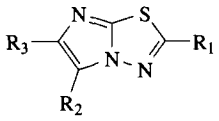
(50) R^1 = H, Me, Ph; R^2 = Me, CH_2CO_2Me; X = I, Br (52) (4)

8.05.5.2 Electrophilic Attack at Ring Carbon

8.05.5.2.1 Bromination and nitration

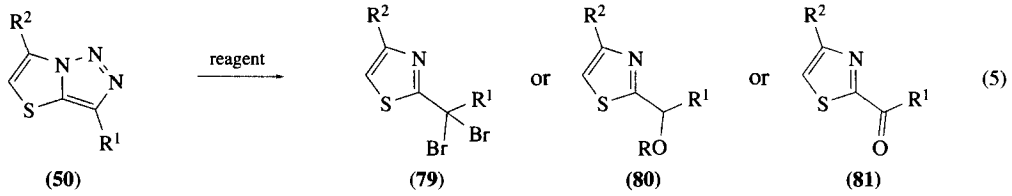
2,6-Disubstituted imidazolo[2,1-*b*][1,3,4]oxadiazole (**77**) and -thiadiazoles (**78**) undergo bromination and nitration at the unsubstituted 5-C position. The monosubstituted 5-aryl derivative (**78**; R^1, R^3 = H) is brominated at 6-C (Table 15).

Table 15 Electrophilic substitution of (**77**) and (**78**).

	R^1	R^2	R^3	*Ref.*
 (**77**)	aryl	H → Br H → NO_2	aryl	93MI 805-01
	aryl	H → Br		89IJC(B)500 89JIC118
	Bu^t	H → Br H → NO_2	Bu^t	83JHC1003
	H	Ar	H → Br	88ZOR199
 (**78**)	S—Pr	H → Br	$NHCO_2Me$	92FES63

8.05.5.2.2 Ring opening induced by acids and electrophiles

When subjected to acids or suitable electrophiles 3-mono- and 3,6-disubstituted thiazolo[3,2-*c*][1,2,3]triazoles (**50**) suffer ring opening yielding 2-mono- and 2,4-disubstituted thiazoles (**79**)–(**81**) (Equation (5) and Table 16) ⟨91T2851, 91T2861⟩.



(50) (79) (80) (81) (5)

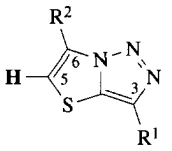
Table 16 Electrophilic ring opening of (**50**).

Reagent	*Product*	R^1	R^2
Br_2	(**79**)	H	H, Me, Ph
		Me	TMS, 1-hydroxycyclohexyl
H_2SO_4,	(**80**; R = H)	H	H, Me, Ph
H_2O		Me	TMS, CH(OH)Ar,
		Ph	1-hydroxycyclohexyl
AcOH	(**80**; R = Ac)	H	H, Me, Ph, 1-hydroxycyclohexyl
		Me	CH(OH)Ar, $Ph_2C(OH)$
SeO_2 in dioxan	(**81**)	H	H, Me, Ph
		Ph	TMS, 1-hydroxycyclohexyl

8.05.5.2.3 Reaction of electrophiles with lithiated heterocycles

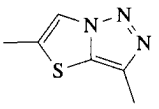
The mixture of 3- and 6-lithio derivatives (**50**; R^1 = Li, R^2 = H) and (**50**; R^1 = H, R^2 = Li) and 3-substituted 6-lithiothiazolo[2,3-*c*][1,2,3]triazoles (**50**; R^1 = Me, Ph, R^2 = Li) (obtained from lithiation of thiazolo[2,3-*c*][1,2,3]triazoles (see Section 8.05.5.4) reacts with electrophiles (methyliodide, trimethylchlorosilane, carbonyl compounds) to give 6-substituted and 3,6-disubstituted thiazolo[2,3-*c*][1,2,3]triazoles, respectively (Table 17) ⟨91T2851, 91T2861⟩.

Table 17 Reactions of lithiated (**50**) with electrophiles.

	Lithio derivative R^1/R^2	*El*	*Products* R^1/R^2
 (**50**)	**a**; Li/H **b**; H/Li **c**; Me, Ph/Li		**a**; H/H **b**; H/R **c**; Me, Ph/R

El = MeI, TMSCL, R^1R^2C = O. R = Me, TMS, $C(OH)R^1R^2$. R^1, R^2 = H, alkyl, cycloalkyl, aryl, het.

Methylation of 6-lithio-3-methylthiazolo[2,3-*c*][1,2,3]triazole (**50c**; R^1 = Me) with methyl iodide in tetrahydrofuran gives a mixture of 3,6-dimethylthiazolo[2,3-*c*][1,2,3]triazole (**50**; R^1, R^2 = Me) and 3,5-dimethylthiazolo[2,3-*c*][1,2,3]triazole (**82**) ⟨91T2851⟩.

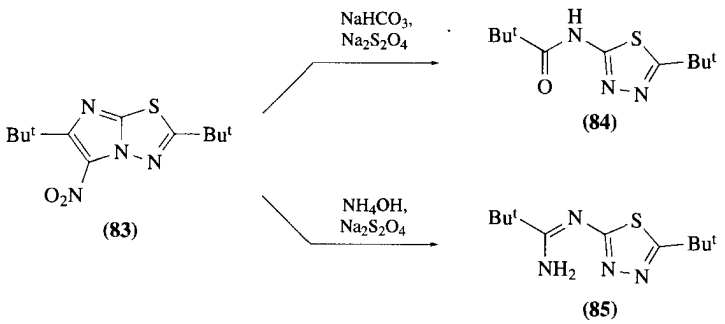


(**82**)

8.05.5.3 Reaction with Nucleophiles

8.05.5.3.1 Ring opening induced by nucleophiles and a reducing reagent

Reaction of 2,6-di-*t*-butyl-5-nitroimidazo[2,1-*b*][1,3,4]thiadiazole (**83**) with sodium bicarbonate or with ammonium hydroxide in the presence of sodium dithionite results in the cleavage of the imidazole ring and affords the respective 5-*t*-butyl-2-pivaloylamino-1,3,4-thiadiazole (**84**) or its amidine derivative (**85**) ⟨83JHC1003⟩.



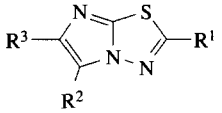
(**83**) (**84**) (**85**)

Scheme 3

8.05.5.3.2 Displacement of bromide by cyanide

Copper(I) cyanide in dimethylformamide displaces bromine in positions 5 or 6 of disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles (**56**) forming the corresponding heteroaromatic nitriles (Table 18) ⟨83JHC1003, 88ZOR199⟩.

Table 18 Nucleophilic substitution of (**56**) bromides.

	R^1	R^2	R^3	*Ref.*
 (**56**)				
	(**a**) Bu^t	Br → CN	Bu^t	83JHC1003
	(**b**) H, alkyl, cycloalkyl	aryl	Br → CN	88ZOR199

8.05.5.4 Lithiation

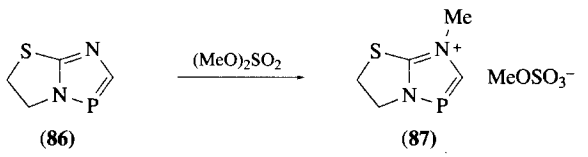
Lithiation of thiazolo[2,3-*c*][1,2,3]triazole (**50**) gives a mixtures of 3- and 6-lithiated derivatives; 3-substituted thiazolo[2,3-*c*][1,2,3]triazoles (**50**; R^1 = Me,Ph) are selectively lithiated at the 6-position ⟨91T2851, 91T2861⟩ (see Section 8.05.5.2.3).

8.05.6 REACTIVITY OF NONCONJUGATED RINGS

8.05.6.1 Electrophilic Attack at Ring Nitrogen

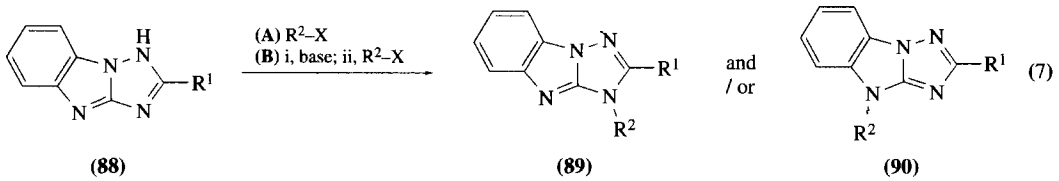
8.05.6.1.1 N-Alkylation

Methylation of 5,6-dihydrothiazolo[3,2-*b*][1,3,4]diazaphosphole (**86**) is achieved with dimethylsulfate to give the 1-methyl-5,6-dihydrothiazolo[3,2-*b*][1,3,4]diazaphospholium methylsulfate (**87**) (Equation (6)) ⟨86PS(28)289⟩.



(**86**) (**87**) (6)

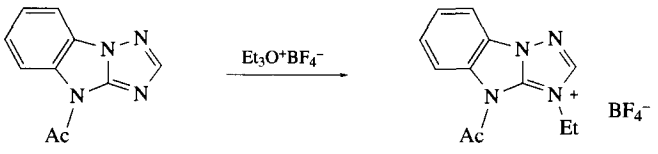
Alkylation of 2-substituted 1*H*-[1,2,4]triazolo[1,5-*a*]benzimidazoles (**88**) with alkyl halides and dialkyl sulfates occurs at positions 3 or 4 (but not position 1): alkylation of the neutral substrates (path A, Equation (7)) gives predominantly or exclusively 2,3-disubstituted 3*H*-[1,2,4]triazolo[1,5-*a*]benzimidazoles (**89**) ⟨89KGS209⟩ whereas alkylation of the anion (path B, Equation (7), in the presence of potassium hydroxide or sodium acetate) leads preferentially to 2,4-disubstituted 4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazoles (**90**) ⟨88SC1995, 89KGS209⟩.



(**88**) (**89**) (**90**) (7)

R^1 = H, Me, Ph
R^2 = Me, Et, Bn

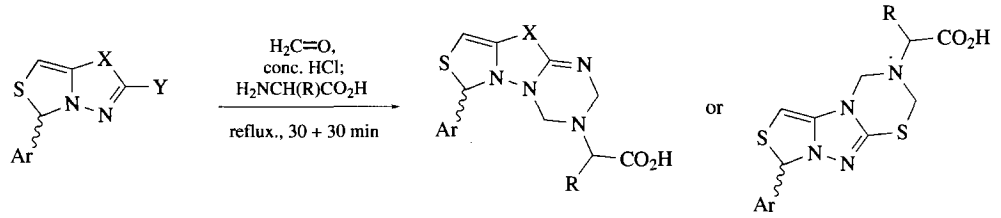
Treatment of 4-acetyl-4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**91**) with triethyloxonium tetrafluoroborate gives 4-acetyl-3-ethyl-4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazolium tetrafluoroborate (**92**) (Equation (8)) ⟨89KGS209⟩.



(91) (92) (8)

8.05.6.1.2 Formation of aminals and thioacetals

Condensation of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,2,4]oxadiazoles (**93**; X = O) and -thiadiazoles (**93**; X = S) with formaldehyde and α-amino acids leads to 7-aryl-3-(carboxyalkyl)thiazolo[3′,4′ : 3,2][1,3,4]oxadiazoles (**94**; X = O) and -thiadiazoles (**94**; X = S), respectively. Under the same reaction conditions 5-aryl-2-sulfonyl-1,5-dihydrothiazolo[3,4-*b*][1,2,4]triazoles (**95**) are converted into 7-aryl-3-(carboxyalkyl)thiazolo[3′,4′ : 2,3][1,2,4]triazoles (**96**) (Equation (9)) ⟨94MI 805-01⟩.

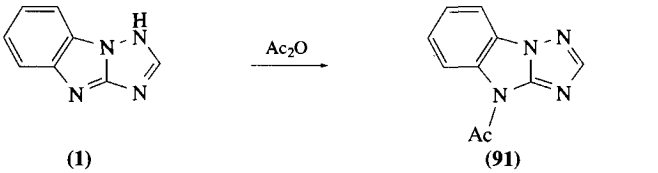


(**93**) X = O, S; Y = NH_2
(**95**) X = NH; Y = SH

(**94**) X = O, S (**96**) (9)

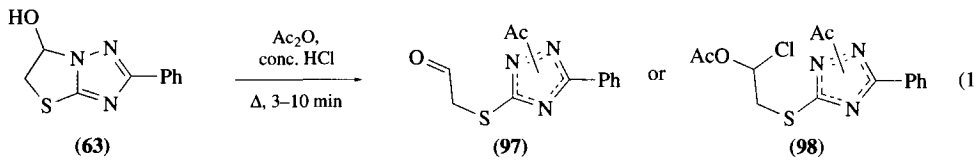
8.05.6.1.3 N-Acylation

Acetic anhydride converts 1*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**1**) into 4-acetyl-4*H*-[1,2,4]-triazolo[1,5-*a*]benzimidazole (**91**) (Equation (10)) ⟨89KGS209⟩.



(**1**) (**91**) (10)

Acetylation of 6-hydroxy-2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**63**) with acetic anhydride and variable amounts of concentrated hydrochloric acid and variable reaction times occurs with concomitant ring opening and formation of either an *N*-acetyl derivative (**97**) of 3-(2-oxoethylthio)-5-phenyl[1,2,4]triazole or an *N*-acetyl derivative (**98**) of 3-(2-acetoxy-2-chloroethyl)-5-phenyl[1,2,4]triazole (Equation (11)); the site of *N*-acetylation of the products is undetermined ⟨87AP(320)528⟩.

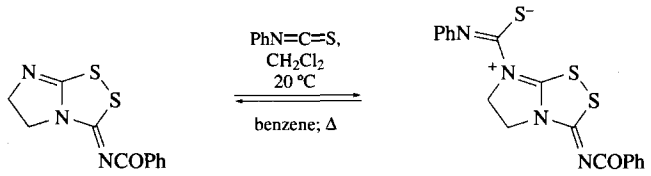


(**63**) (**97**) (**98**) (11)

The equilibrium existing in solution between (*Z*)-1-benzoylimidazole oxime (**70**) and 3-phenyl-7*H*-imidazo[1,2-*d*][1,2,4]oxadiazole (**71**) (see Section 8.05.4) has been proved in a cross-over experiment.

8.05.6.1.4 N-*Thiocarbamoylation*

The reaction of 3-benzoylimino-5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**19**) with phenylisothiocyanate gives the yellow adduct (**99**) Equation (12) upon heating in boiling benzene it reverts to the components ⟨86S751⟩.



(19) (99) (12)

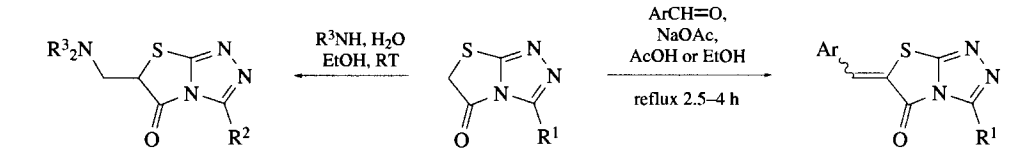
8.05.6.2 Electrophilic Attack at Carbon

8.05.6.2.1 Condensation with aldehydes

Aromatic aldehydes undergo aldol condensation with the 6-methylene group of 5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazol-5-ones (**100**) to give the 6-arylidene derivatives (**101**) (Scheme 4) ⟨89JIC832, 90JIC226, 90JIC409⟩.

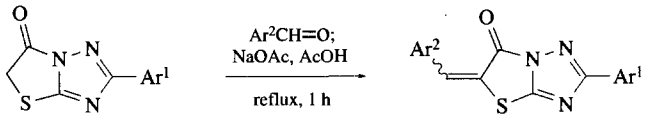
Similarly, 5-arylidene derivatives (**103**) are prepared from 2-aryl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-6-one (**102**) (Equation (13)) ⟨91IJC(B)38⟩ .

The Mannich condensation of the 5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazol-5-one (**102**) with dialkylamine, formaldehyde and hydrochloric acid affords the 6-dialkylaminomethyl derivatives (**104**) (Scheme 4) ⟨90JIC409⟩.



(**104**) R^2 = CH_2SHet; R^2 = Me,Et (**100**) (**101**)

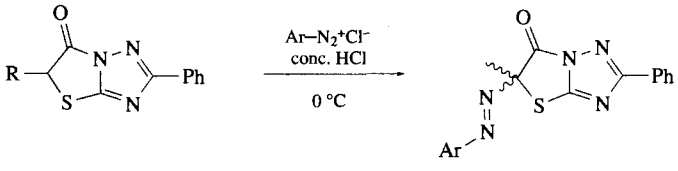
Scheme 4



(**102**) (**103**) (13)

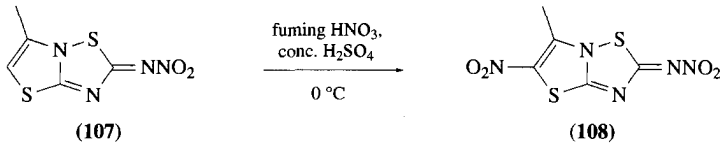
8.05.6.2.2 Azo coupling and nitration

Azo coupling with aromatic diazonium ions converts 5-methyl-2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-6-one (**105**) into the 6-arylazo derivatives (**106**) (Equation (14)) ⟨83JPR869⟩.



(**105**) (**106**) (14)

Nitration of 6-methyl-2-nitroimino-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazole (**107**) provides the 5-nitro derivative (**108**) (Equation (15)) ⟨84CPB3483⟩.

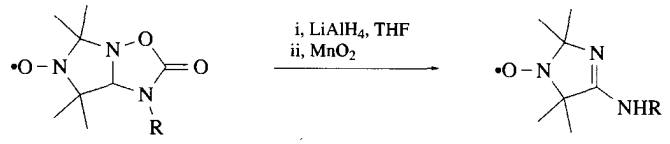


(107) (108) (15)

8.05.6.3 Nucleophilic Attack at Ring Carbon with Concomitant Ring Opening

8.05.6.3.1 Hydride ion

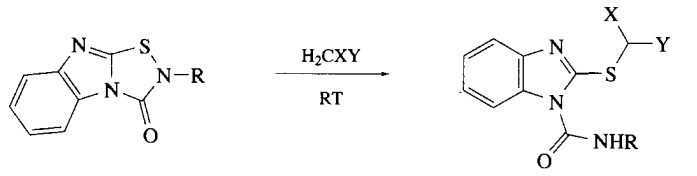
Reaction of lithium aluminum hydride followed by manganese dioxide converts 5-oxyl-1,2,5,6,7,7a-hexahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2-one (**109**) into the 1-oxyl-2,5-dihydro-1*H*-imidazole (**110**) (Equation (16)) ⟨93T10693⟩.



(109) R = $H_2N(CH_2)_3$ (110) (16)

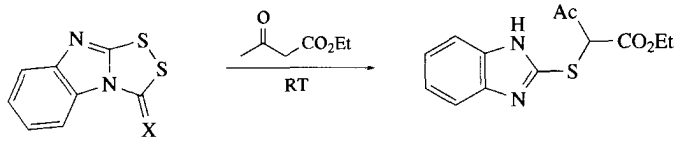
8.05.6.3.2 C-Nucleophiles

C,H-Acidic compounds cleave the *S*,*N*-bond of 2,3-dihydro[1,2,4]thiadiazolo[5,1-*a*]benzimidazol-3-ones (**111**) forming the corresponding ω-disubstituted 1-carbamoyl-2-methylthiobenzimidazoles (**112**); with monoethyl malonate the reaction proceeds with evolution of carbon dioxide and formation of the 2-(ethoxycarbonylmethylthio) derivatives (**112**; Y = H) (Equation (17)) ⟨85JCS(P1)1007⟩.



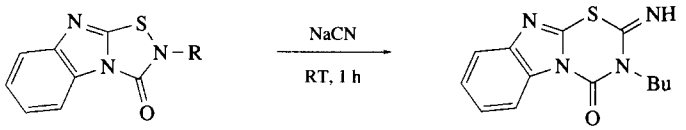
(111) R = alkyl, cyclohexyl
X = Ac, CO_2Et, CN
Y = Ac, CO_2Et, H, CN
(112) (17)

N-Substituted 3-imino-3*H*-[1,2,4]dithiazolo[4,5-*a*]benzimidazoles (**113**) react with ethyl acetoacetate affording 2-[acetyl(ethoxycarbonyl)methylthio]benzimidazole (**114**) (Equation (18)) ⟨85JCS(P1)1007⟩.



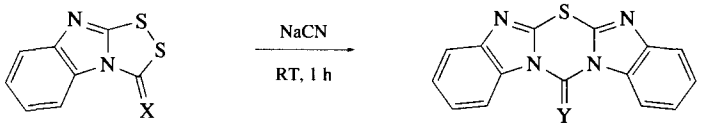
(113) X = NR (114) (18)

Cyanide ion inserts into the *S*,*N*-bond of 1-butyl-2,3-dihydro[1,2,4]thiadiazolo[4,5-*a*]benzimidazol-3-ones (**111**; R = Bu^n) forming 3-butyl-2-imino-3,4-dihydro-2*H*-[1,3,5]thiadiazino[3,2-*a*]-benzimidazol-4-one (**115**) (Equation (19)) ⟨85JCS(P1)1007⟩.



(111) R = Bu^n (115) (19)

The compounds (**113**; X = NAr) react with cyanide ion affording 13-arylimino-13*H*-dibenzimidazo[2,1-*b*:1′,2′-*e*][1,3,5]thiadiazines (**116**; Y = N-Ar), and 3*H*-[1,2,4]dithiazol[4,5-*a*]benzimidazole-3-thione (**113**; X = S) similarly gives the 13-thione (**116**; Y = S) (Equation (20)) ⟨85JCS(P1)1007⟩.

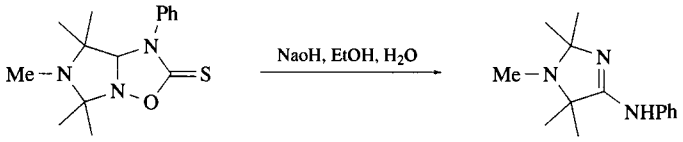


(113) X = S, NAr (116) (20)

8.05.6.3.3 O-*Nucleophiles*

Aqueous alkali or sodium methoxide convert the radicals (**109**) into the oxylimidazoles (**110**) (see Section 8.05.6.3.1) ⟨92S1223, 93JCS(P2)2157, 93T10693⟩.

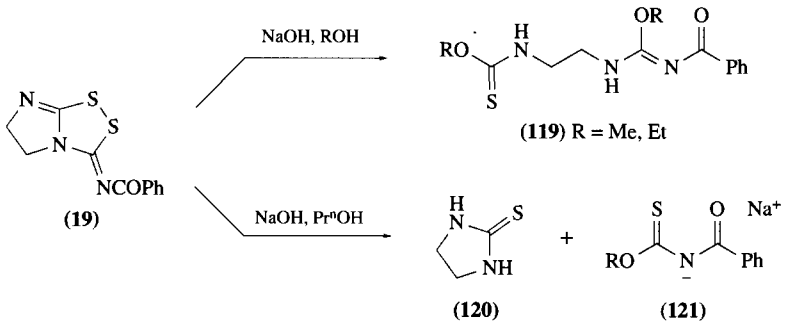
Hydrolysis with sodium hydroxide transforms 5,5,6,7,7-pentamethyl-1,2,5,6,7,7a-hexahydroimidazo[3,4-*b*][1,2,4]oxadiazole-2-thione (**117**) to the corresponding 1*H*-imidazole (**118**) (Equation (21)) ⟨91IZV2642⟩.



(117) (118) (21)

When 3-benzoylimino-5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**19**) is treated with methanol or ethanol in the presence of sodium hydroxide *O*-alkyl-*N*-[2-(2-alkyl-1-benzoyl-3-isoureido)ethyl]thiocarbamates (**119**) are formed as a result of the opening of both rings. Under analogous conditions the reaction with *n*-propanol affords imidazolidine-2-thione (**120**) and the sodium salt of *N*-benzoyl-*O*-propylcarbamate (**121**) (Scheme 5) ⟨86S751⟩.

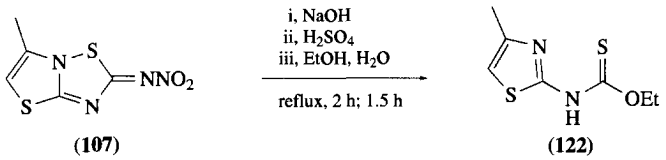
Boiling in sodium hydroxide followed by acidification with sulfuric acid and boiling in ethanol



(19) (119) R = Me, Et (120) (121)

Scheme 5

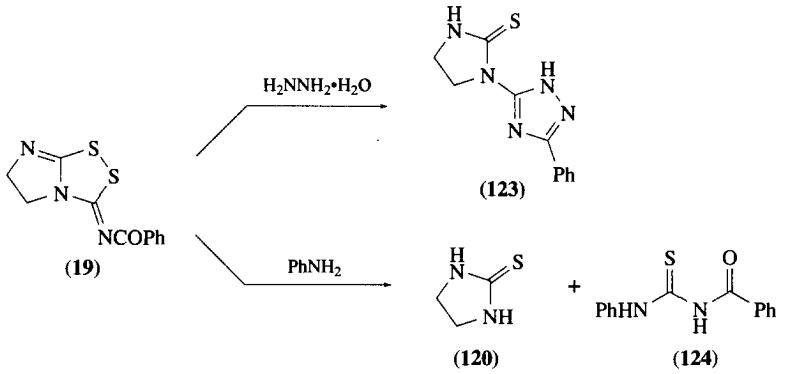
converts 6-methyl-2-nitroimino-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazole (**107**) into 2-ethoxythiocarbonylamino-4-methylthiazole (**122**) (Equation (22)) ⟨84MI3483⟩.



(107) (122) (22)

8.05.6.3.4 N-*Nucleophiles*

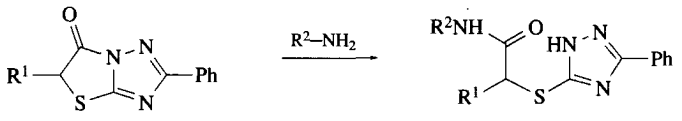
Hydrazine hydrate reacts with 3-benzoylimino-5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**19**) opening the dithiazole ring and forming a triazole ring, giving (**123**). Reaction with aniline leads to the formation of imidazolidine-2-thione (**120**) and 1-benzoyl-3-phenylthiourea (**124**) (Scheme 6) ⟨86S751⟩.



(19) (123) (120) (124)

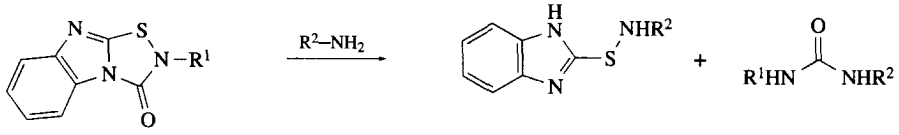
Scheme 6

Hydrazine and primary amines induce ring opening of the thiazole ring of 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole-6-ones (**105**) forming the respective 2-([1,2,4]thiazol-2-yl)alkanoic acid hydrazides and amides (**125**) (Equation (23)) ⟨83JPR869⟩.



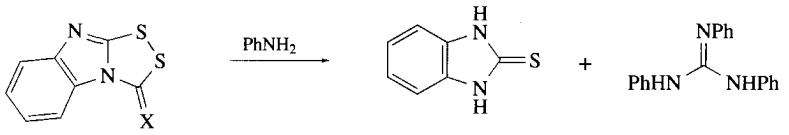
(105) (125) (23)

Behaving like cyclic sulfenamides the 2,3-dihydro[1,2,4]thiadiazolo[4,3-*a*]benzimidazo-3-ones (**111**) react with amines suffering cleavage of the *N*,*S*-bond; *N*-substituted benzimidazol-2-ylsulfenamides (**126**) and the corresponding 1,3-disubstituted ureas are obtained (Equation (24)) ⟨85JCS(P1)1007⟩.



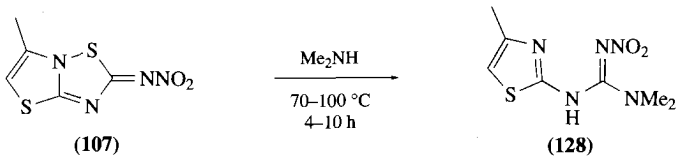
(111) (126) (24)

By contrast, reaction of 3-phenylimino-3*H*-[1,2,4]-dithiazolo[4,3-*a*]benzimidazole (**113**; X = NPh) with aniline results in extrusion of sulfur and formation of 2,3-dihydro-1*H*-benzimidazole-2-thione (**127**) and triphenylguanidine (Equation (25)) ⟨85JCS(P1)1007⟩.



(113) X = NPh (127) (25)

Dimethylamine converts 6-methyl-2-nitroimino-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazole (**107**) into *N*,*N*-dimethyl-*N'*-(4-methyl-2-thiazol-2-yl)-*N''*-nitroguanidine (**128**) (Equation (26)) ⟨84MI3483⟩.



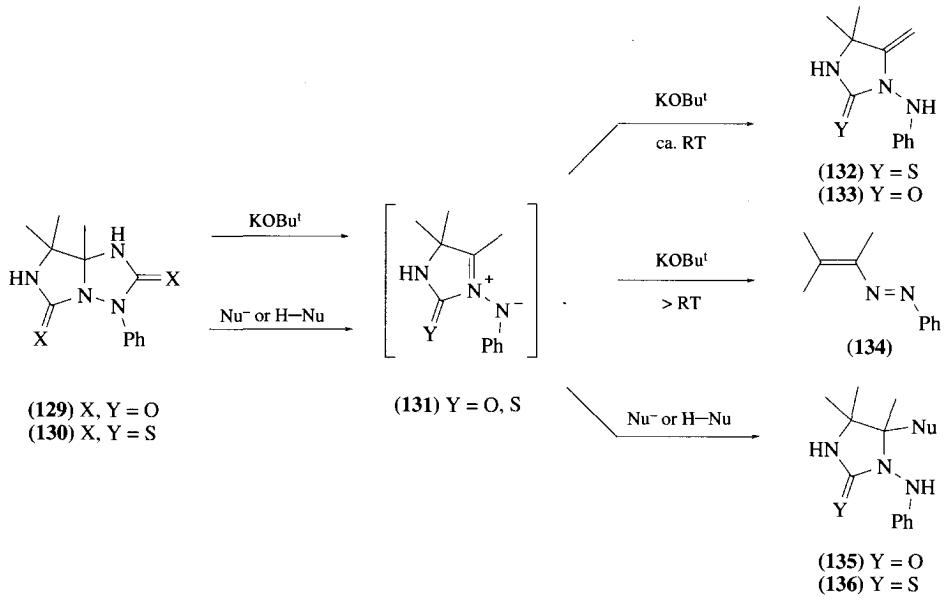
(107) (128) (26)

8.05.6.4 Elimination

8.05.6.4.1 Elimination of two ring members

3,7,7a-Trimethyl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione (**129**) and -2,5-dione (**130**) undergo base induced [3 + 2] cycloelimination. With potassium *t*-butoxide slightly above room temperature the heterocumulene moiety of the triazole ring is eliminated; the putative elimination product (**131**) with an azomethine imine function is not isolable but the isomerized products 1-arylamino-4,4-dimethyl-5-methylene-2,3,4,5-tetrahydro-1*H*-imidazole-2-thione (**132**) and -2-one (**133**) are obtained. At higher temperatures both heterocumulene moieties are eliminated and the aryazo-alkene (**134**) is recovered (Scheme 7) ⟨93TH 805-01, 95FES379⟩.

With nucleophilic bases 3,7,7a-trimethyl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]-triazole-2,5-dione (**130**) and -2,5-dithione (**129**) the [3 + 2] cycloelimination of the heterocumulene moiety from the triazole ring is followed by nucleophilic addition of the base to give 4-substituted 4,5,5-trimethyl-2,3,4,5-tetrahydro-1*H*-imidazol-2-ones (**135**) and -2-thiones (**136**), respectively (Scheme 7) ⟨93TH 805-01, 95FES379⟩.



(**129**) X, Y = O
(**130**) X, Y = S

(**131**) Y = O, S

(**132**) Y = S
(**133**) Y = O

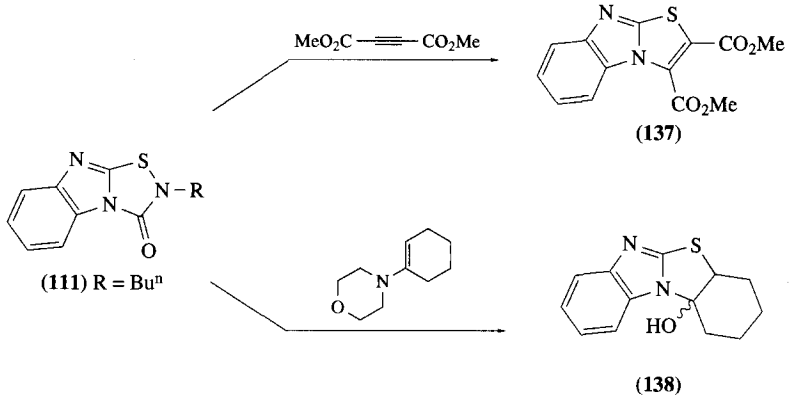
(**134**)

(**135**) Y = O
(**136**) Y = S

Scheme 7

8.05.6.4.2 Elimination of two ring members followed by addition of two ring members: Exchange of two ring members

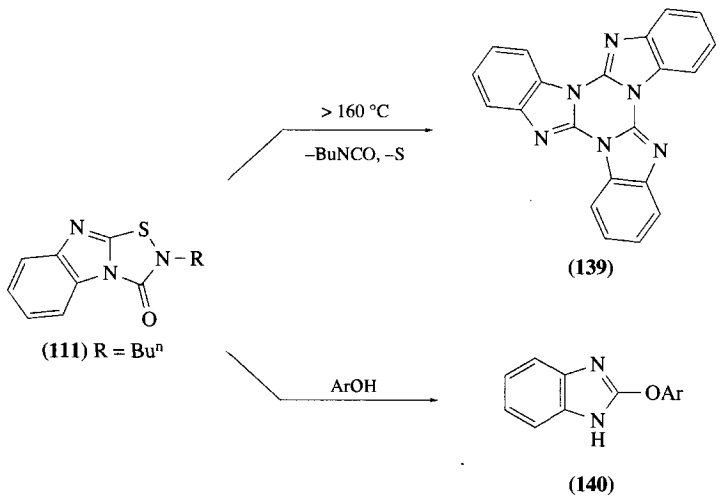
2-Butyl-2,3-dihydro[1,2,4]thiadiazolo[4,5-*a*]benzimidazol-3-one (**111**; R = Bu^n) undergoes exchange of the isocyanate moiety (see Section 8.05.10). With DMAD 2,3-dimethoxycarbonylthiazolo[3,2-*a*]benzimidazole (**137**) is obtained. The reaction with 4-(1-cyclohexen-1-yl)morpholine gives 10a-hydroxy-6a,7,8,9,10,10a-hexahydrobenzimidazo[2,1-*b*][1,3]benzothiazole (**138**) (Scheme 8) ⟨85JCS(P1)1007⟩.



Scheme 8

8.05.6.4.3 Elimination of three ring members

On heating in inert solvents at 160 °C 2-butyl-2,3-dihydro[1,2,4]thiadiazolo[1,2-*d*]benzimidazol-3-one (**111**; R = Bu^n) suffers elimination of isocyanate and sulfur, to give tribenzimidazo[1,2-*a*:1′2′-*c*:1″,2″-*e*][1,3,5]triazine (**139**); thermolysis in the presence of phenols produces 2-aryloxybenzimidazoles (**140**) (Scheme 9) ⟨85JCS(P1)1007⟩.



Scheme 9

8.05.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON

8.05.7.1 Straightforward Conversions

A number of straightforward reactions typical of heteroaromatic substituents has been reported:

- $CO_2R \rightarrow CO_2H$ ⟨89CC1702, 91AP(324)49, 92AP(325)609, 92TA51⟩;
- $CO_2H \rightarrow Br$ ⟨91AP(324)49⟩;
- $CH_3 \rightarrow CH_2Br$ ⟨91AP(324)49⟩;
- $CH_2Br \rightarrow CH_2OH$ ⟨92AP(325)609⟩;
- $CH_2OH \rightarrow CH_2OAc$ ⟨92AP(325)609⟩;
- $CH_2OH \rightarrow CH{=}O$ ⟨92AP(325)609⟩.
- —NH—C(=S)— → —N=C(—SMe)— ⟨86SUL51⟩.

8.05.7.2 Reduction

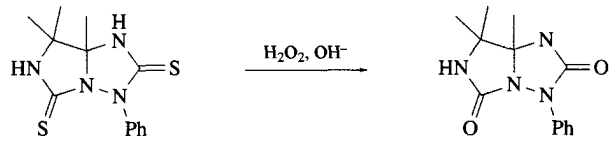
The reduction of 2,6-di-*t*-butyl-5-nitroimidazo[2,1-*b*][1,3,4]thiadiazole (**83**) with aluminum amalgam produces the 5-imino derivative (**141**) (Equation (27)) (see Section 8.05.5.3) ⟨83JHC1003⟩.



(83) (141) (27)

8.05.7.3 Oxidation

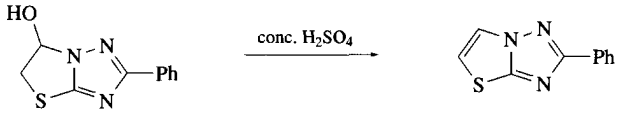
By treatment with alkaline hydrogen peroxide 3,7,7a-trimethyl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione (**142**) is converted into the corresponding -2,5-dione (**143**) (Equation (28)) ⟨93TH 805-01, 95FES379⟩.



(142) (143) (28)

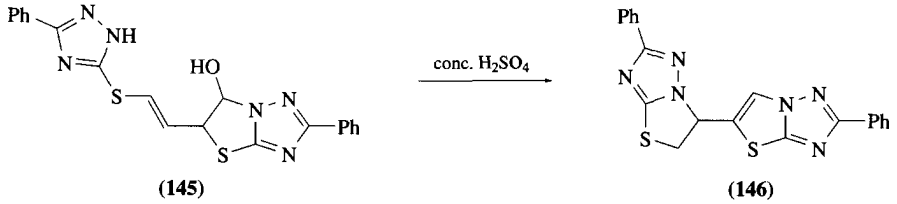
8.05.7.4 Elimination

Acid-catalyzed elimination of water from 6-hydroxy-2-phenyl-5,6-dihydrothiazolo[2,3-*b*][1,2,4]triazole (**144**) forms 2-phenylthiazolo[3,2-*b*][1,2,4]triazole (**52**) ⟨87AP(330)528⟩.



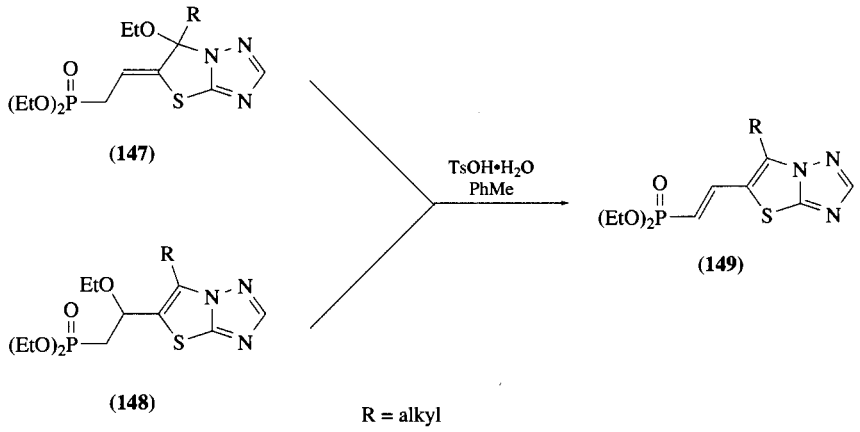
(144) (52) R^1 = Ph, R^2 = R^3 = H (29)

Acid catalyzed dehydration of 1-[(3-phenyl-1,2,4-triazol-5-yl)thio-2-(5-hydroxy-5,6-dihydro-2-phenylthiazolo[3,2-*b*][1,2,4]triazol-6-yl)ethene (**145**) brings about aromatization and formation of a new fused ring, giving 2-phenyl-6-(2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-5-yl)thiazolo[3,2-*b*][1,2,4]triazole (**146**) (Equation (30)) (see Section 8.05.9.1.9) ⟨87AP(320)528⟩.



(145) (146) (30)

p-Toluenesulfonic acid effects the formation of diethyl (*E*)-2-(6-alkylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethene-1-phosphonate (**149**) by the 1,4-elimination of ethanol from diethyl 2-(6-alkylthiazolo[3,2-*b*][1,2,4]-triazol-5-yl)-2-ethoxyethanephosphonate (**147**) as well as the 1,2-elimination of ethanol from diethyl 2-(6-alkyl-6-ethoxy-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-5-yliden)-ethanephosphonate (**148**) (Scheme 10) ⟨88CB977⟩.

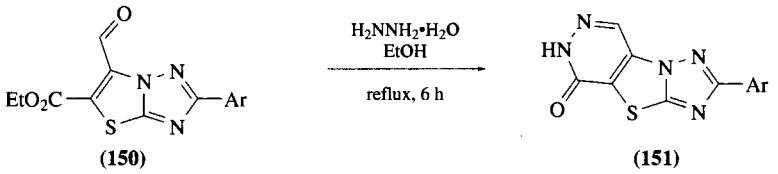


Scheme 10

8.05.7.5 Condensation Forming an Additional Fused Ring

For the heterocondensation of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,2,4]oxadiazoles and -thiadiazoles (**93**) and 5-aryl-2-sulfonyl-1,5-dihydrothiazolo[3,4-*b*][1,2,4]triazoles (**95**) with formaldehyde and α-amino acids see Section 8.05.6.1.2 ⟨94MI 805-01⟩.

Hydrazine hydrate transforms 2-aryl-6-ethoxycarbonyl-5-formylthiazolo[3,2-*b*][1,2,4]triazole (**150**) into 2-aryl-5,6-dihydro[1,2,4]triazolo[2′,3′ : 3,2]thiazolo[4,5-*d*]pyridazin-5-one (**151**) (Equation (31)) ⟨92AP(325)609⟩.



(31)

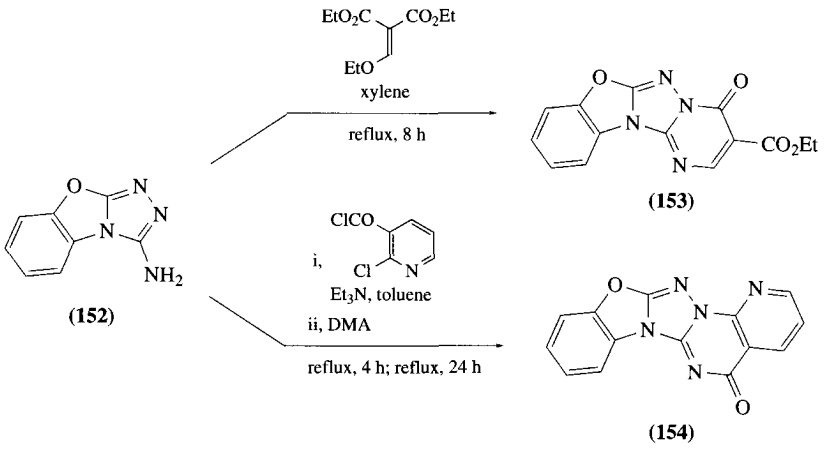
The reactions of 3-amino[1,2,4]triazolo[3,4-*b*]benzoxazole (**152**) with diethyl ethoxymethylenemalonate and with 2-chloropyridine-3-carboxylic acid chloride afford 3-carbethoxy-4*H*-pyrimido[1′,2′ : 1,5][1,2,4]triazolo[3,4-*b*]benzoxazole-4-one (**153**) and 5*H*-pyrido[3″,2″ : 5′,6′]-pyrimido[1′,2′ : 1,5][1,2,4]triazolo[3,4-*b*]benzoxazolo-5-one (**154**) respectively (Scheme 11) ⟨89H(29)925⟩.

8.05.7.6 Ylide Formation

Upon treatment with excess triethylamine in dimethylformamide 2-arylamino-5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazolium bromides (**155**) are converted into the ylides (**156**) (Equation (32)) ⟨88S729⟩.



(32)



Scheme 11

8.05.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO A RING HETEROATOM

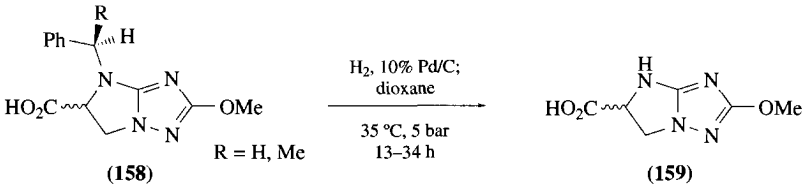
8.05.8.1 Detachment of a Substituent

Deacetylation of 4-acetyl-3-ethyl[1,2,4]triazolo[1,5-*a*]-benzimidazolium tetrafluoroborate (**92**) is achieved with aqueous ammonia to give 3-ethyl-3*H*-[1,2,4]triazolo[1,5-*b*]benzimidazole (**157**) (Equation (33)) ⟨89KGS209⟩.



(33)

Catalytic hydrogenation removes the *N*-benzyl and *N*-(1-phenyl)ethyl groups from the corresponding 7-substituted derivatives (**158**) of 6-carboxy-2-methoxy-5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]triazoles (**159**) (Equation (34)) ⟨92TA51⟩.

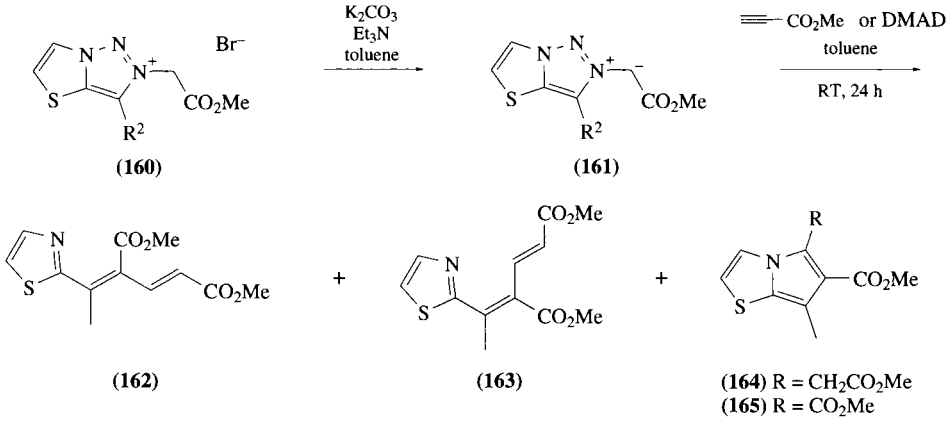


(34)

8.05.8.2 Ylide Formation

Potassium carbonate and triethylamine converts 2-methoxycarbonylmethyl-3-methylthiazolo[3,2-*c*][1,2,3]triazolium bromide (**160**) into the yellow azomethine ylide (**161**) which reacts with methyl propiolate to give a mixture of (2*E*,4*Z*) and (2*E*,4*E*) isomers of methyl 4-methoxycarbonyl-5-(thiazol-2-yl)-2,4-hexadienoate (**162**) and (**163**) beside traces of 6-methoxycarbonyl-5-methoxycarbonylmethyl-7-methylpyrrolo[2,1-*b*]thiazole (**164**) (Scheme 12) ⟨94H2017⟩.

The azomethine ylide (**161**) (see above) reacts with DMAD to give 7-methyl-5,6-dimethoxycarbonylpyrrolo[2,1-*b*]thiazole (**165**) (Scheme 12) ⟨94H2017⟩.



Scheme 12

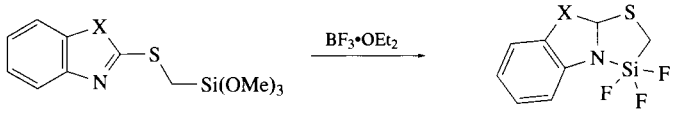
8.05.9 RING SYNTHESES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

8.05.9.1 Ring Closure of a Substituent Providing Three Ring Atoms of the Second Ring: (5)3 → (5,5)

8.05.9.1.1 (5)S1C2Si3 → 13{4}7:

*(i) SSi/O Oxazolo[2,3-*b*][1,3,4]thiazasilole, SSi/S Thiazolo[2,3-*b*][1,3,4]thiazasilole*

Treatment of (2-benzoxazolylthiomethyl)- and (2-benzthiazolylthiomethyl)trimethoxysilanes (**166**) with boron trifluoride etherate gives 3,3,3-trifluoro-3,9a-dihydro-2*H*-[1,3,4]thiazasilano[2,3-*b*]benzoxazole (**9**) and -benzthiazole (**10**), respectively (Equation (35)) ⟨93JOM(461)27⟩.



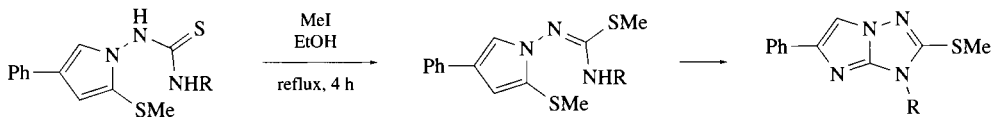
(35)

8.05.9.1.2 (5)N1C2N3 → 134{7}:

*(i) NNN/ Imidazo[1,2-*b*][1,2,4]triazole*

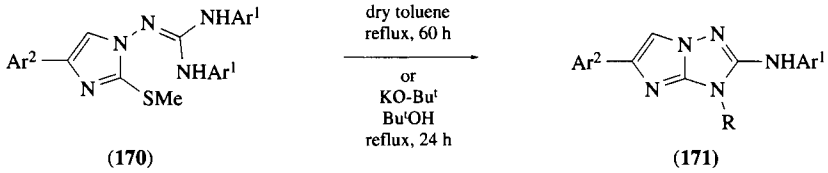
On treatment with methyl iodide in refluxing ethanol 1-substituted 3-(2-methylthio-4-phenylimidazo-2-yl)thioureas (**167**) give 1-substituted 2-methylthio-6-phenyl-1*H*-imidazo[1,2-*b*][1,2,4]-triazoles (**168**) via the *S*-methylisothioureido intermediate (**169**) (isolated with R = 4-MeC$_6$H$_4$) (Scheme 13) ⟨89S843⟩.

The 1-guanidinoimidazoles (**170**) similarly undergo cyclization either by heating in dry toluene



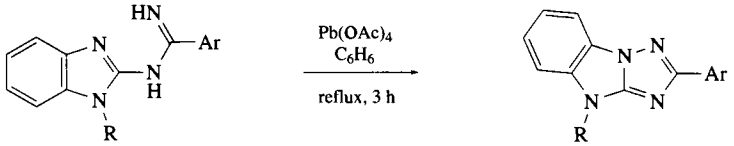
Scheme 13

or by the action of potassium *t*-butoxide in *t*-butanol to give 3,5-diaryl-2-arylamino-3*H*-imidazo[1,2-*b*][1,2,4]triazoles (**171**) (Equation (36)) ⟨88H(27)161⟩.



(170) (171) (36)

Oxidative cyclization with lead tetraacetate converts *N*-(benzimidazol-2-yl)arylamidines (**172**) into 2-aryl[1,2,4]triazolo[1,5-*a*]benzimidazoles (**173**) (Equation (37)) ⟨92IJC(B)191⟩.



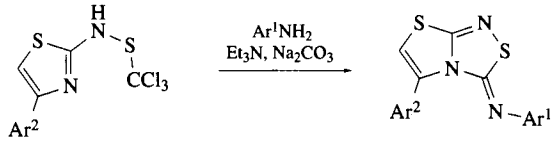
(172) (173) (37)

R = H, Bn

8.05.9.1.3 (5)N1S2C3→12{4}7:

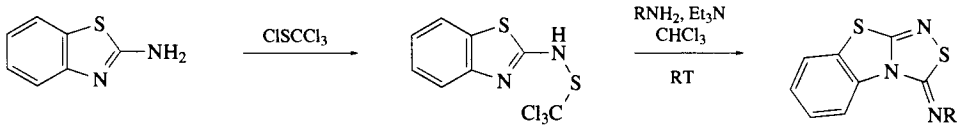
(i) NS/S Thiazolo[2,3-c][1,2,4]thiadiazole

Treatment of 2-[[(trichloromethyl)sulfonyl]amino]1,3-thiazoles (**174**) with anilines gives 3-arylimino-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles (**175**) (Equation (38)) ⟨88IJC(B)501⟩.



(174) (175) (38)

Trichloromethanesulfenyl chloride converts 2-aminobenzothiazole into 1,1,1-trichloro-*N*-(benzothiazol-2-yl)methanesulfenamide (**176**) which, in turn, reacts with aromatic and heteroaromatic amines to yield *N*-substituted 3-imino-3*H*-[1,2,4]thiadiazolo[3,4-*b*]benzothiazoles (**62**) (Scheme 14) ⟨89JHC1289⟩.



(176) R = aryl, het (62)

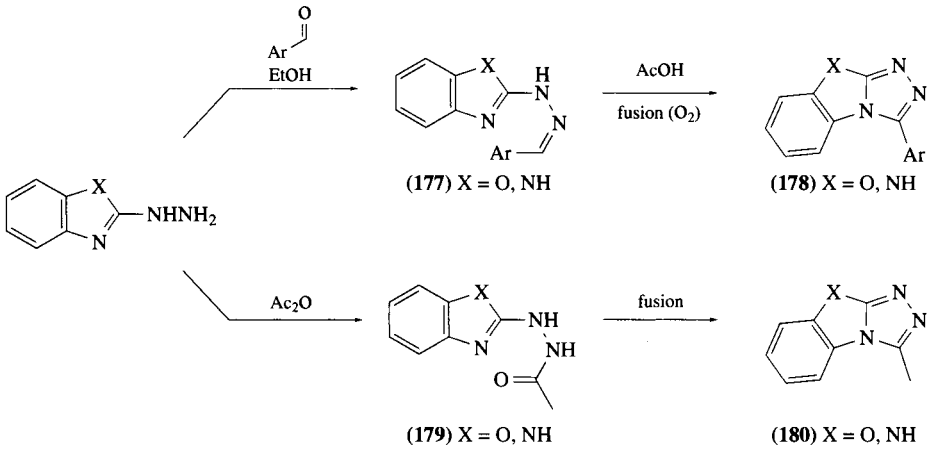
Scheme 14

8.05.9.1.4 (5)N1N2C3→12{4}7:

(i) NN/O Oxazolo[2,3-c][1,2,4]triazole, NN/N Imidazo[2,3-c][1,2,4]triazole

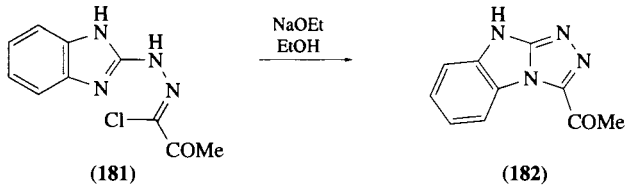
Aldehyde (2-benzoxazolyl)hydrazones (**177**; X = O) and (2-benzimidazolyl)hydrazones (**177**; X = NH) (from aromatic aldehydes and 2-hydrazinobenzoxazole and 2-hydrazinobenzimidazole, respectively) when boiled with glacial acetic acid or fused with air oxidation, undergo ring closure

to give 3-aryl[1,2,4]-triazolo[3,4-*b*]benzoxazoles (**178**; X = O) and 3-aryl[1,2,4]triazolo[3,4-*a*]benzimidazoles (**178**; X = NH). Refluxing 2-hydrazinobenzoxazole and 2-hydrazinobenzimidazole with acetic anhydride produces the corresponding monoacetyl derivatives (**179**; X = O, NH) which cyclize on heating above their melting points into 3-methyl[1,2,4]triazolo[3,4-*b*]benzoxazoles (**180**; X = O) or 3-methyl[1,2,4]triazolo[4,3-*a*]benzimidazoles (**180**; X = NH) (Scheme 15) ⟨88BCJ1339⟩.



Scheme 15

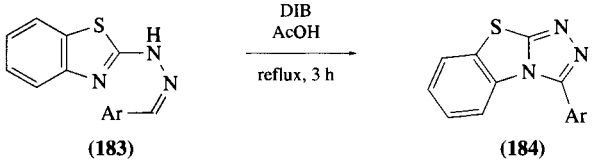
Upon treatment with sodium ethoxide 2-oxopropanoic[2-(2-benzimidazolyl)hydrazonyl] chloride (**181**) is converted into 3-acetyl-1*H*-[1,2,4]triazolo[4,3-*a*]benzimidazole (**182**) (Equation (39)) ⟨83PJC327⟩.



(39)

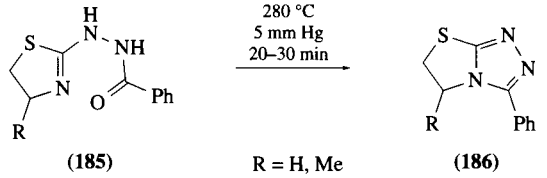
(ii) NN/S Thiazolo[2,3-c][1,2,4]triazole

Reaction of arenecarbaldehyde benzothiazol-2-ylhydrazones (**183**) with (diacetoxyiodo)benzene (DIB) results in the formation of 3-aryl-[1,2,4]triazolo[3,4-*b*]benzothiazoles (**184**) (Equation (40)) ⟨93JCR(S)244⟩.



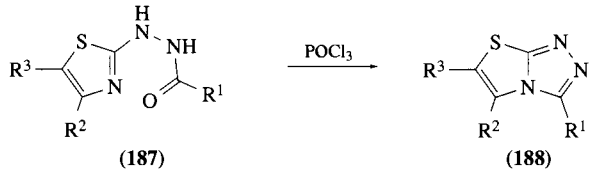
(40)

Thermally induced cyclodehydration of 2-[2-(2-benzoylhydrazino)-4,5-dihydrothiazoles (**185**) yields 3-phenyl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles (**186**) (Equation (41)) ⟨84CPB5040, 84T2703⟩.



(41)

Upon treatment with phosphorus oxychloride, usually at reflux temperature, 2-(2-aroylhydrazino)thiazoles (**187**) give thiazolo[2,3-*c*][1,2,4]triazoles (**188**) (Equation (42)) (Table 19).

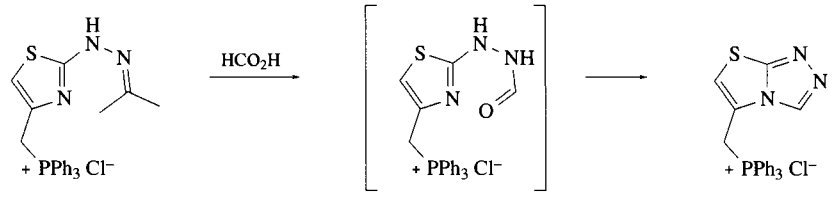


(187) (188) (42)

Table 19 Thiazolo[2,3-c][1,2,4]triazoles (**188**).

R^1	R^2	R^3	*Ref.*
Het	CO_2Et	H	86CZP233450
Ph	CO_2Et	H	91KGS537
Ph	Ph	H.HBr	86JHC1439
aryl	aryl	H	85IJC(B)1221, 87MI 805-02, 87IJC(B)526, 88CAT91, 90IJC(B)88, 91EJM929, 92JIC268, 93MI 805-05
Me, Ph, het	CH_2CO_2Et	H	89LA75
CONHPh	Me	H	91PS(61)119
Ph	het	H.HBr	94IJC(B)579

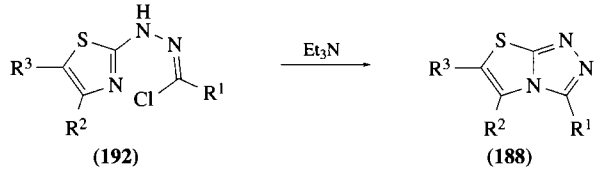
Similarly, [2-[2-(methylethylidenehydrazino)]thiazol]-4-yl]methyltriphenylphosphonium chloride hydrochloride (**189**) undergoes cyclization with formic acid. Presumably, the first formed formylhydrazino substituted intermediate (**190**) undergoes cyclodehydration providing [(thiazolo-[2,3-*c*][1,2,4]triazol-5-yl)methyl]triphenylphosphonium chloride (**191**) (Scheme 16) ⟨85JHC1185⟩.



(189) (190) (191)

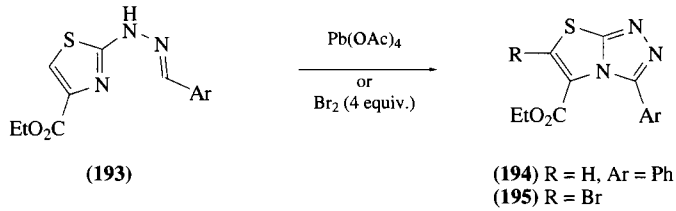
Scheme 16

Base-induced dehydrochlorination of 2-(thiazol-2-yl)-hydrazonyl chlorides (**192**) also gives thiazolo[2,3-*c*]-[1,2,4]triazoles (**188**) (Equation (43)) ⟨83JHC285, 88PS(36)129⟩.



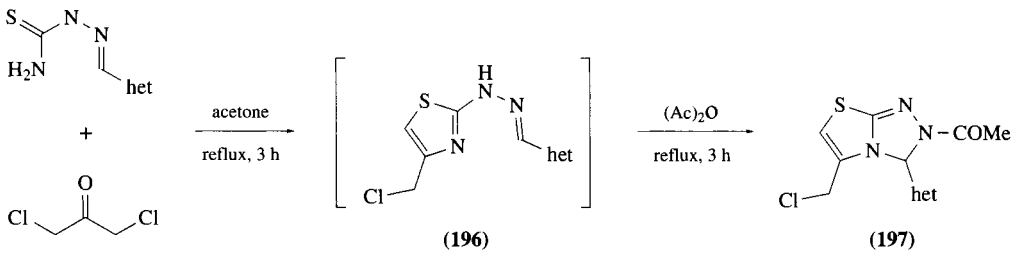
(192) (188) (43)

Oxidation of benzaldehyde hydrazone (**193**) brings about cyclization affording the thiazolo[2,3-*c*][1,2,4]triazole (**194**) (Equation (44)) ⟨91KGS537⟩. Similarly, treatment of 2-[4-(ethoxycarbonyl)thiazol-2-yl]hydrazones of aromatic aldehydes (**193**) with excess bromine induces bromination of the thiazole ring followed by ring-closure to form the bromo derivatives (**195**) ⟨93KGS257⟩.



(193) (194) R = H, Ar = Ph
(195) R = Br (44)

The treatment of the 2-(4-chloromethylthiazol-2-yl)hydrazone of a heteroaromatic aldehyde (**196**) (formed as an intermediate in the reaction of some thiosemicarbazones with 1,3-dichloroacetone) with acetic anhydride gives rise to 3-hetaryl-substituted 2-acetyl-5-chloromethyl-2,3-dihydrothiazolo[2,3-*c*][1,2,4]triazoles (**197**) (Scheme 17) ⟨92JIC596⟩.



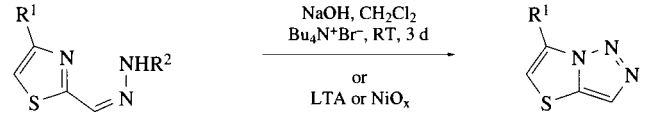
Scheme 17

8.05.9.1.5 (5)C3N2N1 → 124{7}:

(i) NNS/ Thiazolo[3,2-c][1,2,3]triazole

Thiazole-2-carbaldehyde 4-toluenesulfonylhydrazones (**198**; R^2 = Ts) under Bamford–Stephens reaction conditions are converted into thiazolo[3,2-*c*][1,2,3]triazoles (**68**) which in the solid state exist exclusively in the bicyclic state (see Section 8.05.4.2) (Equation (45)) ⟨92JHC713⟩.

Thiazole-2-carbaldehyde hydrazones (**198**; R^2 = H) when treated with oxidizing agents (preferably nickel peroxide) also give thiazolo[3,2-*c*][1,2,3]triazoles (**68**) ⟨91T2851⟩.

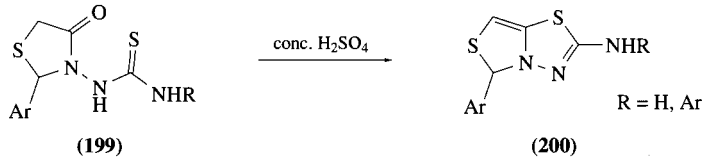


(45)

8.05.9.1.6 (5)N3C2S1

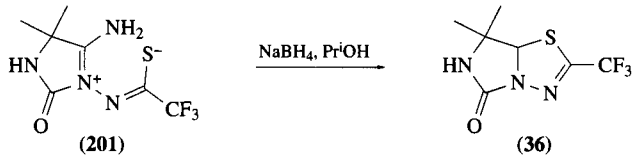
(i) (5)N3C2S1 → 13{4}6:

(a) SN/S Thiazolo[4,3-b][1,3,4]thiadiazole. Cyclodehydration of 2-aryl-3-(*N*-thioureido)-4,5-dihydro-2*H*-thiazol-4-ones (**199**) with concentrated sulfuric acid furnishes 2-amino-4-aryl-5*H*-thiazolo[4,3-*b*]thiadiazoles (**200**) (Equation (46)) ⟨91JIC144, 92MI 805-02, 94MI 805-01⟩.



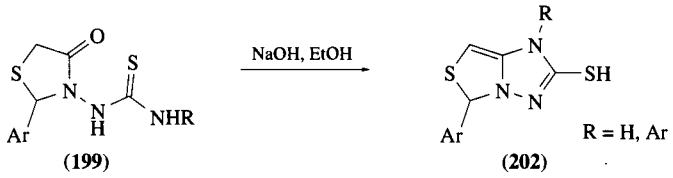
(46)

(b) SN/N Imidazo[5,1-b][1,3,4]thiadiazole. Reduction of 5-(dimethylamino)-3,4-dihydro-4,4-dimethyl-2-oxo-2*H*-imidazolium-trifluorothioacetamidate (**201**) with sodium borohydride furnishes 5,6,7,7a-tetrahydro-7,7-dimethyl-2-(trifluoromethyl)[5,1-*b*][1,3,4]thiadiazol-5-one (**36**) (Equation (47)) ⟨90HCA492⟩.



(201) (36) (47)

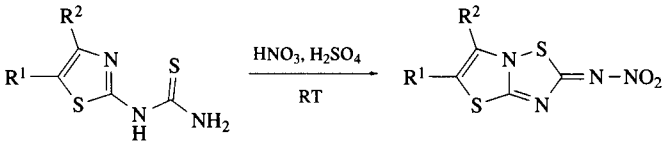
*(c) NN/S Thiazolo[4,3-*b*][1,2,4]triazole.* In contrast to the reaction with sulfuric acid (see above) sodium hydroxide converts 2-aryl-3-(N-thioureido)-4,5-dihydro-2*H*-thiazol-4-ones (**199**) into 5-aryl-2-sulfonyl-1,5-dihydrothiazolo[3,4-*b*][1,3,4]triazole (**202**) (Equation (48)) ⟨92MI 805-02, 94MI 805-01⟩.



(199) (202) (48)

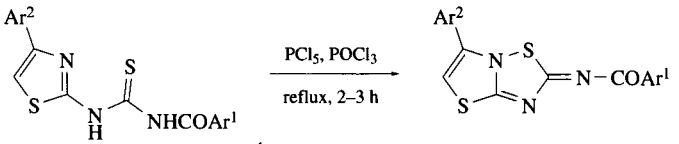
(ii) (5)N3C2S1 → 134{7}:

*(a) SNS/ Thiazolo[3,2-*b*][1,2,4]thiadiazole.* Nitration of *N*-(thiazol-2-yl)thiourea derivatives (**203**) with fuming nitric acid gives 2-nitroiminothiazolo[3,2-*b*][1,2,4]thiadiazoles (**204**) (Equation (49)) ⟨84CPB3483, 84MI 805-02⟩.



(203) (204) (49)

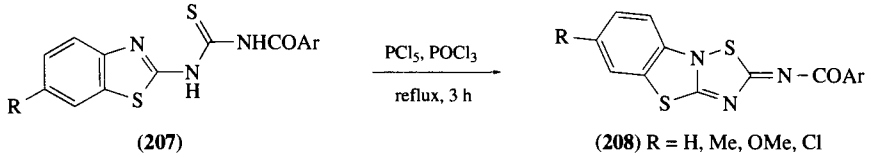
Cyclization of 1-(4-arylthiazol-2-yl)-3-aroylthioureas (**205**) with phosphorus pentachloride or phosphorus oxychloride leads to 5-aryl-2-aroylimino-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazoles (**206**) (Equation (50)) ⟨87SUL1⟩.



(205) (206) (50)

R^1 = H, Me, aryl
R^2 = alkyl, H

Under the same reaction conditions, or with various oxidizing reagents, 1-aroyl-3-(benzothiazol-2-yl)thioureas (**207**) undergo cyclization to give 2-aroylimino-2*H*-[1,2,4]thiadiazolo[3,2-*b*]benzothiazole (**208**) (Equation (51)) ⟨90IJC(B)778⟩.



(207) (208) R = H, Me, OMe, Cl (51)

also with Br_2, AcOH; Br_2, $HCCl_3$; $Pb(OAc)_4$; NBS

*(b) SNN/ Imidazo[1,2-*b*][1,2,4]thiadiazole.* Similarly, 1-aroyl-3(benzoimidazol-2-yl)thioureas

(**209**) are cyclized to 2-aroylamino[1,2,4]thiadiazolo[1,2-*a*]benzimidazoles (**210**) (Equation (52)) ⟨89SC965⟩.



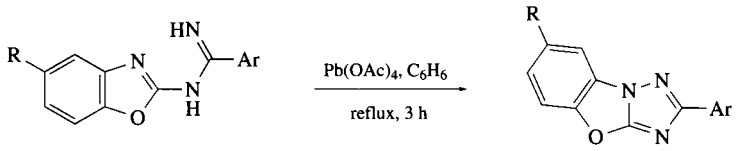
(**209**) (**210**) (52)

also with Br_2, AcOH; Br_2, $HCCl_3$; $Pb(OAc)_4$

8.05.9.1.7 (5)N3C2N1 → 134{7}:

*(i) NNO/ Oxazolo[3,2-*b*][1,2,4]triazole*

Oxidative cyclization of *N*-(benzoxazol-2-yl)benzamidines (**211**) with lead tetraacetate leads to the formation of 2-aryl[1,2,4]triazolo[5,1-*b*]benzoxazoles (**212**) (Equation (53)) ⟨90S422⟩.

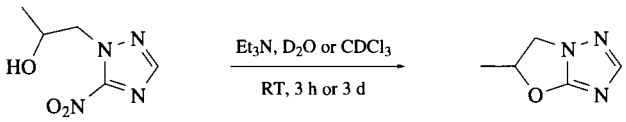


(**211**) R = H, Me (**212**) (53)

8.05.9.1.8 (5)O4C5C6 → 134{7}:

*(i) NNO/ Oxazolo[3,2-*b*][1,2,4]triazole*

By treatment of 2-(2-hydroxypropyl)-3-nitro[1,2,4]triazole (**213**) with triethylamine affords 5,6-dihydro-6-methyloxazolo[3,2-*b*][1,2,4]triazole (**214**) is formed (Equation (54)) ⟨90T3211⟩.

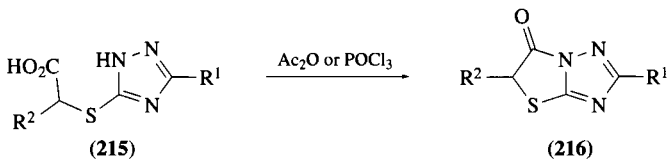


(**213**) (**214**) (54)

8.05.9.1.9 (5)S4C5C6 → 134{7}:

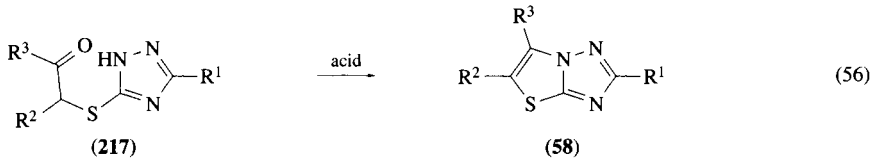
*(i) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole*

Cyclodehydration of 3-carboxymethylthio-1,2,4-triazoles (**215**) with acetic anhydride or phosphorus oxychloride yields 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2-ones (**216**) (Equation (55)) ⟨83JPR869, 88MI 805-01, 91IJC(B)38⟩.



(**215**) (**216**) (55)

Similarly, 2-(2-oxoalkylsulfonyl)-1,2,4-triazoles (**217**) are cyclized through dehydration with acids such as PPA to give thiazolo[3,2-*b*][1,2,4]triazoles (**58**) (Equation (56) and Table 20).

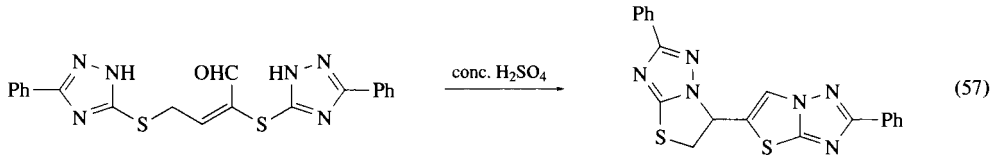


(217) (58) (56)

Table 20 Thiazolo[3,2-b][1,2,4]thiadiazoles (**58**).

R^1	R^2	R^3	*Reagent*	*Ref.*
alkyl, aryl	H	alkyl, Ph	PPA; 105–110°C	85JAP60011493
het	Me, aryl	H, Ac, COCH=CHAr		85MI 805-01
aryl	H	aryl	PPA	85IJC(B)1221, 90IJC(B)88, 92JIC268, 93MI 805-05
H	H	Ph, CH=CHPh	PPA	86JHC1531
aryl	H	Me, aryl	PPA; conc. HCl	87PJC547, 91EJM929
aryl	H, CO_2Et	Me	conc. H_2SO_4	91AP49
Ph	H	het	PPA	94IJC(B)579

Upon treatment with concentrated sulfuric acid 2-[(3-phenyl[1,2,4]triazol-5-yl)thio]-4-[(2-phenyl-[1,3,4]triazol-5-yl)thiobut-2-enal (**65**) undergoes two-fold cyclization to give compound (**146**) (Equation (57)). Boiling (**65**) in ethanol induces the formation of its ring tautomer (**66**) (see Section 8.05.4.2) ⟨87AP(320)528⟩.



(65) (146) (57)

8.05.9.1.10 (5)C6C5N4→134{7}:

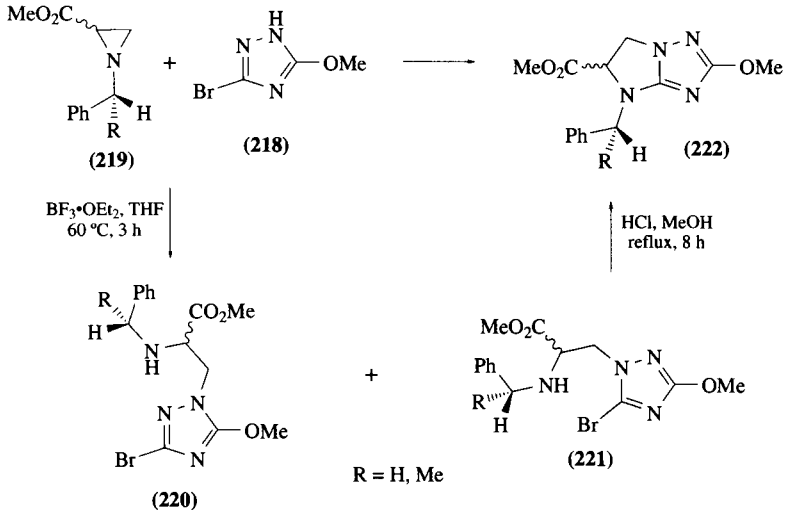
*(i) NNN/ Imidazo[1,2-*b*][1,2,4]triazole*

The reaction of 3-bromo-5-methoxy-1*H*[1,2,4]triazole (**218**) with 1-benzyl-2-methoxycarbonyl-aziridine (**219**) in the presence of boron trifluoride diethylether complex leads to an unseparable mixture of the two isomeric alkylation products methyl 2-benzylamino-3-bromo-5-methoxy-1,2,4-triazol-1-yl)propionate (**220**) and methyl 2-benzylamino-3-(5-bromo-3-methoxy[1,2,4]triazol-1-yl)-propionate (**221**). Treatment of the unseparated mixture with hydrogen chloride in methanol affords methyl 4-benzyl-5,6-dihydro-2-methoxy-5-methoxy-carbonylimidazo[1,2-*b*][1,2,4]triazole (**222**; R = H) ⟨92TA51⟩. Under identical reaction conditions the use of 2-(*S*)-methoxycarbonyl-1-(*R*)-phenylethylaziridine (*S,R*-(**219**)) results in a reaction mixture from which the bicyclic product (*S,R* (**222**); R = Me) is isolated (Scheme 18) ⟨92TA51⟩.

8.05.9.1.11 (5)S7C6C5→12{4}7:

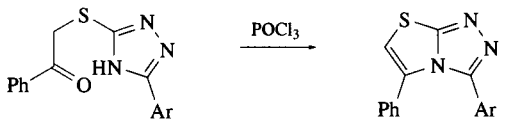
*(i) NN/S Thiazolo[2,3-*c*][1,2,4]triazole*

As an alternative to the formation of the triazole ring of thiazolo[2,3-*c*][1,2,4]triazole (**188**; R^1 = Ar,R^2 = Ph) (as described in the foregoing section, Table 19), the thiazole moiety can be



Scheme 18

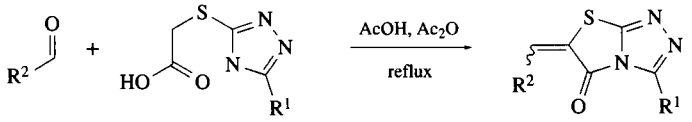
formed through cyclodehydration of 3-aroylmethyl-thio-5-aryl-1,2,4-triazole (**223**) with phosphorus oxychloride (Equation (58)) ⟨91EJM929⟩.



(58)

(**223**) (**188**) R^1 = Ar, R^2 = Ph, R^3 = H

The cyclocondensation of (1,2,4-triazol-5-yl) thioacetic acid (**224**) with aldehydes in acids gives 3-substituted 5,6-dihydro-6-methylenethiazolo[3,2-*c*][1,2,4]triazol-5-ones (**225**) (Equation (59)) ⟨84KFZ1324, 90MI 805-05⟩.



(59)

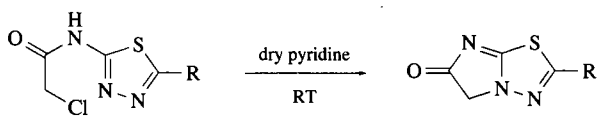
(**224**) (**225**)

R^1 = H, Me, Ph
R^2 = aryl, CH=CHAr, CH=CHhet

8.05.9.1.12 (5)N7C6C5→13{4}7:

*(i) NN/S Imidazo[2,1-*b*][1,3,4]thiadiazole*

Upon treatment with pyridine 5-substituted 2-chloroacetamido[1,3,4]thiadiazoles (**226**) are converted into imidazo[2,1-*b*][1,3,4]thiadiazoles (**227**) (Equation (60)) ⟨90FES1341, 89IJC(B)358⟩.



(60)

(**226**) R = CH_2het, CH_6OR (**227**)

8.05.9.2 Ring Closure of Two Adjacent Substituents Providing Two and One Ring Atoms: (5)2,1 → (5,5)

8.05.9.2.1 N1C2,N3 → 13{4}5:

(i) NN/N [1,2,4]Triazolo[2,3-b]indazoles

The 3-(*N*-acyl-*N*-benzylamino-2-(triphenylphosphoranylidene)-amino-2*H*-indazoles (**228**) on treatment with concentrated hydrochloric acid cyclize to 2-alkyl-1-benzyl-1*H*-[1,2,4]triazolo-[1,5-*b*]indazoles (**229**) (Equation (61)) ⟨90JOC4724⟩.



(228) (229) R = alkyl (61)

8.05.9.2.2 (5)N1C2,N3 → 134{7}:

(i) NNS/ Thiazolo[3,2-b][1,2,4]triazole

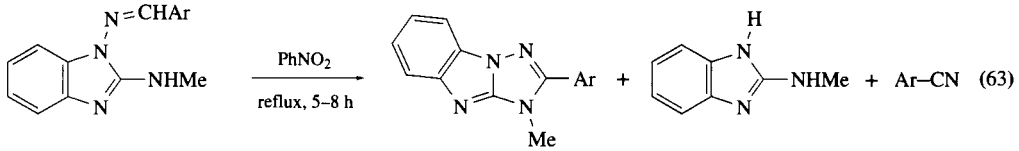
Polyphosphoric acid induces ring-closure of 4-alkyl-3-(chloroacetylamino)-2-imino-2,3-dihydro-thiazole (**230**) to give 6-alkyl-2-chloromethylthiazolo[3,2-*b*][1,2,4]triazoles (**231**) (Equation (62)) ⟨86JAP61286387⟩.



(230) (231) (62)

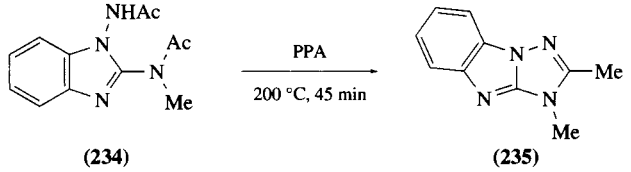
(ii) NNN/ Imidazolo[1,2-b][1,2,4]triazole

When 1-arylidenamino-2-methylaminobenzimidazoles (**232**) are heated in nitrobenzene 2-aryl-3-methyl[1,2,4]triazolo[1,5-*a*]benzimidazoles (**233**) are obtained together with 2-methylamino-benzimidazole and the corresponding benzonitrile (Equation (63)) ⟨88KGS1226⟩.



(232) (233) (63)

Cyclization of 1-acetamino-2-(*N*-acetyl-*N*-methylamino)benzimidazole (**234**) with polyphosphoric acid gives 2,3-dimethyl[1,2,4]triazolo[1,5-*a*]benzimidazole (**235**) (Equation (64)) ⟨88KGS1070⟩.



(234) (235) (64)

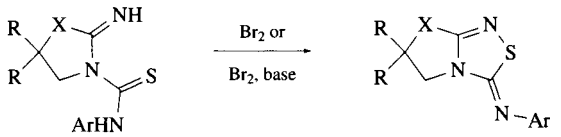
8.05.9.2.3 (5)C3C2,N1 → 12{4}7:

(i) NS/O Oxazolo[2,3-c][1,2,4]thiadiazole

Oxidative ring-closure transforms 3-(*N*-arylthiocarbamoyl)-2-imino-4,5-dihydro-2*H*-oxazoles (**236**; Z = O) into 3-arylimino-5,6-dihydro-3*H*-oxazolo[2,3-*c*][1,2,4]thiadiazoles (**237**; Z = O) (Equation (65) ⟨84GEP3528583⟩.

(ii) NS/S Thiazolo[2,3-c][1,2,4]thiadiazole

Similarly the 3-(*N*-arylthiocarbamoyl)-2-imino-4,5-dihydro-2*H*-thiazoles (**236**; Z = S) are transformed into 3-arylimino-5,6-dihydro-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles (**237**; Z = S) (Equation (65) ⟨84GEP3528583, 85JAP60214791, 87JAP62181283, 93MI 805-02⟩



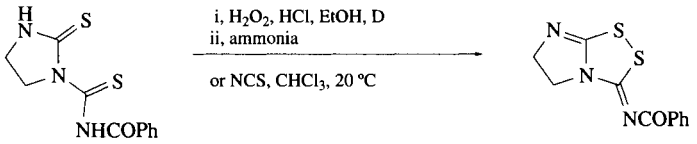
(65)

(**236**) (**237**)

8.05.9.2.4 (5)C3S2,S1 → 12{4}7:

(i) SS/N Imidazo[2,1-c][1,2,4]dithiazole

1-(*N*-Benzoylthiocarbamoyl)imidazolidine-2-thione (**238**) is oxidized with hydrogen peroxide in acid solution to give after neutralization 3-benzoylimino-5,6-dihydroimidazo[2,1-*c*][1,2,4]dithiazole (**19**) ⟨93MI 805-03⟩ which can also be obtained from the reaction of (**238**) with *N*-chlorosuccinimide (Equation (66)) ⟨86S751⟩.



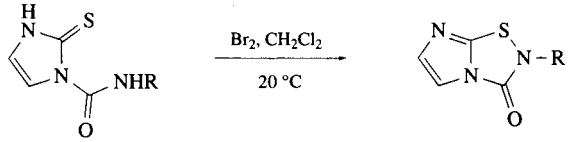
(66)

(**238**) (**19**)

8.05.9.2.5 (5)C3N2,S1 → 12{4}7:

(i) SN/N Imidazo[1,2-d][1,2,4]thiadiazole

Upon reaction with bromine 1-cyclohexylcarbamoylimidazoline-2-thione (**239**) is converted into 2-cyclohexyl-2,3-dihydroimidazo[1,2-*d*][1,2,4]thiadiazol-3-one (**240**) (Equation (67)) ⟨88JPC338⟩.

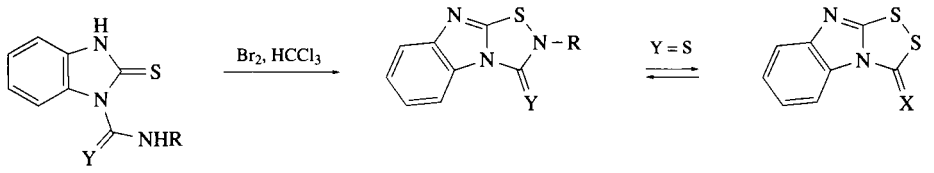


(67)

(**239**) (**240**) R = cyclohexyl

Oxidative cyclization by bromine converts the 1-carbamoyl- and 1-thiocabamoyl-benzimidazoline-2-thiones (**241**) and (**242**) into the respective 2-substituted 2,3-dihydro-[1,2,4]thia-

diazolo[4,5-*a*]benzimidazol-3-ones (**109**) and 3-thiones (**243**) (Scheme 19). The latter colorless compounds coexist in an equilibrium with the tautomeric yellow form of 3-imino-3*H*-[1,2,4]dithiazolo[4,3-*a*]benzimidazoles (**113**; X = NR) (see Section 8.05.4.2) ⟨83T2311⟩.



(**241**) Y = O
(**242**) Y = S

(**111**) Y = O
(**243**) Y = S

(**113**) X = NR

Scheme 19

8.05.9.2.6 (5)N3C2,O1 → 13{4}6:

*(i) ON/S Thiazolo[4,3-*b*][1,3,4]oxadiazole*

Intramolecular cyclization of 3-thioureido-thiazolidin-4-ones (**199**) is achieved selectively in different ways (see Section 8.05.9.1.6.1. Methyl iodide in methanol ⟨92MI 805-02⟩ or iodine in alkaline KI ⟨94MI 805-01⟩ afford 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,3,4]oxadiazoles (**33**) (Equation (68))



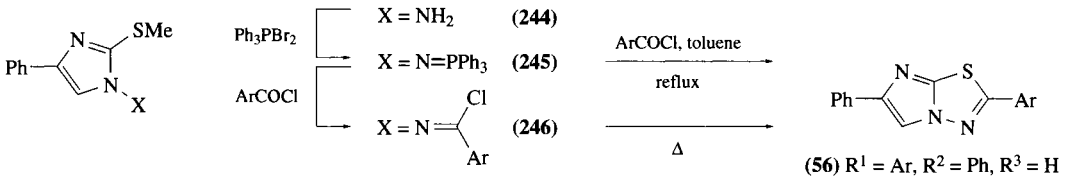
(68)

(**199**) (**33**)

8.05.9.2.7 (5)N3C2,S1 → 13{4}7:

*(i) SN/N Imidazo[2,1-*b*][1,3,4]thiadiazole*

1-Amino-2-methylsulfonyl-4-phenylimidazole (**244**) reacts with triphenylphospine dibromide; the resultant 2-methylsulfonyl-4-phenyl-1-triphenylphosphoranylideneaminoimidazole (**245**) reacts with aroyl chlorides in dry toluene at reflux temperature to give 2-aryl-6-phenylimidazo[2,1-*b*][1,3,4]-thiadiazoles (**56**). This conversion involves aryl-*N*-(2-methylsulfonyl-4-phenylimidazol-1-yl)imidoyl chlorides (**246**) as intermediates; they can be isolated, and upon heating they are transformed into the fused heterocycles (Scheme 20).



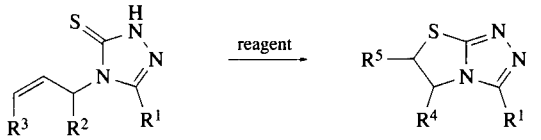
(**56**) R^1 = Ar, R^2 = Ph, R^3 = H

Scheme 20

8.05.9.2.8 (5)C5C6,S7→12{4}7:

(i) NN/S Thiazolo[2,3-c][1,2,4]triazole

The alkenic double bond of 3-aryl-4-(2-alken-1-yl)-4,5-dihydrotriazole-5-thiones (**247**) is involved in the ring closure to form substituted 5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles (**248**) (Equation (69), Table 21).



(247) (248) (69)

Table 21 5,6-Dihydrothiazolo[2,3-c][1,2,4]triazoles (**47**) and (**48**).

R^1	R^2	R^3	R^4	R^5	*Reagent*	*Ref.*
CH_2Ph, aryl	H	H	H	Me	HBr, H_2O; Δ, sealed tube, 5-20 h	83PJC567
aryl		$(CH_2)_3$	$(CH_2)_3CHI$		I_2, pyridine	84KGS843

Treatment of 3-substituted 4,5-dihydro-4-(2-dimethoxyethyl)-1,2,4-triazole-5-thiones (**249**) with a Lewis acid effects cyclization yielding 3-substituted 5,6-dihydro-6-methoxythiazolo[2,3-*c*][1,2,4]triazoles (**250**) (Equation (70)) ⟨91MI 805-01⟩.



(249) (250) (70)

8.05.9.2.9 (5)C5C6,N7→13{4}7:

(i) SN/N Imidazo[2,1-b][1,3,4]thiadiazole

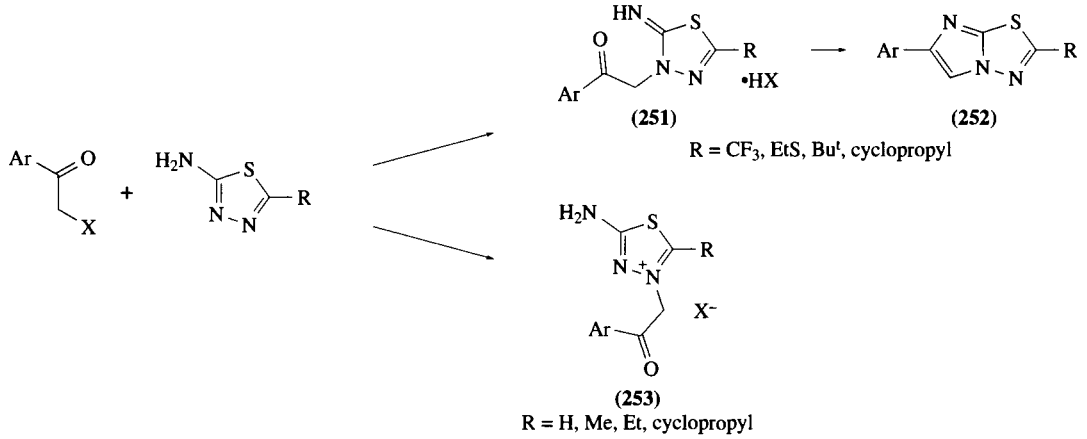
The investigation of the synthesis of 6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles (**252**) through the quaternization of 2-amino-1,3,4-thiadiazoles with α-haloacetophenones revealed the control by the nature of the substituent R at position 5 of the thiadiazole. Electron-withdrawing or bulky groups at this position direct alkylation to 3-N, and via 3-aroylmethyl-2,3-dihydro-2-imino[1,3,4]thiadiazole hydrohalides (**251**) the fused heterocyclic system (**252**) is formed. With hydrogen or a small alkyl group at position 5 of the thiadiazole, alkylation occurs at 4-N resulting in the formation of 2-amino-4-aroylmethyl[1,3,4]thiadiazolium halides (**253**) (Scheme 21) ⟨93H(35)763⟩.

To obtain 2-methyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (**252**; R = Me, Ar = Ph) from 2-amino-5-methyl[1,3,4]thiadiazole (**254**; X = NH_2) the 2-(*N*,*N*-dimethylaminomethyleneamino)-5-methyl[1,3,4]thiadiazole (**254**; X = $Me_2NCH{=}N$) must be prepared. This derivative reacts with phenacyl bromide at 3-N; the resultant 2-amino-3-benzoylmethyl-5-methyl[1,3,4]thiadiazolium bromide (**255**) upon heating in polyphosphoric acid (PPA) affords the fused heterocycle (Scheme 22) ⟨86H(24)379⟩.

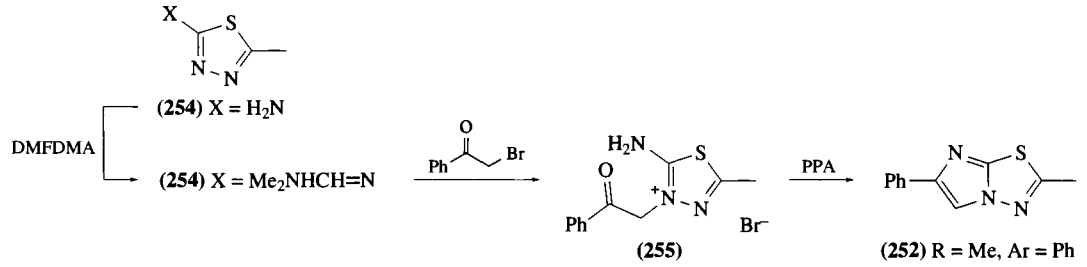
8.05.9.2.10 (5)C6C5,N4→134{7}:

(i) NNN Imidazo[1,2-b][1,2,4]triazole

When heated with acid (3-),4-(di)substituted 5-amino-1-(1-aroylalkyl)-4*H*[1,2,4]triazolium bromides (**257**) (accessible by quaternization of (3),4-(di)substituted 5-amino[1,2,4]triazoles with

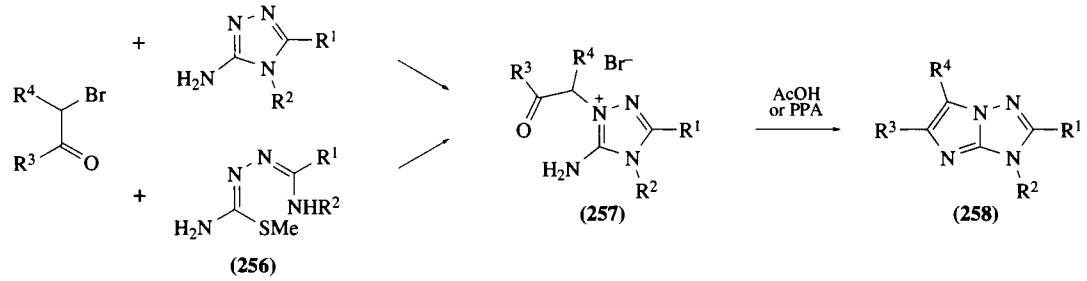


Scheme 21



Scheme 22

1-aroyl-1-haloketones or by alkylating cyclization of 4-arylmethylvaleramide *S*-methylisothiosemicarbazide (**256**; R^1 = Bu) with phenacyl bromide) undergo cyclization affording (2),3,5,(6)-substituted imidazo[1,2-*b*][1,2,4]triazoles (**258**) (Scheme 23) ⟨84UKZ1279, 92EUP505111, 93JMC591⟩.



Scheme 23

Heated without solvent, the 5-amino-1-(1-carboxyalkyl)-3-methylthio-1*H*[1,2,4]triazoles (**259**) undergo cyclization to yield 5,6-dihydro-2-methylsulfonyl-4*H*-imidazo[1,2-*b*][1,2,4]triazol-5-ones (**260**) (Equation (71)) ⟨85JHC385⟩.

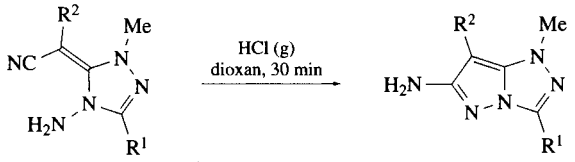


(71)

8.05.9.2.11 (5)C7aC6,N5 → 12{4}5:

(i) NN/N Pyrazolo[5,1-c][1,2,4]triazole

Dry hydrogen chloride rapidly induces the cyclization of 1,3-disubstituted 4-amino-5-cyanomethylene[1,2,4]triazoles (**261**) into 1,3,7-trisubstituted 6-aminopyrazolo[5,1-*c*][1,2,4]triazoles (**262**) (Equation (72)) ⟨85H641⟩.



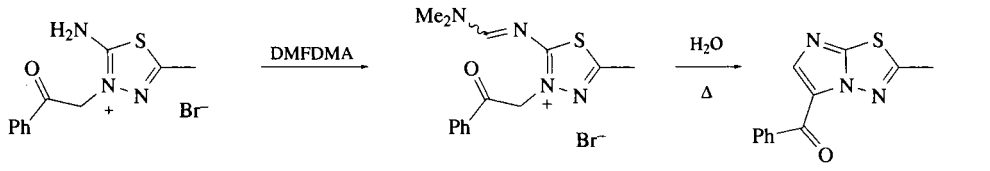
(72)

(**261**) R^1 = Me, SMe; R^2 = CN, CO_2R, $CONH_2$ (**262**)

8.05.9.2.12 (5)N7C6,C5 → 13{4}7:

(i) SN/N Imidazo[2,1-b][1,3,4]thiadiazole

DMFDMA converts 2-amino-5-methyl-3-phenacyl-1,3,4-thiadiazolium bromide (**255**) (see Section 8.05.9.2.9) into 3-benzoylmethyl-5-methyl-2-(*N*,*N*-dimethylaminomethyleneamino)-1,3,4-thiadiazolium bromide (**263**); heating this compound in water produces 5-benzoyl-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (**55**; R^1 = Me, R^2 = PhCO, R^3 = H) (Scheme 24) ⟨86H(24)379⟩.



(**255**) (**263**) (**55**) R^1 = Me, R^2 = PhCO, R^3 = H

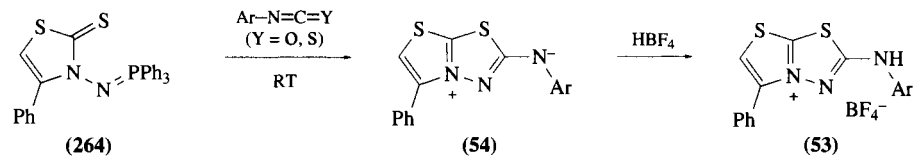
Scheme 24

8.05.9.3 Formation of the Second Ring by Insertion of a One-atom Ring Member between Two Adjacent Substituents at the First Ring, Each Providing One Atom for the Second Ring: (5)1,1 + 1 → (5,5)

8.05.9.3.1 (5)S1,N3 + C2 → 13{4}7:

(i) SN/S Thiazolo[2,3-b][1,3,4]thiadiazole

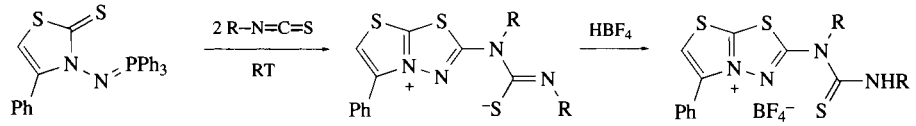
The reaction of iminophosphorane (**264**) with aromatic iso(thio)cyanates leads to anhydro 2-arylamino-5-phenyl-thiazolo[2,3-*b*][1,3,4]thiadiazol-4-ium hydroxides (**54**) which upon treatment with tetrafluoroboric acid give the corresponding 2-arylamino-5-phenylthiazolo[2,3-*b*][1,3,4]-thiadiazolium tetrafluoroborates (**53**) (Scheme 25) ⟨92T1282⟩.



(**264**) (**54**) (**53**)

Scheme 25

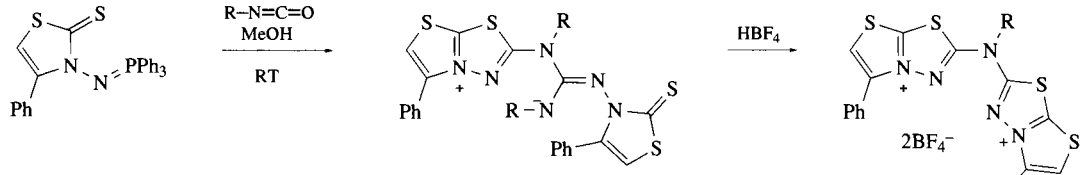
By contrast, the reaction of (**264**) with aliphatic isothiocyanates affords the betaines (**265**) which upon treatment with tetrafluoroboric acid yield 5-phenyl-2-(1,3-dialkylthioureido)thiazolo[2,3-*b*][1,3,4]thiadiazolium terafluoroborates (**266**) (Scheme 26) ⟨92T1285⟩.



(**264**) (**265**) (**266**)

Scheme 26

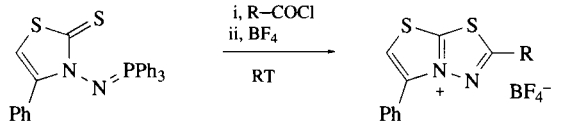
From the reaction of iminophosphorane (**264**) with aliphatic isocyanates zwitterionic *N,N'*-bisheteroarylguanidines (**267**) are obtained; treatment with fluoroboric acid induces the conversion into alkylbis-(thiazolo[2,3-*b*][1,3,4]thiadiazolium-2-yl)amin bis(tetrafluoroborates) (**268**) (Scheme 27) ⟨92T1285⟩.



(**264**) (**267**) (**268**)

Scheme 27

The reaction of iminophosphorane (**264**) with acyl chlorides followed by fluoroboric acid affords 2-substituted 5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazolium salts (**269**) (Equation (73)) ⟨92T1285⟩.

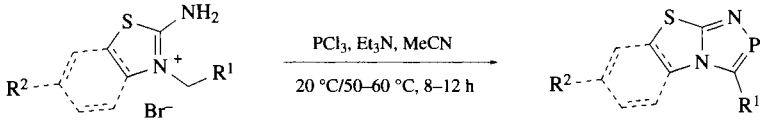


(**264**) (**269**) (73)

8.05.9.3.2 (5)N1,C3 + P2 → 12{4}7:

(i) NP/S Thiazolo[3,2-d][1,4,2]diazaphosphole

The 3-substituted 2-aminothiazolium bromides undergo cyclocondensation with phosphorus trichloride in the presence of triethylamine to give 3-substituted thiazolo[3,2-*d*][1,4,2]diazaphospholes (**271**), the 5,6-dihydro and the benzo derivatives (Equation (74)) ⟨92S267⟩.



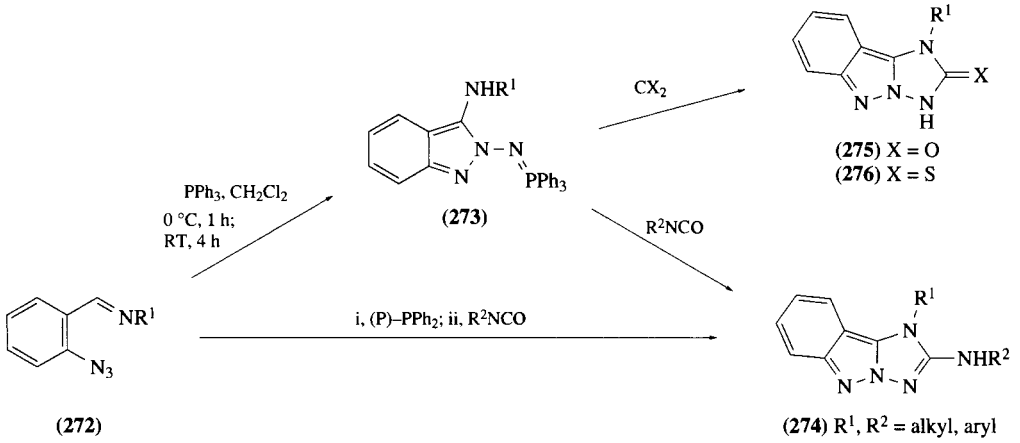
(**270**) (**271**) (74)

8.05.9.3.3 (5)N1,N3 + C2

(i) (5)N1,N3 + C2 → 13{4}5:

(a) NN/N Pyrazolo[1,5-b][1,2,4]triazole. Heterocumulenes react with 3-amino-2-(triphenylphosphoranylidene)amino-2*H*-indazoles (**273**) (available from the reaction of 2-azidobenzaldimines

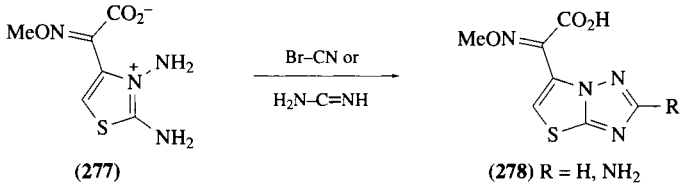
(**272**) with triphenylphosphine) to give 1*H*-[1,2,4]triazolo[1,5-*b*]indazole derivatives: isocyanates produce 1-substituted 2-amino-1*H*-[1,2,4]triazolo[1,5-*b*]indazoles (**274**) ⟨89TL6237, 90JOC4724⟩, which can also be prepared from 2-azidobenzaldimines (**272**) by sequential treatment with polystyryldiphenylphosphine and isocyanates ⟨90JOC4724⟩. Carbon dioxide and carbon disulfide give the respective 2,3-dihydro-1*H*-[1,2,4]triazolo[1,5-*b*]indazol-2-one (**275**) and -2-thione (**276**) (Scheme 28) ⟨90JOC4724⟩.



Scheme 28

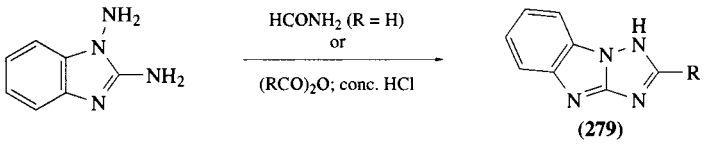
(ii) (5)N1,N3 + C2 → 134{7}:

*(a) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole.* The cyclization of 2,3-diaminothiazolium-5-yl (*N*-methoxyimino)acetate (**277**) with cyanogen bromide or formamidine furnishes the respective 5-[carboxy(*N*-methoxyimino)methyl]-thiazolo[3,2-*b*][1,2,4]triazole derivatives (**278**) (Equation (75)) ⟨90MI 805-04⟩.



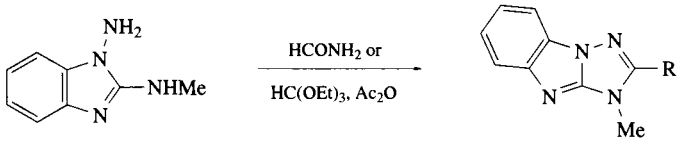
(75)

*(b) NNN/ Imidazo[1,2-*b*][1,2,4]triazole.* Heating 1,2-diaminobenzimidazole with formamide or with anhydrides followed by treatment with concentrated hydrochloric acid gives (in the latter case the 2-substituted) 1*H*-[1,2,4]triazolo[1,5-*a*]benzimidazoles (**279**) (Equation (76)) ⟨87KGS278, 89KGS209⟩.



(76)

Heating 1-amino-2-methylaminobenzimidazole (**280**) with formamide or triethyl orthoformate in acetic anhydride affords 3-methyl-3*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**281**) (Equation (77)) ⟨87KGS278, 88KGS1070, 89KGS209⟩.



(280) (281) (77)

Formamide and anhydrides (most efficiently in the presence of potassium carbonate) convert the 3-alkyl-1,2-diaminobenzimidazolium salts (**282**) into the respective 2-substituted 4-alkyl-4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**283**) (Equation (78)) ⟨87KGS278, 88KGS1226, 89KGS209⟩.



(282) (283) (78)

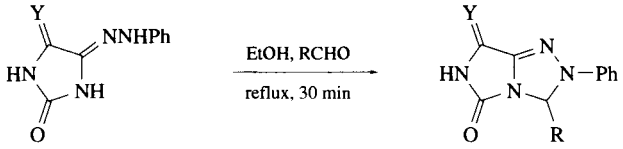
reagent: $HCONH_2$ (R^1 = H), or $(R^1CO)_2O$ or R^1COY, K_2CO_3

8.05.9.4 Formation of the Second Ring by Insertion of a One-atom Ring Member between a Substituent at the First Ring Providing Two Ring Atoms, and the Adjacent Ring Atom: (5)2 + 1 → (5,5)

8.05.9.4.1 (5)N1N2 + C3 → 12{4}6:

(i) NN/N Imidazo[5,1-c][1,2,4]triazole

The 4-phenylhydrazonoimidazolidin-2-ones (**284**) undergo cyclocondensation with aldehydes to give the corresponding 2-phenyl-3,5,6,7-tetrahydro-2*H*-imidazo[5,1-*c*][1,2,4]triazol-5-ones (**285**) (Equation (79)) ⟨83JHC189⟩.

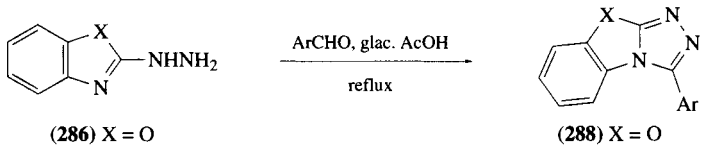


(284) (285) Y = Ar, H (79)

8.05.9.4.2 (5)N1N2 + C3 → 12{4}7:

(i) NN/O Oxazolo[2,3-c][1,2,4]triazole, NN/S Thiazolo[2,3-c][1,2,4]triazole, NN/N Imidazo[2,3-c][1,2,4]triazole

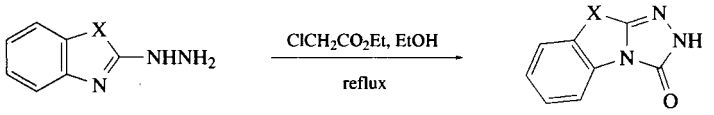
Condensation of 2-hydrazinobenzoxazoles (**286**) with aromatic aldehydes in glacial acetic acid yields 3-aryl[1,2,4]triazolo[3,4-*b*]benzoxazoles (**288**) ⟨88BCJ1339⟩. Similarly, 3-aryl-9*H*-[1,2,4]triazolo[4,3-*b*]benzimidazoles (**287**) are obtained from 2-hydrazinobenzimidazoles (**289**) (Equation (80)) ⟨88BCJ1339⟩.



(286) X = O
(287) X = NH

(288) X = O
(289) X = NH (80)

Ethyl chloroacetate converts 2-hydrazinobenzoxazole (**286**) into 2*H*-[1,2,4]triazolo[3,4-*b*]benzoxazol-3-ones (**291**) ⟨88BCJ1339⟩. Also 2,9-dihydro[1,2,4]triazolo[4,3-*b*]benzimidazol-3-ones (**292**) and 2*H*-[1,2,4]triazolo[3,4-*b*]benzthiazol-3-ones (**293**) are formed from the respective 2-hydrazinobenzimidazole (**287**) and 2-hydrazinobenzthiazole (**290**) (Equation (81)) ⟨88BCJ1339⟩.

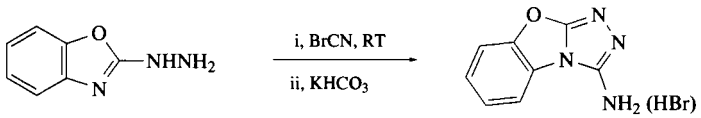


(81)

(**286**) X = O
(**287**) X = NH
(**290**) X = S

(**291**) X = O
(**292**) X = NH
(**293**) X = S

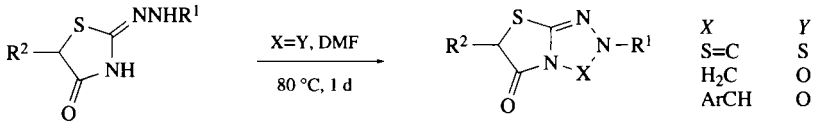
The reaction of 2-hydrazinobenzoxazole (**286**) with cyanogen bromide gives 4-amino-[1,2,4]triazolo[3,4-*b*]benzoxazole hydrobromide (**294**·HBr); the free base (**294**) is obtained with potassium hydrogen carbonate (Equation (82)) ⟨89H(29)925⟩.



(82)

(**286**) (**294**)

Cyclocondensation of 2-hydrazonothiazolidin-4-ones (**295**) with carbon disulfide, paraformaldehyde or 4-chlorobenzaldehyde affords the corresponding 3-functionalized 2,3,5,6-tetrahydrothiazolo[2,3-*c*][1,2,4]triazol-5-ones (**296**) (Equation (83)) ⟨91MI 805-02⟩.

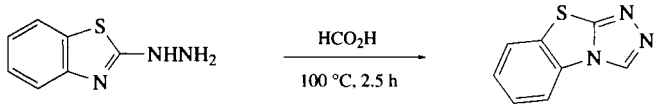


X	*Y*
S=C	S
H_2C	O
ArCH	O

(83)

(**295**) R^1 = H, Ph; R^2 = H, Me (**296**)

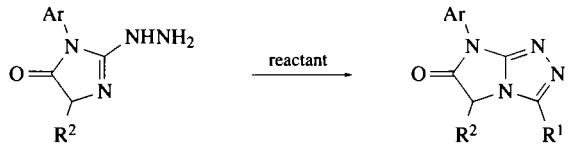
With formic acid 2-hydrazinobenzthiazole (**290**) is cyclized to [1,2,4]triazolo[4,3-*b*]benzthiazole (**47**) (Equation (84)) ⟨84KGS40⟩.



(84)

(**290**) (**47**)

Cyclocondensation of 1-aryl-2-hydrazino-4,5-dihydro-3*H*-imidazol-5-ones (**297**) with carboxylic acids or carbonic acid derivatives gives the corresponding 7-aryl-6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6-ones (**298**) (Equation (85)) ⟨91MI 805-03, 91MI 805-04⟩.

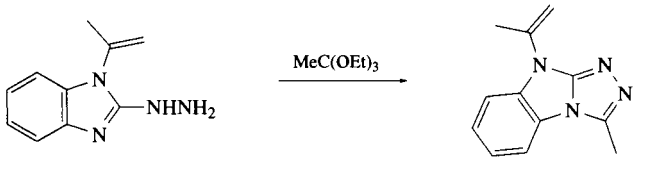


Reactant	*R*^{1}
2,4-$Cl_2C_6H_3OCH_2CO_2H$	2,4-$Cl_2C_6H_3OCH_2$
HCO_2H	H
$ClCO_2Et$	OH
CS_2	SH

(85)

(**297**) (**298**)

Triethyl orthoacetate converts 2-hydrazino-1-(2-propenyl)-1*H*-benzimidazole (**299**) into 3-methyl-9-(2-propenyl)-9*H*-[1,2,4]triazolo[4,3-*a*]benzimidazole (**300**) (Equation (86)) ⟨88TL195⟩.

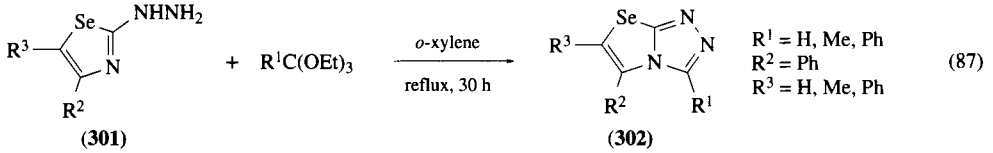


(86)

(**299**) (**300**)

(ii) NN/Se Selenazolo[2,3-c][1,2,4]triazole

The reaction of 2-hydrazinoselenazoles (**301**) with orthoesters provides selenazolo[2,3-*c*][1,2,4]-triazoles (**302**) (Equation (87)) ⟨91GEP289273, 91MI 805-01⟩.



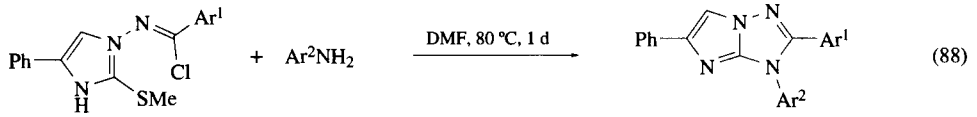
(87)

(**301**) (**302**)

8.05.9.4.3 (5)N1C2 + N3 → 134{7}:

(i) NNN/ Imidazo[1,2-b][1,2,4]triazole

Imidoyl chlorides (**303**) react with primary aromatic amines to give 2,3-diaryl-5-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazoles (**304**) (Equation (88)) ⟨89JCR(S)262⟩.



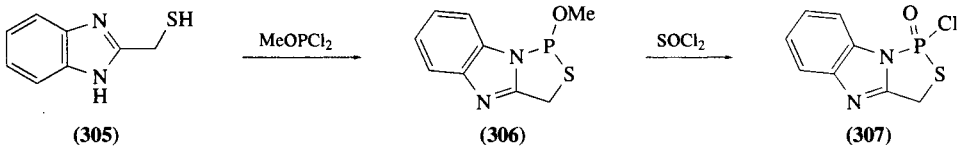
(88)

(**303**) (**304**)

8.05.9.4.4 (5)C3S2 + P1 → 12{4}7:

(i) PS/N Imidazo[1,2-c][1,3,2]thiazaphosphole

The reaction of methoxy phosphorus dichloride and 2-mercaptomethylbenzimidazole (**305**) give 1-methoxy-[1,3,2]thiazaphospholo[3,4-*a*]benzimidazole (**306**); thionylchloride converts it into the unstable 1-chloro-1-oxo-1λ^5-[1,3,2]thiazaphospholo[3,4-*a*]benzimidazole (**307**) (Scheme 29) ⟨90PS(51-52)57⟩.



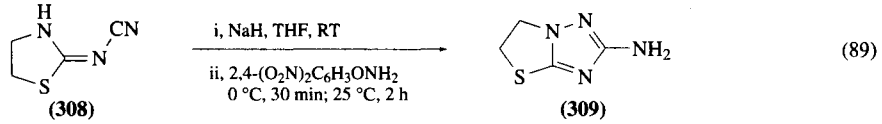
(**305**) (**306**) (**307**)

Scheme 29

8.05.9.4.5 (5)N3C2 + N1 → 134{7}:

(i) NNS/ Thiazolo[3,2-b][1,2,4]triazole

Treatment of the sodium salt of 2-(cyanoimino)tetrahydro-thiazole (**308**) with *O*-(2,4-dinitrophenyl)hydroxylamine affords 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**309**) (Equation (89)) ⟨88S261⟩.



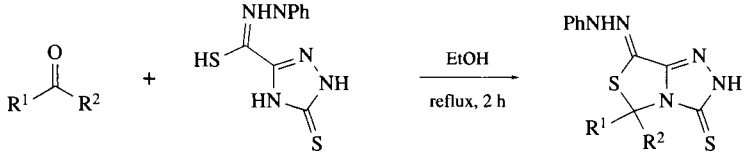
(89)

(**308**) (**309**)

8.05.9.4.6 (5)C7S6 + C5 → 12{4}6:

(i) NN/S Thiazolo[4,3-c][1,2,4]triazole

Carbonyl compounds and 4-(1-sulfonyl-1-phenylhydrazonomethyl)-2,3-dihydro-1,2,4-triazole-2-thione (**310**) undergo cyclocondensation to give 7-phenylhydrazono-2,3,5,7-tetra-hydrothiazolo[4,3-*c*][1,2,4]triazole-3-thiones (**311**) (Equation (90)) ⟨90AP(323)57⟩.



R^1 = H, Me, Ph
R^2 = H, Me

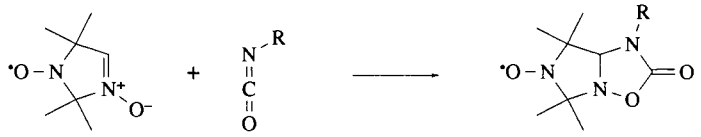
(310) (311) (90)

8.05.9.5 Formation of the Second Ring by Insertion of a Two-atom Ring Member between a Substituent at the First Ring Providing One Atom and the Adjacent Ring Atom: (5)1 + 2 → (5,5)

8.05.9.5.1 (5)O1 + C2N3 → 13{4}6:

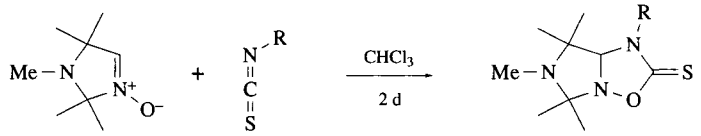
(i) NO/N Imidazo[1,5-b][1,2,4]oxadiazole

The cycloaddition of 2,2,5,5-tetramethyl-1-oxyl-2,5-dihydro-1*H*-imidazol-3-oxide (**312**) with isocyanates yields the 6-oxyl-1*H*-imidazo[1,5-*b*][1,2,4]oxadiazol-2-ones (**109**) (Equation (91)) ⟨85TL4801, 90MI 805-03, 92S1223, 93JCS(P2)2157, 93T10693⟩.



(312) (109) (91)

Similarly, 2,2,3,4,4-pentamethyl-2,5-dihydro-1*H*-imidazol-1-oxide (**313**) undergoes [3 + 2] cycloaddition with isothiocyanates to give 5,5,6,7,7-pentamethyl-1,2,5,6,7,7a-hexahydroimidazo[1,5-*b*][1,2,4]oxadiazole-2-thione (**314**) (Equation (92)) ⟨91IZV2642⟩.

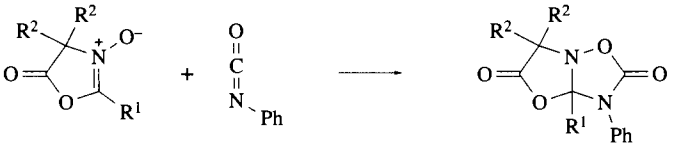


(313) (314) (92)

8.05.9.5.2 (5)O1 + C2N3 → 134{7}:

(i) ONO/ Isoxazolo[3,2-b][1,2,4]oxadiazole

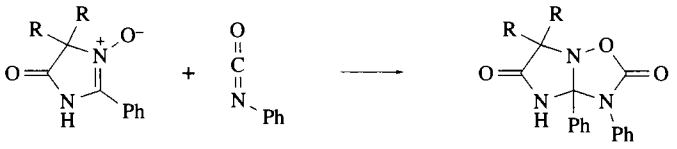
The cyclic nitrones (**315**) undergo [3 + 2]cycloaddition with phenylisocyanate to give 6,6-di- and 3a,6,6-trisubstituted 3-phenyl-3,3a,6-tetrahydro-2*H*-isoxazolo[1,2-*b*][1,2,4]oxadiazole-2,5-diones (**316**) (Equation (93)) ⟨84JOC3127, 85JOC3076⟩.



(315) R^1 = H, Me, Ph; R^2 = alkyl (316) (93)

*(ii) ONN/ Imidazo[1,2-*b*][1,2,4]oxadiazole*

Similar cyclic nitrones (**317**), with phenylisocyanate give 6,6-disubstituted 3,3a-diphenylhexahydroimidazo[1,2-*b*][1,2,4]oxadiazole-2,5-diones (**318**) (Equation (94)) ⟨84BAP195⟩.

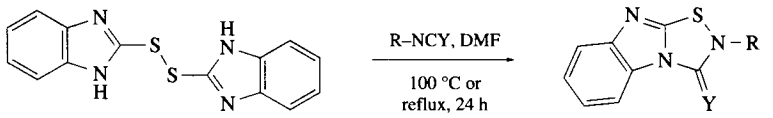


(317) R = Me, $(CH_2)_5$ (316) (94)

8.05.9.5.3 (5)S1 + C2N3 → 12{4}7:

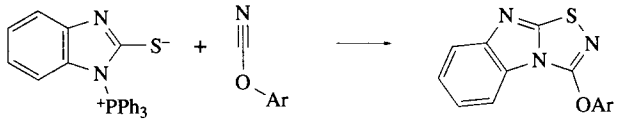
*(i) SN/N Imidazo[1,2-*d*][1,2,4]thiadiazole*

Bis(benzimidazoyl)disulfide (**319**) undergoes cycloaddition with isocyanates and also with phenylisothiocyanate to give 2,3-dihydro[1,2,4]thiadiazolo[4,5-*a*]benzimidazol-3-ones (**320**; Y = O) and the 3-thione (**320**; Y = S), respectively (Equation (95)) ⟨83T2311⟩.



(319) R = alkyl, Ph; Y = O; R = Ph; Y = S (320) (95)

Triphenylphosphonio-2-thiobenzimidazolate (**321**) reacts with (4-methylphenyl)cyanate to furnish 3-(4-methylphenyloxy)[1,2,4]thiadiazolo[4,5-*a*]benzimidazole (**322**) (Equation (96)) ⟨88JPC338⟩.

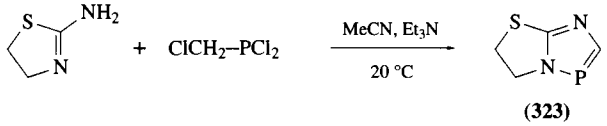


(321) (322) (96)

8.05.9.5.4 (5)N1 + C2P3 → 13{4}7:

*(i) NP/S Thiazolo[2,3-*b*][1,3,4]diazaphosphole*

From the reaction of 2-aminothiazolidine with chloromethyldichlorophosphane the only product isolated is 5,6-dihydrothiazolo[2,3-*b*][1,3,4]diazaphosphole (**323**) (Equation (97)) ⟨86PS(28)289⟩.

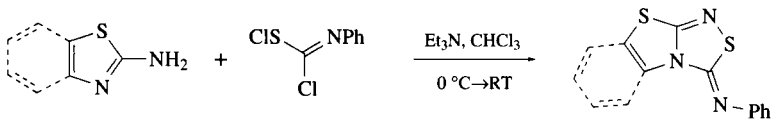


(323) (97)

8.05.9.5.5 (5)N1 + S2C3→

(i) (5)N1 + S2C3 → 12{4}7:

(a) NS/S Thiazolo[2,3-c][1,2,4]thiadiazole. The reactions of 1-chloro-1-phenyliminomethanesulfenyl chloride with 2-aminothiazole or with 2-aminobenzthiazole yield 3-phenylimino-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (**45**; R^1 = Ph, R^2 = H) and 3-phenylimino-3*H*-[1,2,4]thiadiazolo[3,4-*b*]benzothiazole (**62**; Ar = Ph), respectively (Equation (98)) ⟨86S1027⟩.

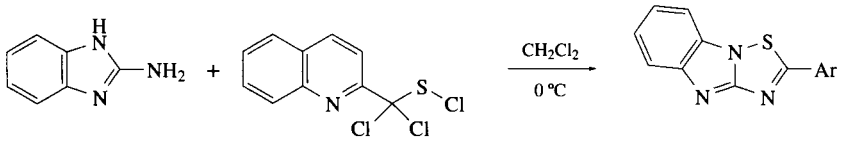


(98)

(**45**) R^1 = Ph, R^2 = H
(**62**) Ar = Ph

(ii) (5)N1 + S2C3 → 134{7}:

(a) SNN/ Imidazo[1,2-b][1,2,4]thiadiazole. Reaction of dichloro-(2-quinolinyl)methanesulfenyl chloride (**324**) with 2-aminobenzimidazole gives 2-(2-quinolinyl)[1,2,4]thiadiazolo[2,3-*a*]benzimidazole (**325**) (Equation (99)) ⟨88JCS(P1)3019⟩.



(99)

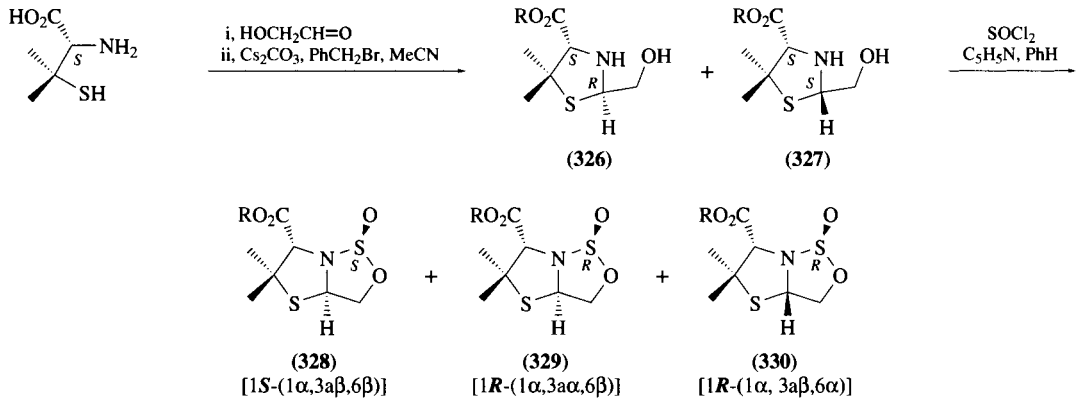
(**324**)

(**325**) Ar = 2-quinoline

8.05.9.5.6 (5)C3 + S102 → 124{7}:

(i) SOS/ Thiazolo[3,2-c][1,2,3]oxathiazole

Reaction of the mixture of diastereomers of (2*R*,4*S*)- and (2*S*,4*S*)-2-hydroxymethyl-5,5-dimethyl-4-phenylmethoxycarbonyltetrahydrothiazoles (**326**) and (**327**) (obtained from the condensation of D-(−)-penicillamine with glycolaldehyde followed by esterification) with thionyl chloride gives three bicyclic sulfamidites, the [1*S*-(1α,3aβ,6β)]-, [1*R*-(1α,3aα,6α)]-, and [1*S*-(1α,3aβ,6α)]-5,5-dimethyl-6-phenylmethoxycarbonyl-3,3a,4,6-tetrahydro-thiazolo[3,2-*c*][1,2,3]oxathiazole-1-oxides (**328**), (**329**) and (**330**) (Scheme 30) ⟨89CC1702⟩.



(**326**) (**327**)

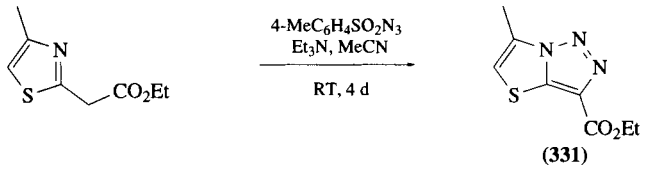
(**328**) [1*S*-(1α,3aβ,6β)] (**329**) [1*R*-(1α,3aα,6β)] (**330**) [1*R*-(1α, 3aβ,6α)]

Scheme 30

8.05.9.5.7 (5)C3 + N1N2 →

(i) (5)C3 + N1N2 → 124{7}:

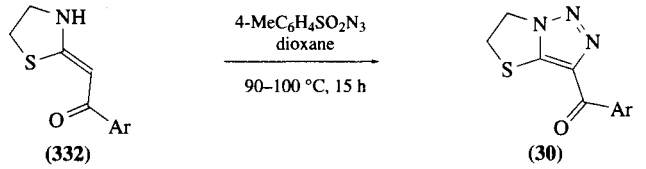
(a) NNS/ Thiazolo[3,2-c][1,2,3]triazole. Tosyl azide converts 2-ethoxycarbonylmethyl-4-methylthiazole into 3-ethoxycarbonyl-6-methylthiazolo[3,2-*c*][1,2,3]triazole (**331**) (Equation (100)) ⟨92JHC713⟩.



(100)

(331)

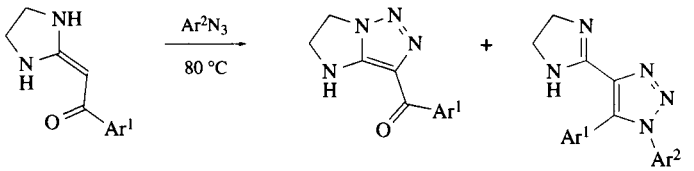
The reaction of 2-aroylmethylenetetrahydrothiazole (**332**) with tosyl azide furnishes 3-aroyl-5,6-dihydrothiazolo[3,2-*c*][1,2,3]triazoles (**30**) (Equation (101)) ⟨88S851⟩.



(101)

(332) (30)

(a) NNN/ Imidazo[1,2-c][1,2,3]triazole. Similarly, the reaction between the cyclic ketene aminals 2-(aroylmethylene)imidazolidines (**333**) and arylazides affords 3-aroyl-5,6-dihydro-4*H*-imidazo[1,2-*c*][1,2,3]triazoles (**334**) and, in addition, 1,5-diaryl-4-(2-imidazolinyl)-1,2,3-triazoles (**335**) (Equation (102)) ⟨92JOC184⟩. The reaction rate is increased by the electron-donating ability of the substituents of the aroyl group of the ketene aminal, and the electron-withdrawing ability of the substituents of the aryl azide. The ratio of triazole to the fused heterocyclic product (**334**) is increased with the enhanced electron-withdrawing ability of the substituent of the azide. The mechanism is discussed ⟨88S851⟩.

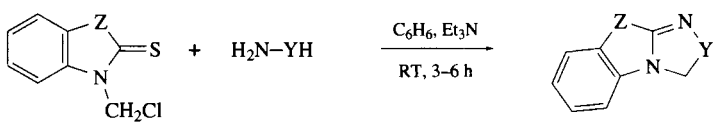


(102)

(333) (334) (335)

(ii) (5)C3 + N102 → 12{4}7:

(a) NO/O Oxazolo[2,3-c][1,2,4]oxadiazole, NO/S Thiazolo[2,3-c][1,2,4]oxadiazole. Condensations of 3-chloromethyl-2-thioxo-2,3-dihydro-benzoxazole (**336**; Z = O) and -benzothiazole (**336**; Z = S) with hydroxylamine afford 3*H*-[1,2,4]oxadiazolo[3,4-*b*]benzoxazole (**20**) and -benzothiazole (**21**) (Equation (103)) ⟨93PS(85)183⟩



(103)

(336) Z = O, S

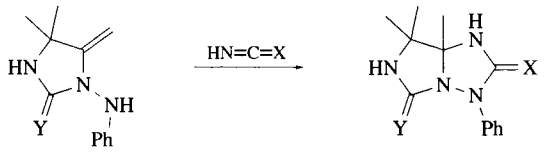
(20) Y = Z = O
(21) Y = O, Z = S
(337) Y = NH, N–Ph; Z = O, S

*(b) NN/O Oxazolo[2,3-*c*][1,2,4]triazole, NN/S Thiazolo[2,3-*c*][1,2,4]triazole.* By analogy, condensation of 3-chloromethyl-2,3-dihydrobenzoxazole-2-thione (**336**; Z = O) and -benzothiazole (**336**; Z = S) with hydrazine or with phenyl-hydrazine yields the corresponding 3*H*-[1,2,4]triazolo[3,4-*b*]benzoxazoles (**337**; Z = O) and -benzothiazoles (**337**; Z = S) (Equation (103)) ⟨93PS(85)183⟩.

8.05.9.5.8 (5)N3 + N1C2 → 13{4}6:

*(i) NN/N Imidazo[3,4-*b*][1,2,4]triazole*

The reaction of 1-arylamino-4,4-dimethyl-5-methylene-2,3,4,5-tetrahydro-1*H*-imidazol-2-one (**338**; Y = O) and -2-thione (**338**; Y = S) with protic heterocumulenes affords 7,7,7a-trimethyl-3-aryl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]triazol-2,5-diones (**339**; X = Y = O), and *N*- and *S*-derivatives of these functions in 2- and 5-positions (Equation (104)) ⟨93TH 805-01, 95FES379⟩.

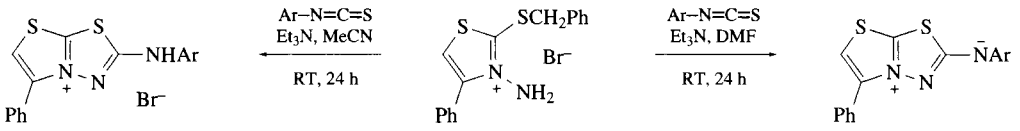


(**338**) Y = O, S (**339**) X = O, S, NH; Y = O, S (104)

8.05.9.5.9 (5)N3 + S1C2 → 13{4}7:

*(i) SN/S Thiazolo[2,3-*b*][1,3,4]thiadiazole*

From 3-amino-2-benzylthio-4-phenylthiazolium bromide (**340**) and arylthiocyanates in the presence of triethylamine 2-arylamino-5-phenyl-thiazolo[2,3-*b*][1,3,4]thiadiazolium bromides (**53**) are formed. In dimethylformamide as solvent the yellow mesoionic compounds anhydro-2-arylamino-5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazolium hydroxides (**54**) are obtained (Scheme 31) ⟨88S729⟩.



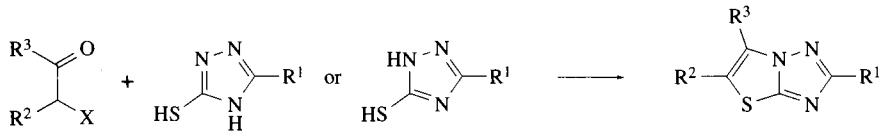
(**53**) R^1 = H, R^2 = Ar (**340**) (**54**) R = Ar

Scheme 31

8.05.9.5.10 (5)S4 + C5C6 → 134{7}:

*(i) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole*

α-Haloketones react with 3-sulfonyl-4*H*-1,2,4-triazoles or with 3-sulfonyl-2*H*-1,2,4-triazoles (the tautomeric 3-thione form has not been considered) at 2-N and the thiol function to give thiazolo[3,2-*b*][1,2,4]triazoles (**58**) (Equation (105), Table 22).

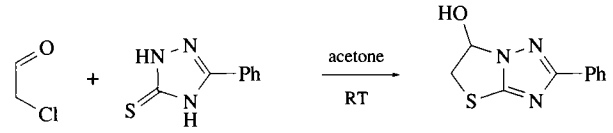


(**58**) (105)

Table 22 Thiazolo[2,3-b][1,2,4]triazoles (**58**).

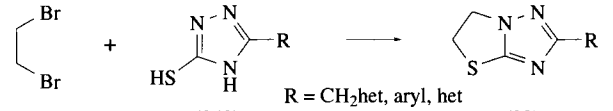
X	R^1	R^2	R^3	*Ref.*
Br, Cl	CH_2CO_2R	H,	het	87CZP237132
Cl	aryl	H	Me	87PJC547
Br	Ph	H	aryl	86JHC1439
Br	aryl	H	aryl	85IJC(B)808, 85IJC(B)1221, 87IJC(B)526, 88CAT91
Cl	aryl	H, CO_2Et	Me, aryl	91EJM929
Cl	NH_2	H	alkyl, Ph, het	90JAP02142797
			1-β-D-ribofuranose	92SC2815
Cl	SCH_2Ph	H	Me	87EUP244098

Cyclocondensation of chloroacetaldehyde and 3-phenyl-1*H*[1,2,4]triazole-5-thione (**341**) gives 6-hydroxy-2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**342**) (Equation (106)) ⟨87AP528⟩.



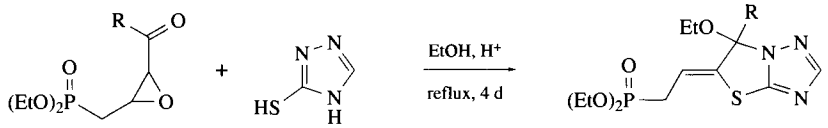
(341) (342) (106)

Similarly, 5-substituted 4*H*[1,2,4]triazole-3-thioes (**343**) cyclocondense with 1,2-dibromoethane to afford 2-substituted 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazoles (**39**) (Equation (107)) ⟨83IJC(B)249, 83IJC(B)712, 86JHC1439, 88MI 805-02⟩.



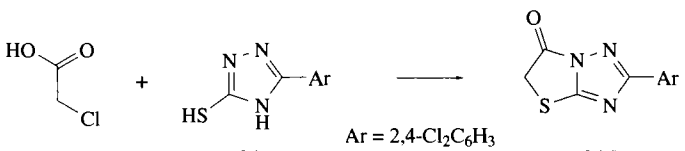
(343) (39) (107)

The reaction of diethyl 2,3-epoxy-4-oxopentanephosphonate (**344**; R = Me) with 3-sulfonyl-[1,2,4]triazole gives diethyl 2-(6-ethoxy-5,6-dihydro-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-ylidene)ethanephosphonate (**147**; R = Me) (Equation (108)). Further conversions are shown in Section 8.05.7.4. Compound (**149**) can also be obtained directly from the monocyclic starting materials in a one-pot procedure upon successive treatment with ethanol and sulfuric acid at room temperature followed by *p*-toluenesulfonic acid monohydrate in toluene ⟨88CB977⟩.



(344) (147) (108)

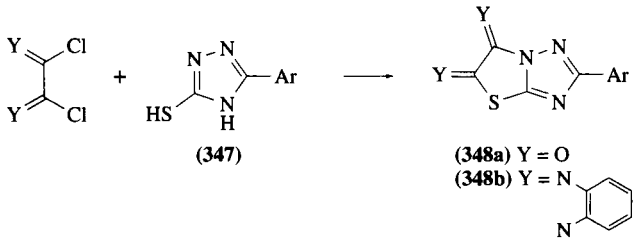
The cyclocondensation of 3-(2,4-dichlorophenyl)-5-sulfonyl[1,2,4]triazole (**345**) with chloroacetic acid affords 2-(2,4-dichlorophenyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]-triazol-6-ones (**346**) (Equation (109)) ⟨91H(32)231⟩. The same reaction in the presence of an aromatic aldehyde gives rise to 6-arylidene-2-(2,4-dichlorophenyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-6-ones (**103**) (see Section 8.05.6.2.1) ⟨91H(32)231⟩.



(345) (346) (109)

The reaction of 3-(2,4-dichlorophenyl)-5-sulfonyl[1,2,4]triazole (**347**) with oxalyl chloride gives

2-(2,4-dichlorophenyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-6-one (**348a**; Y = O). Reaction with 2,3-dichloroquinoxaline yields 2-(2,4-dichlorophenyl)[1,2,4]triazolo[3′,2′-2,3]thiazolo[4,5-*b*]quinoxaline (**348b**; Y = O) (Equation (110)) ⟨91H(32)231⟩.

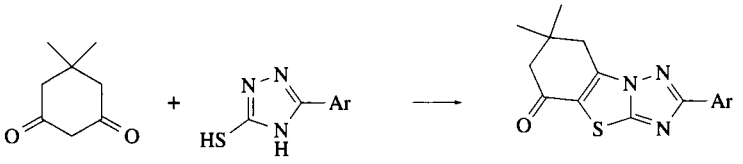


(110)

(347)

(348a) Y = O
(348b) Y = N

The reaction of 3-(2,4-dichlorophenyl)-5-sulfonyl[1,2,4]triazole (**347**) with dimedone furnishes 2-(2,4-dichlorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,2-*b*]benzothiazol-5-one (**349**) (Equation (111)) ⟨91H(32)231⟩.



(111)

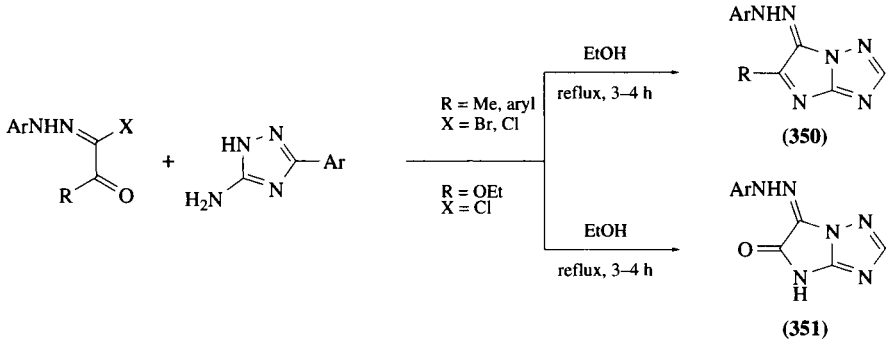
(347)

(349) Ar = 2,4-$Cl_2C_6H_3$

8.05.9.5.11 (5)N4 + C5C6 → 134{7}:

*(i) NNN/ Imidazo[1,2-*b*][1,2,4]triazole*

Hydrazidoyl halides react with 2-amino[1,2,4]triazole to give 5-substituted 6-arylhydrazono-6*H*-imidazo[1,2-*b*][1,2,4]triazoles (**350**) and 6-arylhydrazono-5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]-triazol-5-ones (**351**), respectively; the latter products are not determined with respect to the tautomeric structures of the 1*H*-, 3*H*-, or 4*H*-form (Scheme 32) ⟨83JHC639⟩.

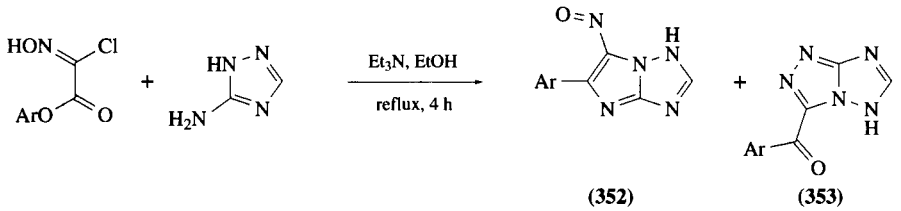


(350)

(351)

Scheme 32

The reaction of the α-ketohydroximoyl chlorides converts 2-amino[1,2,4]triazole into a mixture of 5-aryl-6-nitrosoimidazo[1,2-*b*][1,2,4]triazoles (**352**) and 3-aroyl-5*H*-[1,2,4]triazolo[3,2-*c*][1,2,4]-triazoles (**353**) (Equation (112)) ⟨84JHC1029⟩.

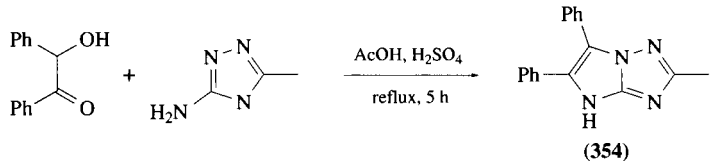


(112)

(352)

(353)

Benzoin cyclocondenses with 3-amino-5-methyl-4*H*[1,2,4]triazole to give 2-methyl-5,6-diphenyl-4*H*-imidazo[2,1-*b*][1,2,4]triazole (**354**) (Equation (113)) ⟨88IJC(B)421⟩.

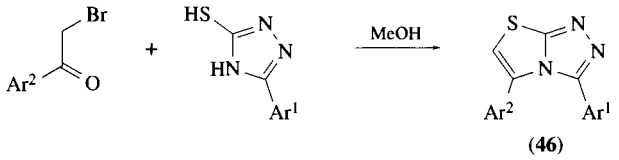


(354) (113)

8.05.9.5.12 (5)S7 + C5C6 → 12{4}7:

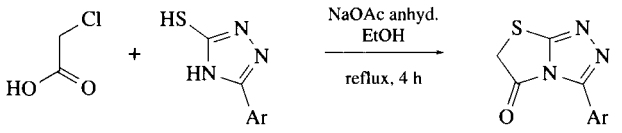
(i) NN/S Thiazolo[2,3-c][1,2,4]triazole

The reaction of 3-aryl-5-sulfonyl-4*H*[1,2,4]triazole with phenacyl bromides in methanol gives 3,5-diarylthiazolo[2,3-*c*][1,2,4]triazoles (**46**) in one step (see Section 8.05.9.1.11) (Equation (114)) ⟨88CAT91⟩.



(46) (114)

The products obtained from the reaction of 2-aryl-5-sulfonyl-4*H*-1,2,4-triazoles with chloroacetic acid have been shown to be 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles (**26**) (see Section 8.05.9.1.11) (Equation (115)) ⟨89JIC832, 90JIC226⟩.

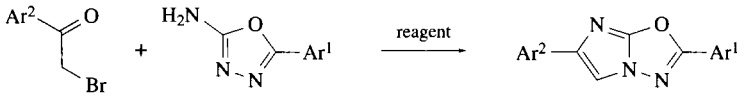


(26) (115)

8.05.9.5.13 (5)N7 + C5C6 → 13{4}7:

(i) ON/N Imidazo[2,1-b][1,3,4]oxadiazole

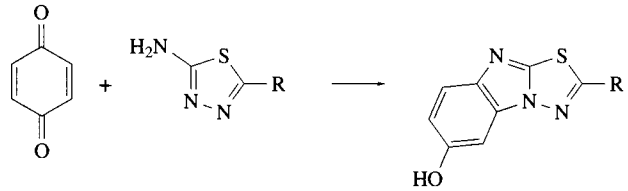
The reaction of 2-amino-5-aryl[1,3,4]oxadiazoles with phenacyl bromides yields 2,4-diaryl-imidazo[2,1-*b*][1,3,4]oxadiazoles (**355**) (Equation (116)) ⟨93MI 805-01⟩.



(355) (116)

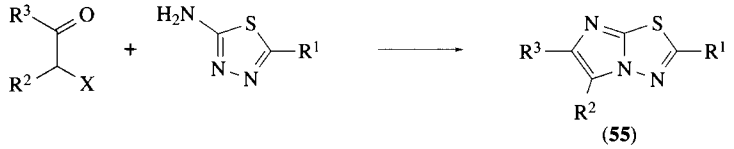
(ii) SN/N Imidazo[2,1-b][1,3,4]thiadiazole

By condensation of 2-amino-1,3,4-thiadiazoles with *p*-benzoquinone the 6-hydroxy[1,3,4]-thiadiazolo[3,2-*a*]benzimidazoles (**356**) are prepared (Equation (117)) ⟨86IJC(B)1266⟩.



(356) R = H, Ph (117)

A large variety of α-halocarbonyl compounds undergo cyclo-condensation with 5-substituted 2-amino[1,3,4]thiadiazoles to give 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles (**56**) (Equation (118)) (Table 23a).



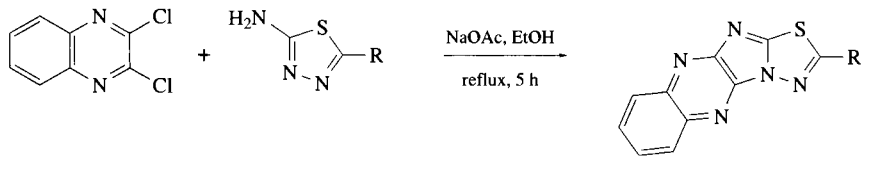
(**55**) (118)

Table 23 2,5,6-Trisubstututed imidazo[2,1-*b*][1,3,4]thidiazoles (**56**).

X	R^1	R^2	R^3	*Ref.*
Br, Cl	H, alkyl	H, CO_2H	Me, CO_2H, CO_2H	85FES190
Cl	H, alkyl	H	$NHCO_2Me$	85FES34
Br	Bu^t	H	t-Bu	83JHC1003
Br	Me	H	aryl	88JMC2221
Br	alkyl	H	aryl	89JIC118, 92MI 805-01
Br	alkyl	H	het	86CCC2214
Br	cycloalkyl	H, alkyl	aryl	88ZOR199
Br	cycloalkyl, aryl	H	cycloalkyl, aryl	88ZOR192
Br	CH(Me)OAr	H	Ph	91IJC(B)620
Br, Cl	CF_3, EtS, Bu^t, cyclopropyl	H	aryl	93H(35)763
Br	$CH_2NR^1R^2$	H	aryl, het	85GEP3329621
Br, Cl	aryl	H	Me, alkyl, CH(Me)OR, aryl, SCH_2het	89USP4880824, 90FES1341, 91IJC(B)620, 92EJM425, 94IJC(B)692, 94JCR(S)38, 93MI 805-01
Br	$NHCO_2Me$, $SCH_2CONHCO_2Me$	H	Ph	92FES63

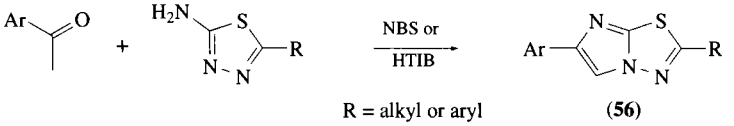
The formation of imidazo[2,1-*b*][1,3,4]thiadiazoles (**56**) in the course of the reaction of phenacyl halides with 5-substituted 2-amino[1,3,4]thiadiazoles has been found to be controled by the nature of the substituents at the 5-position of the thiadiazole which determine the alkylation site (1-N or 2-N) ⟨93H(35)763⟩.

The condensation of 2-amino-5-hexyl[1,2,4]thiadiazole with 2,3-dichloroquinoxaline furnishes 2-hexylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives (**357**) (Equation (119)) ⟨89JIC118⟩.



(**357**) R = $(CH_2)_5Me$ (119)

The synthesis of 2-substituted 6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles (**56**) can be achieved also by treatment of 5-substituted 2-amino[1,2,4]thiadiazoles with acetophenones in the presence of an oxidant (Equation (120)) ⟨89IJC(B)500, 93MI 805-04, 94JCR(S)38⟩.



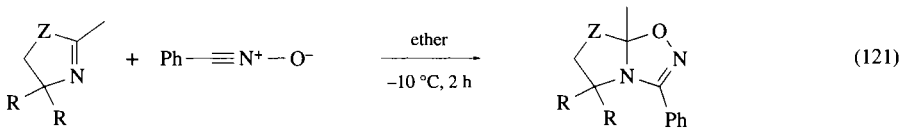
R = alkyl or aryl (**56**) (120)

8.05.9.6 Formation of the Second Ring by Addition of a Three-atom Ring Member to Two Adjacent Ring Positions of the First Ring: (5) + 3 → (5,5)

8.05.9.6.1 (5) [N4C7a] + O1N2C3 → 12{4}7:

*(i) ON/O Oxazolo[3,2-*d*][1,2,4]oxadiazole, ON/S Thiazolo[3,2-*d*][1,2,4]oxadiazole*

The 2-methyl-4,5-dihydrooxazoles (**358**; Z = O) or 2-methyl-4,5-dihydrothiazole (**358**; Z = S) undergo 1,3-dipolar cycloaddition reactions with benzonitrile *N*-oxide to give the corresponding 7a-methyl-3-phenyl-5,6-dihydro-7a*H*-oxazolo[3,2-*d*][1,2,4]oxadiazoles (**16**) or -thiazolo[3,2-*d*]-[1,2,4]oxadiazoles (**17**) (Equation (121)) ⟨92T7703⟩.

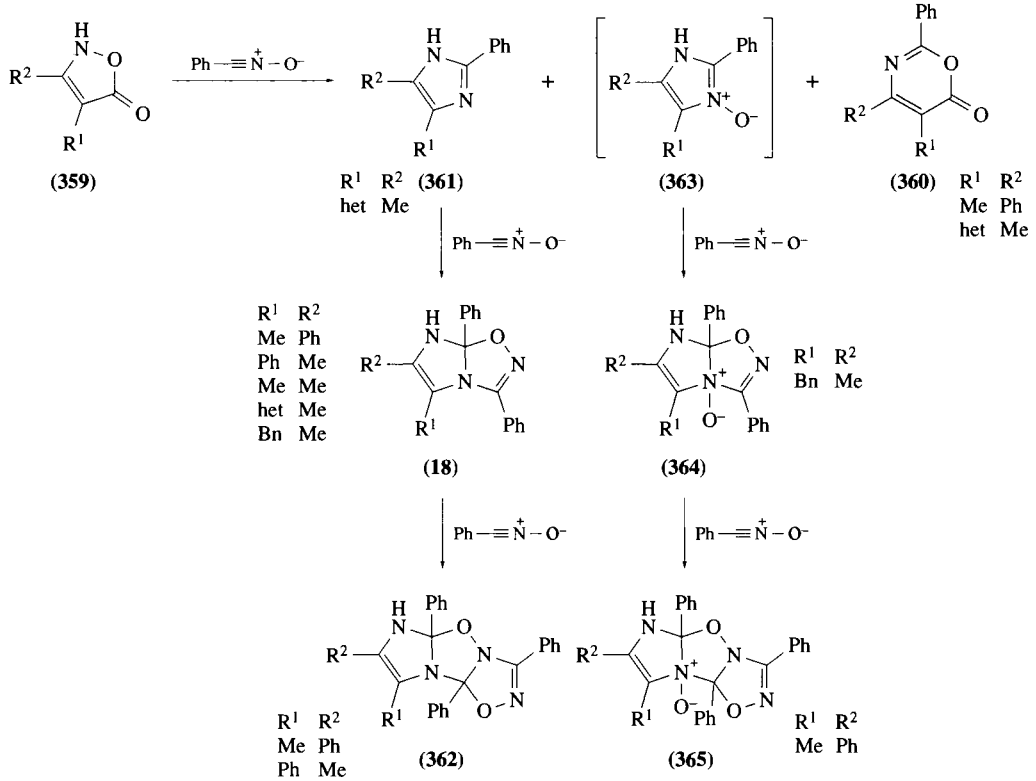


(358) (121)

(**16**) Z = O, R = H, Me
(**17**) Z = S, R = H

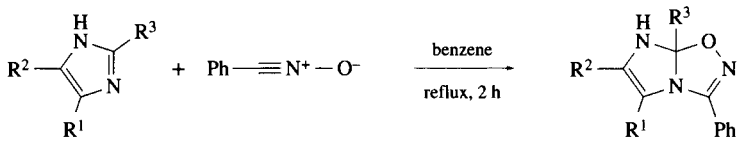
*(ii) ON/N Imidazo[1,2-*d*][1,2,4]oxadiazole*

The reaction of benzonitrile oxide (generated *in situ*) with 1,3-dihydroisoxazol-3-ones (**359**) yields a complex mixture of cycloadducts: the 1,3-oxazin-6-ones (**360**), the imidazoles (**361**), the mono- (**18**) and bis- (**362**) cycloadducts of benzonitrile oxide with the imidazoles (**361**), and the mono- (**364**) and bis- (**365**) cycloadducts of benzonitrile oxide with the imidazole 3-oxides (**363**) (Scheme 33) ⟨83JCR(S)172⟩.



Scheme 33

In analogous manner, imidazoles add benzonitrile oxide to give 7,7a-dihydroimidazo[1,2-*d*][1,2,4]oxadiazoles (**18**) (Equation (122)) ⟨83JCR(S)230⟩.



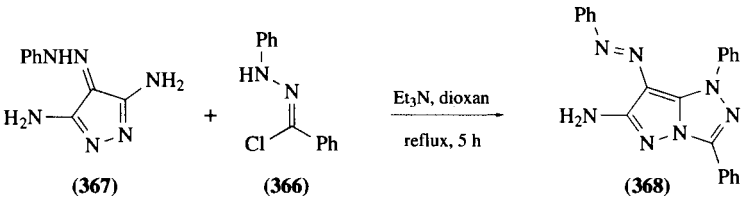
R^1 = H, Ph
R^2 = H, Me, Ph
R^3 = H, Me, Et

(18) (122)

8.05.9.6.2 (5) [N4C7a] + N1N2C3

(i) (5) [N4C7a] + N1N2C3 → 12{4}5:

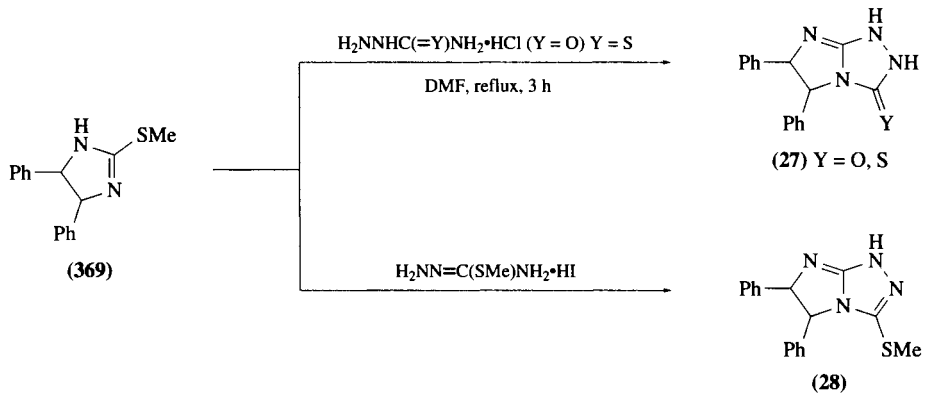
(a) NN/N Pyrazolo[5,1-c][1,2,4]triazole. The α-chlorohydrazone (**366**) in the presence of triethylamine adds to 3,5-diamino-4*H*-pyrazol-4-one phenylhydrazone (**367**) to form 6-amino-1,3-diphenyl-7-phenylazo-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole (**368**) (Equation (123)) ⟨85M223⟩.



(367) (366) (368) (123)

(ii) (5)[N4C7a] + N1N2C3 → 12{4}7:

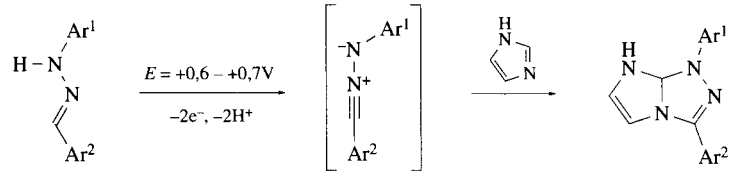
(a) NN/N Imidazo[2,1-c][1,2,4]triazole. The reaction of 2-methylsulfonyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazole (**369**) with semicarbazide hydrochloride affords 5,6-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*c*][1,2,4]triazol-3-one (**27**; Y = O). Similarly, the reactions with thiosemicarbazide or with *S*-methylthiosemicarbazide hydroiodide give 5,6-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*c*][1,2,4]triazole-3-thione (**27**; Y = S) and the *S*-methyl derivative (**28**), respectively (Scheme 34) ⟨86SUL51⟩.



(369) (27) Y = O, S (28)

Scheme 34

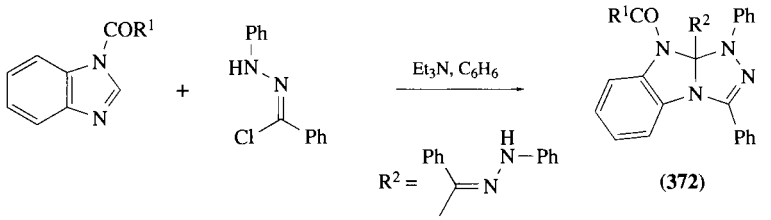
Electrolysis of 4-dimethylaminobenzaldehyde 4-nitrophenylhydrazone (**370**) forms the 1,3-diarylnitrilimine, which in the presence of imidazole forms 3-(4-dimethylaminophenyl)-1-(4-nitrophenyl)-7,7a-dihydro-1*H*-imidazo[2,1-*c*][1,2,4]triazole (**371**) by a [3 + 2] cycloaddition reaction (Scheme 35) ⟨85ZC443⟩.



(**370**) $Ar^1 = 4\text{-}O_2NC_6H_4$, $Ar^2 = 4\text{-}Me_2C_6H_4$ (**371**)

Scheme 35

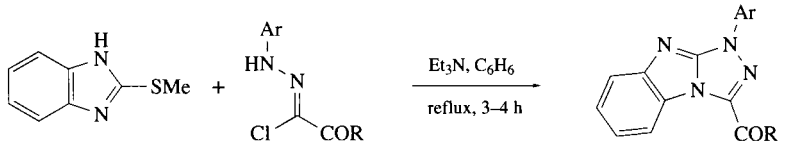
The [3 + 2] cycloaddition reaction of 1-acylbenzimidazoles with 1,3-diphenylnitrilimine (generated from the corresponding hydrazinoyl chloride with base) produces 9-acyl-1,3-diphenyl-9a-[1-phenyl-1-(2-phenyl-hydrazono)methyl]-9,9a-dihydro-1*H*-[1,2,4]triazolo[4,3-*a*]benzimidazoles (**372**) (Equation (124)) ⟨85H(23)2183⟩.



(124)

(**372**)

Similarly, *C*-acyl-substituted *N*-arylhydrazinoyl chlorides in the presence of a base undergo [3 + 2] cycloaddition with 2-methylsulfonylbenzimidazoles forming 3-acyl-1-aryl[1,2,4]triazolo[4,3-*a*]benzimidazoles (**373**) (Equation (125)) ⟨93H(36)1775⟩.



(125)

R = Me, aryl, het, *O*-alkyl, NH–Ph (**373**)

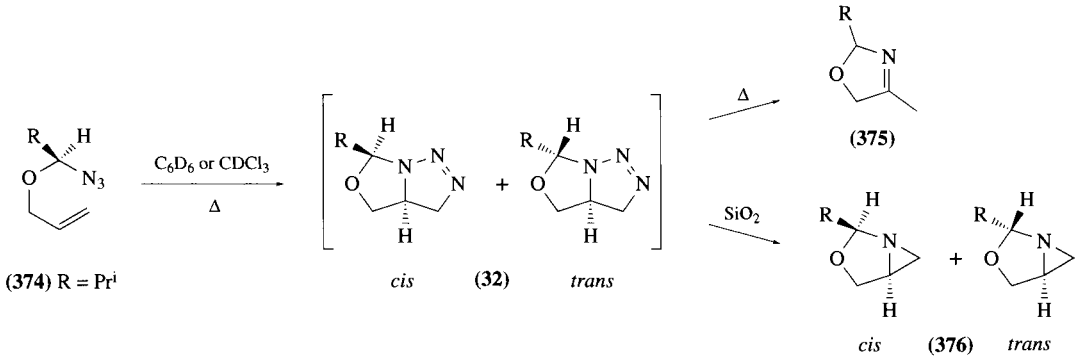
8.05.9.7 Formation of the (5,5)-fused Rings from Chain Fragments

8.05.9.7.1 One fragment: 8 → (5,5)

(i) N2N1{N7}C6O5C4C3aC3 → 125{7}:

(a) NNO/ Oxazolo[3,4-c][1,2,3]triazole. Monitoring (^{1}H NMR) the thermolysis of 1-azido-2-methylpropyl allyl ether (**374**) in hexadeuteriobenzene at 70 °C revealed at partial conversion the formation of 6-isopropyl-3,3a,4,6-tetrahydrooaxazolo[3,4-*c*][1,2,3]triazole (**32**) (*cis* and *trans*) and oxazoline (**375**). After 3 h of heating only oxazoline (**375**) was present. Chromatography on silica of the intermediate mixture gave some aziridinooxazolidines (**376**) (Scheme 36) ⟨88JOC27⟩.

Heating of (**374**) at 50 °C for 1 h brings about conversion (80%) to a 2.9 : 1 mixture of *trans* and *cis* oxazolo[3,4-*c*][1,2,3]triazole (**32**) without appreciable presence of oxazoline (**375**) or aziridino[1,2-*c*]oxazole (**376**) (Scheme 36) ⟨88JOC27⟩.

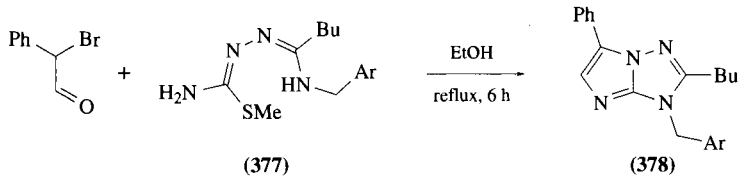


Scheme 36

8.05.9.7.2 Two fragments providing 6 + 2 ring atoms: 6 + 2 → (5,5)

(i) C5C6 + N4C3aN3C2N1{N7} → 134{7}:

*(a) NNN/ Imidazo[1,2-*b*][1,2,4]triazole.* Heating 4-[(2′-cyanobiphenyl-yl)methyl]valeramide *S*-methyl-isothiosemicarbazide (**377**) with α-bromophenylacetaldehyde leads directly to 2-butyl-3-[(2′-cyanobiphenyl-4-yl)-methyl]-6-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (**378**) (see Section 8.05.9.2.10) (Equation (126)) ⟨93JMC591⟩.

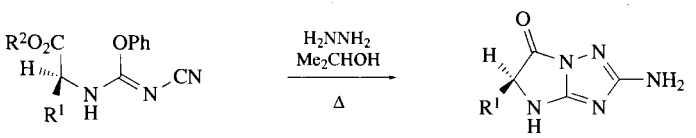


(126)

(377) (378)

(ii) N1{N7} + C2N3C3aN4C5C6 → 134{7}:

*(a) NNN/ Imidazo[1,2-*b*][1,2,4]triazole.* Treatment of 3-(1-alkoxycarbonyl-alkyl)-1-cyano-*O*-phenylisoureas (**379**) with hydrazine gives 2-amino-5,6-dihydro-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-ones (**380**) (Equation (127)) ⟨93T165⟩.



(127)

(379) (380)

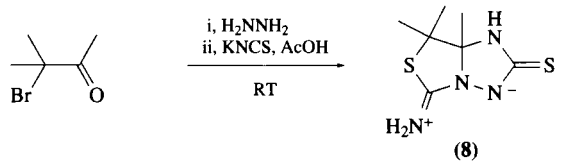
R^1 = Et, Bn, CH_2CO_2Me
R^2 = Me, Bn

8.05.9.7.3 Four fragments providing two atoms each: 2 + 2 + 2 + 2 → (5,5)

(i) C7C7a + C5S6 + N3N4 + N1C2 → 13{4}6:

*(a) NN/S Thiazolo[3,4-*b*][1,2,4]triazole.* The reaction of 3-bromo-3-methylbutan-2-one with hydrazine and potassium thiocyanate in acetic acid affords the mesoionic compound (**8**) (Equation

(128)) ⟨93TH 805-01, 95FES379⟩. The zwitterionic character of product (**8**) is evident from its x-ray structure analysis, see Section 8.05.3.1 ⟨93TH 805-01, 95FES379⟩.



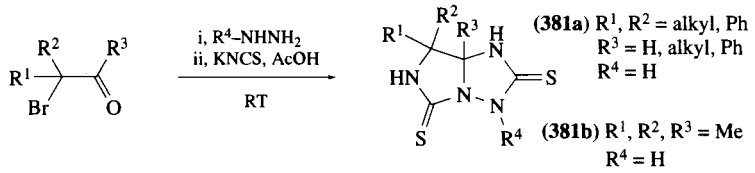
(8) (128)

(ii) C7C7a + N3N4 + C5N6 + N1C2 → 13{4}6:

*(a) NN/N Imidazo[1,5-*b*][1,2,4]triazole.* In a one-pot synthesis α,α-disubstituted α-bromocarbonyl compounds react with arylhydrazines and potassium thio-cyanate in acetic acid to give 7,7-disubstituted 3-aryl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithiones (**381a**) (Equation (129)) ⟨93TH 805-01, 95FES379⟩.

This tandem reaction resembles a new variety of the "criss-cross" reaction (with respect to the relative regiochemistry of the added thiocyanic acid this reaction is a "parallel criss-cross" reaction as opposed to the "antiparallel" cycloaddition of heterocumulenes to azines in the classical "criss-cross" reaction).

Reaction of 3-bromo-3-methylbutan-2-one with triphenylmethylhydrazine and potassium thiocyanate in acetic acid gives 7,7,7a-trimethyl-2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]-triazole-2,5-dithione (**381b**) due to the facile hydrolysis the triphenylmethyl group. ⟨95FES379⟩.



(**381a**) R^1, R^2 = alkyl, Ph; R^3 = H, alkyl, Ph; R^4 = H

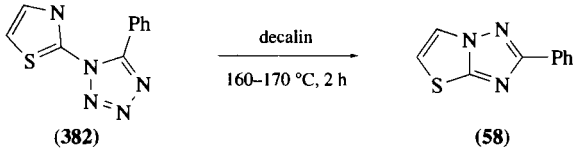
(**381b**) R^1, R^2, R^3 = Me; R^4 = H (129)

8.05.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

8.05.10.1 Extrusion of Dinitrogen: (5)-(5)N3C2N1-N_2-(N_2) → 134{7}

*8.05.10.1.1 NNS/ Thiazolo[3,2-*b*][1,2,4]triazole*

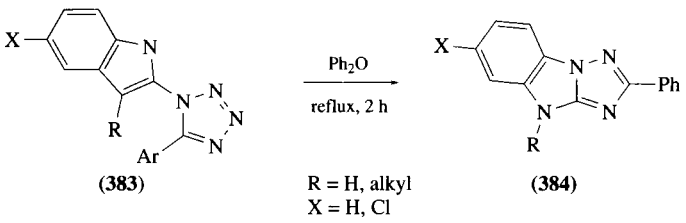
Heating of 1-(thiazol-2-yl)-5-phenyl-1*H*-tetrazole (**382**) induces extrusion of dinitrogen and transformation into 2-phenylthiazolo[3,2-*b*][1,2,4]triazole (**58**; R^1 = Ph, R^2 = R^3 = H) (Equation (130)) ⟨90FES953⟩.



(**382**) (**58**) (130)

*8.05.10.1.2 NNN/ Imidazo[1,2-*b*][1,2,4]triazole*

Similarly, thermal decomposition of 1-(benzimidazol-2-yl)-5-aryl-1*H*-tetrazoles (**383**) gives under loss of dinitrogen 2-aryl-4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole (**384**) (Equation (131)) ⟨88SC1995⟩.



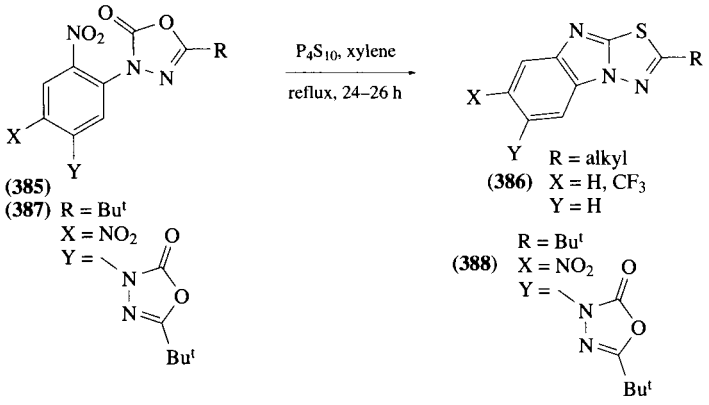
(383) (384) (131)

8.05.10.2 Ring Closure and O/S Exchange

8.05.10.2.1 (5[O])C5C6N7 [S] → 13{4}7:

*(i) SN/N Imidazo[3,2-*a*][1,2,4]thiadiazole*

The reaction of 3-(2-nitroaryl)-2,3-dihydro[1,2,4]oxadiazol-2-ones (**385**) with phosphorus pentasulfide in refluxing xylene transforms the oxadiazole ring into the thiadiazole ring; concomitant reduction of the nitro group and closure of the imidazole ring affords [1,3,4]thiadiazolo[3,2-*a*]benzimidazoles (**386**). The reaction of 1,3-dinitro-4,6-bis[(5-(1,1-dimethylethyl)-2-oxo-2,3-dihydro[1,3,4]oxadiazol-3-yl)benzene (**387**) is only partially successful and gives some 2-(1,1-dimethyl-ethyl)-5-[5-(1,1-dimethylethyl)-2-thioxo-2,3-dihydro-[1,3,4]oxadiazol-3-yl]-6-nitro-5-[1,3,4]thiadiazolo[3,2-*a*]benzimidazole (**388**) (Equation (132)) ⟨88PS(36)139⟩.



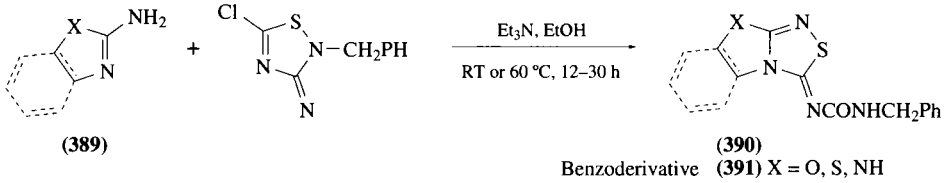
(132)

8.05.10.3 Opening of the Added Ring

8.05.10.3.1 (5)N1 + C3S2 → 14{4}7:

*(i) NS/S Thiazolo[2,3-*c*]thiadiazole*

The reaction of 2-aminothiazoles (**389**; X = S) with 2-benzyl-5-chloro-2,3-dihydro[1,2,4]-thiadiazol-3-ones gives 3-(benzylaminocarbonylimino)thiazolo[2,3-*c*]thiadiazoles (**390**; X = S). With 2-aminobenzazoles the corresponding 3-(benzylaminocarbonylimino)-3*H*-[1,2,4]thiadiazolo[3,4-*b*]benzoxazole, -benzthiazole and -3,9-dihydro[1,2,4]thiadiazolo[4,3-*a*]benzimidazole derivatives (**391**) are obtained (Equation (133)) ⟨94T7019⟩.



(389) (390) (133)

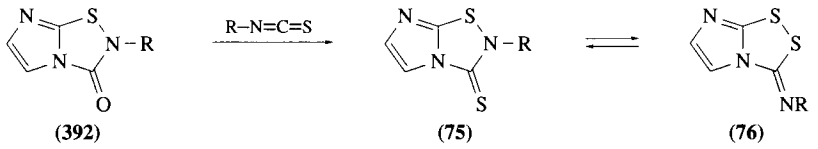
Benzoderivative (391) X = O, S, NH

8.05.10.4 Exchange of Two Ring Members by Elimination Followed by Addition of Heterocumulenes

8.05.10.4.1 (5,5[N2C3]) ⇄ (5,5)[S2C3]): 12{4}7

(i) SN/N Imidazo[4,5-a][1,2,4]thiadiazole, SS/N Imidazo[2,1c][1,2,4]dithiazole

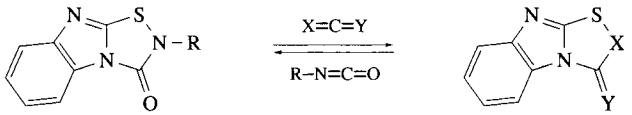
Isothiocyanates react with 2-cyclohexyl 2,3-dihydro-imidazo[1,2-*d*][1,2,4]thiadiazol-3-ones (**392**) with exchange of the isocyanate moiety to give 2,3-dihydro-imidazo[1,2-*d*][1,2,4]thiadiazole-3-thione derivative (**75**) or the isomer 3-imino-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole (**76**), depending on the nature of the group R (see Section 8.05.4.3) (Scheme 37) ⟨88JPC338⟩.



(392) (75) (76)

Scheme 37

The isocyanate moiety of 2-substituted 2,3-dihydro-[1,2,4]thiadiazolo[4,5-*a*]benzimidazol-3-ones (**393**) is exchangeable with other isocyanates or a carbodiimide giving rise to a formal exchange of the 2-substituent as in (**394**) (Equation (134)). With isothiocyanates 2-substituted 2,3-dihydro[1,2,-4]thiadiazolo[4,5-*a*]benzimidazole-3-thiones (**395**) and/or 3-imino-3*H*-[1,2,4]dithiazolo[4,3-*a*]benzimidazoles (**396**) are formed (see Section 8.05.4.3). The reaction with carbon disulfide results in the formation of 3*H*-[1,3,4]-dithiazolo[4,5-*a*]benzimidazole-3-thione (**397**). All these exchange products react with isocyanates and are reconverted into compounds (**393**).

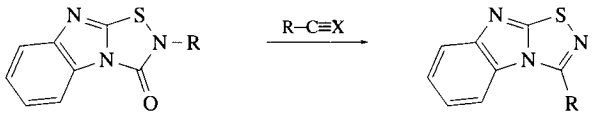


(134)

(393)

(**394**) X = R'N, Y = O
(**395**) X = R'N, Y = S
(**396**) X = S, Y = R'N
(**397**) X = S, Y = S

Exchange of the isocyanate moiety of 2-substituted 2,3-dihydro[1,2,4]thiadiazolo[1,2-*d*]benzimidazol-3-ones (**398**) also occurs with cyanates and trichloroacetonitrile to yield the corresponding 3-substituted [1,2,4]thiadiazolo[1,2-*d*]benzimidazoles (**400**) and (**399**) (see Section 8.05.6.4.2) (Equation (135)) ⟨85JCS(P1)1007⟩



(135)

(398)

(**399**) R = CCl_3
(**400**) R = OAr

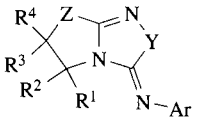
8.05.11 APPLICATIONS

8.05.11.1 Agrobiological Activity

8.05.11.1.1 Herbicidal activity

(i) 12{4}7: NO/N, NS/O, NS/S, NS/N

Mainly 3-arylimino-5,6-dihydro derivatives (**401**) of the following fused system have been found active as herbicides (Table 24):



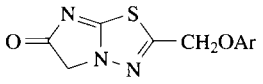
(401)

Table 24 Herbicides.

Y	*Z*	*Ref.*
O	N	86GEP3528583
S	O	87JAP62181283, 89JAP01056603
S	S	85JAP60214791, 86GEP3528583, 87JAP62181283, 89JAP01056603, 93MI 805-02
S	N	86GEP3528583

(ii) 13{4}7: SN/N

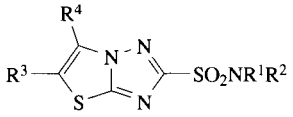
2-Aryloxymethyl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-5-ones (**402**) have been screened for their herbicidal activity ⟨93MI 805-03⟩.



(402)

(iii) 134{7}: NNS/

5,6-Disubstituted 2-sulfonamidothiazolo[3,2-*b*][1,2,4]triazoles (**403**) are selective herbicides in control of *Polygonum lapithifolium*, *Abutilon theophrasti* and *Echinochloa crus-galli* ⟨87EUP244098, 91MI 805-03⟩.

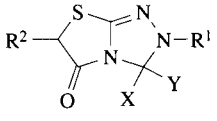


(403)

8.05.11.1.2 Antifungal activity

(i) 12{4}7: NN/S

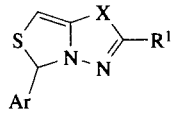
The fungitoxic activity of various 3-functionalized 2,6-disubstituted 2,3,5,6-tetrahydrothiazolo[2,3-*c*][1,2,4]triazoles (**404**) against *Aspergillus flavus* and *Fusarium solani* has been tested ⟨91MI 805-02⟩.



(404)

(ii) 13{4}6: ON/S, SN/S, NN/S

The antifungal activity of 5-aryl-2-(aryl)amino-5*H*-thiazolo[4,3-*b*][1,3,4]oxadiazoles, -thiadiazoles and 1,5-diaryl-2-sulfonyl-1,5-dihydrothiazolo[3,4-*b*][1,2,4]triazoles (**405**) has been evaluated against *Aspergillus flavus* and *Fusarium solani* ⟨92MI 805-01⟩ and against *Aspergillus niger* and *Fusarium oxysporium* ⟨94MI 805-01⟩.

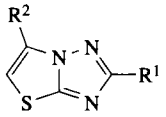


(405) X = O, N–Ar'

8.05.11.2 Insecticidal Activity

8.05.11.2.1 134{7}: NNS/

2,6-Disubstituted thiazolo[3,2-*b*][1,2,4]triazoles (**406**) show insecticidal activity ⟨85JAP60011493⟩.



(406)

8.05.11.3 Pharmacological Activity

8.05.11.3.1 Antibacterial activity

Derivatives of several ring systems have been tested or shown to be active as antibacterials (Table 25).

Table 25 Antibacterials.

Ring system	*Ref.*
12{4}7 : NS/S	88IJC(B)501
NN/S	86JHC1439, 87CZP240395, 87MI 805-02, 90IJC(B)88, 90MI 805-05, 91ESM929, 91MI 805-04, 92JIC268, 93MI 805-05
NN/N	93H(36)1775
13{4}6 : SN/S	91JIC144
13{4}7 : ON/N	93MI 805-02
SN/N	89IJC(B)358, 89JIC118
134{7} : NNS/	86JHC1439, 87CZP240387, 87MI 805-02, 88MI 805-02, 91EJM929, 91MI 805-04, 92JIC268, 93MI 805-05

8.05.11.3.2 Antifungal activity

Derivatives of several ring systems have been evaluated with respect to their antifungal activity (Table 26).

Table 26 Antifungals.

Ring system	*Ref.*
12{4}7 : NS/S	88IJC(B)501
NN/S	87MI 805-02, 89IJC(B)479, 90IJC(B)88, 90JIC226, 90MI 805-06, 92JIC268, 93MI 805-05
13{4}7 : SN/N	89IJC(B)358, 89JIC118, 91IJC(B)620, 93MI 805-05
134{7} : NNS/	83IJC(B)712, 92JIC268, 93MI 805-05

8.05.11.3.3 Various pharmacological activities

Mainly derivatives of three (5,5) (2N1)-fused systems have been found to be pharmacologically active (Table 27).

In addition, the pharmacological activities of a few more (5,5) (2N1)-fused systems has been evaluated (Table 28).

Table 27 Pharmacologically active systems.

Activity	*Ring system*			*Ref.*
	12{4}7 NN/S	*13{4}7 SN/N*	*134{7} NNS/*	
Analgesic		+		84FES585, 85FES190
	+			90MI 805-05
	+		+	91EJM929
Anthelmintic			+	89FES671
Antihypertensive		+		83GEP3208437
Antihypoxic	+			90MI 805-05
Antiinflammatory		+		85FES190
	+			90MI 805-05
	+		+	91EJM929
Antimicrobal	+		+	90IJC(B)88, 91EJM929, 92JIC268
		+		89JIC118, 90FES1341
Antiphlogistic		+		84FES585
Antipyretic		+		85FES190
	+		+	91EJM929
Bronchodilatoric			+	86JAP61286387
Calcium channel blocker		+		88JMC2221, 89USP4880824
Cardiotonic			+	86JAP61286387
Diuretic	+		+	87MI 805-02, 93MI 805-05
		+		83GEP3208437
Neurotropic	+			90MI 805-05
Tuberculostatic	+			93MI 805-03
Ulcerogenic		+		85FES190
			+	90JAP02142797
Vasodilatory			+	93FES707

Table 28 Additional pharmacologically active systems.

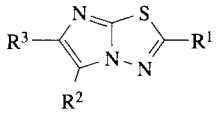
Activity	*Ring system*	*Ref.*
Angiotensin II antagonist	134{7}:NNN/	92EUP505111, 93JMC591
Anthelmintic	13{4}7:NN/S	90FES953
Antiamoebal	13{4}7:ON/N	93MI 805-01
Antimicrobal	12{4}6:NN/S	90AP(323)57
Inhibitor of factor XIIIa	13{4}7:SN/S	88JAP63258428, 90MI 805-02, 90MI 805-02
Spasmolytic	12{4}7:NN/Se	91GEP289273, 91CZ361

8.05.11.4 Materials

8.05.11.4.1 Liquid crystals

Dichroic T-dyes useful for liquid crystal displays comprise 2,6-diaryl-5-arylazoimidazo[2,1-*b*][1,3,4]thiadiazole derivatives (**56**; R^1, R^3 = aryl, R^2 = Ar-N = N) ⟨87MCLC25⟩.

2,6-Disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles (**56**; R^1, R^2, R^3 = H, alkyl, cycloalkyl, aryl) are liquid crystals, and various properties of these compounds have been investigated ⟨88ZOR192, 88ZOR199, 88ZOR1306, 90LC475⟩.



(56)

8.05.11.4.2 Photographic materials

(5,5) (2N1)-Fused heterocycles have found major application as photographic materials.

(i) Magenta coupler

Various imidazo- and pyrazolotriazoles are used as magenta dye-forming couplers for color photography.

12{4}6: NN/N ⟨88JAP63149647, 88JAP63264755⟩.

126{7}: NNN/ ⟨84MI 805-03, 86JAP61198155, 87JAP62141553, 87JAP62237450, 90GEP3912265⟩.

12{4}7: NN/N ⟨87JAP62279338⟩.

13{4}5: NNN/ The most important magenta couplers have a 1*H*-pyrazolo[1,5-*b*][1,2,4]triazole skeleton. Between 1987 and 1994 more than 700 patents have been filed mainly on the application of this system in color photography. Some review articles on 1*H*-pyrazolo[1,5-*b*][1,2,4]triazole magenta couplers have been published ⟨85MI 805-03, 89MI 805-01, 91MI 805-06⟩.

134{7}: NNN/ ⟨92MI 805-01⟩.

(ii) Cyan coupler

Imidazo-, pyrazolo, and thiazolotriazoles are employed as cyan couplers in color photography and related purposes:

12{4}5: NN/N ⟨90EUP379110, 91JAP03051188⟩.

125{7}: NNN/ ⟨89EUP342637⟩.

12{4}6: NN/N ⟨89EUP342637⟩.

126{7}: NNN/ ⟨88EUP269436, 88JAP63199352, 89JAP64000556, 90EUP379110, 90JAP02188749, 90JAP02197841, 90JAP02203337, 90JAP02300744⟩.

12{4}7: NN/S ⟨92JAP04260034⟩.

134{7}: NNS/ ⟨92JAP04260034⟩.

134{7}: NNN/ ⟨93EUP556777⟩.

(iii) Related applications

A 1,3,4-trisubstituted derivative of 1*H*-imidazo[1,5-*c*][1,2,3]triazole is a photographic development-inhibitor-releasing coupler ⟨91JAP03184043⟩. 3,4,5-Trisubstituted 1*H*-pyrazolo[1,5-*c*][1,2,3]-triazoles are employed as (unspecified) dyes in photographic films ⟨91JAP0305237⟩.

8.05.11.5 Analytical Application

A 3,4,5-trisubstituted 1*H*-pyrazolo[5,1-*c*][1,2,4]triazole derivative is the preferred coupling component in an analytical method for the detection of hydrogen peroxide ⟨88EUP268167⟩.

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8.06
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 3 : 0

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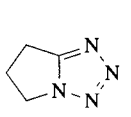
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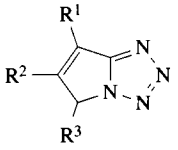
8.06.1 INTRODUCTION

Trimethylenetetrazole (**1**) and, to a much lesser extent, pyrrolotetrazole derivatives (**2**) and (**3**), appear to be the only reported heterocyclic structures among fused bicyclic 5-5 ring systems with one ring junction nitrogen atom and three other heteroatoms all in the same ring. While numerous reports describing various aspects of the chemistry of polycyclomethylenetetrazoles have appeared in the chemical literature, the literature is limited to a few journal articles in the case of the pyrrolotetrazoles (**2**) and (**3**). No major reviews exclusively devoted to fused bicyclic tetrazoles have

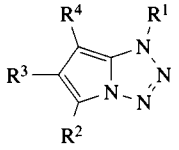
been published; however, all reviews on tetrazole and its derivatives contain some material on the fused systems (see Chapter 4.17 on tetrazoles).



(1)



(2)



(3)

Various authors have referred to compound (**1**) as trimethylenetetrazole, 1,5-trimethylenetetrazole, as well as 6,7-dihydro-5*H*-pyrrolotetrazole while the parent bicyclic ring systems for (**2**) and (**3**) have been cited as 5*H*-pyrrolo[1,2-*d*]tetrazole ⟨90JOC571⟩ and 1*H*-pyrrolotetrazole ⟨92JCS(P1)1483, 94H(37)683⟩, respectively.

8.06.2 STRUCTURE

8.06.2.1 Structural Methods

8.06.2.1.1 X-ray diffraction

Ward *et al.* have examined the crystal structure of trimethylenetetrazole (**1**) and found that this molecule contains a planar tetrazole ring and the trimethylene ring is also planar to within ±0.02Å and lies 0.5° from the plane of the tetrazole ring ⟨79AX(B)1413⟩. The interatomic distances (Å) and angles for this molecule are shown in Table 1. The numbering of the atoms is according to Figure 1. Refinement studies have shown that atoms 1 and 5 refine equally well as C and N or N and C and further refinements using composite 'NC' atoms ($\frac{1}{2}$N + $\frac{1}{2}$C) gave a much better agreement.

Table 1 Interatomic distances (Å) and angles (°) for trimethylenetetrazole.

Bond distances (Å)		*Bond angles* (°)		*Ref.*
NC(1)—N(2)	1.329(3)	N(2)—NC(1)—NC(5)	109.4(2)	79AX(B)1413
NC(1)—NC(5)	1.307(3)	N(2)—NC(1)—C(8)	137.2(3)	79AX(B)1413
NC(1)—C(8)	1.473(3)	NC(5)—NC(1)—C(8)	113.4(2)	79AX(B)1413
N(2)—N(3)	1.332(3)	NC(1)—N(2)—N(3)	104.8(3)	79AX(B)1413
N(3)—N(4)	1.324(3)	N(2)—N(3)—N(4)	111.6(3)	79AX(B)1413
N(4)—NC(5)	1.335(3)	N(3)—N(4)—NC(5)	104.5(3)	79AX(B)1413
NC(5)—C(6)	1.473(3)	NC(1)—NC(5)—N(4)	109.7(2)	79AX(B)1413
C(6)—C(7)	1.517(5)	NC(1)—NC(5)—C(6)	113.5(2)	79AX(B)1413
C(7)—C(8)	1.500(5)	N(4)—NC(5)—C(6)	136.9(3)	79AX(B)1413
		NC(5)—C(6)—C(7)	101.0(3)	79AX(B)1413
		C(6)—C(7)—C(8)	110.6(3)	79AX(B)1413
		C(7)—C(8)—NC(1)	101.4(3)	79AX(B)1413

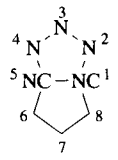


Figure 1 Numbering of atoms in tetramethylenetetrazole.

8.06.2.1.2 IR spectroscopy

IR spectroscopy has been used for structural characterization of tetrazole derivatives (see Chapter 4.17 for specific IR absorption bands assigned to the tetrazole ring) as well as for other studies on

tetrazoles. For example, Boyer and Millar employed IR to investigate the tetrazole–azidoazomethine equilibrium for a series of fused tetrazoles. For trimethylenetetrazole (**1**), they have established its tetrazole structure for solid and solution states based on IR absorption bands from KBr disks, Nujol mull, and from chloroform solutions (Table 2) ⟨59JA(81)4671⟩. IR bands from $CDCl_3$ solutions at 1520, 1530, 1460, and 1245 cm^{-1} have also been reported for some derivatives of 5*H*-pyrrolo[1,2-*d*]tetrazole (**2**) ⟨90JOC571⟩ and 1645, 1625 cm^{-1} ⟨92JCS(P1)1483⟩, and 3140, 1705 cm^{-1} ⟨94H(37)683⟩ from KBr disks for some alkyl and acyl substituted derivatives of (**3**).

Table 2 IR absorption bands (cm^{-1}) for trimethylenetrazole (**1**).

KBr disk	*Nujol mull*	*$CHCl_3$ solution*	*Ref.*
3425m, 2976m	3344m, 2924s	3460w, 3003m	59JA4671
1531s, 1499s	2865s, 1529m	2469w, 1531w	59JA4671
1471m, 1439m	1497m, 1466s	1502m, 1464m	59JA4671
1323m, 1266m	1383s, 1321m	1443w, 1328m	59JA4671
1244m, 1186m	1264m, 1242m	1263w, 1245w	59JA4671
1145m, 1080s	1186m, 1144m	1179w, 1143w	59JA4671
996w, 964m	1080m, 994w	1082m, 962w	59JA4671
907m, 842w	964m, 906m	905w, 840w	59JA4671
708w, 675w	844w, 735m, 673m		59JA4671

8.06.2.1.3 NMR spectroscopy

Proton and carbon NMR spectra have also been used for structural characterization or structural assignment between isomeric substituted tetrazoles (Chapter 4.17). Tables 3 and 4 show the ^1H and ^{13}C chemical shifts for the ring hydrogens and carbons for the fused tetrazole (**1**) and some derivatives of (**2**). For pyrrolotetrazole (**3**) where R^1 = Me, R^2 = Ac, R^3 = Me, R^4 = Ac, the ^{13}C chemical shifts of the quaternary carbons are 102.0, 117.0, 137.3, 138.5 ppm ⟨92JCS(P1)1483⟩. Proton and carbon-13 NMR spectral data have also been reported for the ring hydrogens and carbons of a few derivatives of (**3**) by Moderhack and Decker but no assignments have been made ⟨94H(37)683⟩.

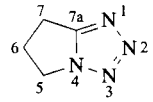


Table 3 Proton and carbon-13 NMR chemical shifts (δ ppm) for (**1**).

Solvent	*H-5*	*H-6 and H-7*	*C-5*	*C-6*	*C-7*	*C-7a*	*Ref.*
$CDCl_3$	4.39–4.15	3.05–2.81	44.18	18.26	27.21	162.5	91JOC7261

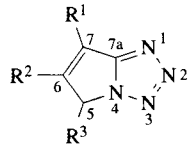


Table 4 Proton and carbon-13 NMR chemical shifts (δ ppm) for ring H and C for (**2**).

R^1	*R^2*	*R^3*	*Solvent*	*H-5*	*H-6*	*H-7*	*C-5*	*C-6*	*C-7*	*C-7a*	*Ref.*
H	Me	H	$CDCl_3$	4.73		6.50	53.5	154.7	112.5	164.2	90JOC571
Me	H	H	$CDCl_3$	4.78	6.65		50.3	135.0	127.9	164.0	90JOC571
Me	Me	H	$CDCl_3$	4.74			53.1	133.9	120.8	164.6	90JOC571

Baker and Popov obtained the ^{14}N NMR spectrum of a 1.5M aqueous solution of (**1**) which exhibits four partially resolved bands ⟨72JPC2403⟩. Assignment of the resonances was based on

comparison with ^{14}N resonances for pyrazole, imidazole and some triazoles. Thus the highest field peak was assigned to N-4, being bonded to two carbons and one nitrogen, while the next highest peak was assigned to N-1. The two most downfield bands were assigned to N-2 and N-3. All chemical shifts were relative to the NO_3^- line of ammonium nitrate used as external reference through sample interchange.

8.06.2.1.4 Mass spectrometry

The mass spectral fragmentation of trimethylenetetrazole (**1**), obtained by cold direct inlet, involves loss of N_2 and $N_2 + H$, and the fragment with m/z 54 as the main fragment. High-resolution mass measurement has shown the elemental composition of this fragment as $C_2H_2N_2$. At 150°C using a heated inlet, complete decomposition of **1** occurs featuring no parent peak and the spectrum reveals peaks for ethylene (*m/z* 28), $C_2H_2N_2$ (*m/z* 54) and *m/z* 53 formed by loss of H from *m/z* 54. The chemical composition of these peaks have been determined by high-resolution mass spectrometry and shows decomposition of (**1**) into nitrogen, ethylene, and $C_2H_2N_2$ ⟨71T1281⟩. Routine mass spectral data including the molecular ion for (**2**) ⟨90JOC571⟩ and (**3**) ⟨92JCS(P1)1483⟩ have also been reported.

8.06.2.1.5 Dipole moments

In connection with a dipole moment study of annular tautomerism in 5-*p*-tolyltetrazole, the electric dipole moment of 1,5-trimethylenetetrazole (**1**) has been measured in benzene solution at 30.0°C and was found to be 5.88 ± 0.04 Debye ⟨80JHC1373⟩.

8.06.2.2 Thermodynamic Aspects

8.06.2.2.1 Melting points

The absence of a ring NH hydrogen in the fused tetrazoles (**1**), (**2**), and (**3**) and their inability to associate intermolecularly through hydrogen bonding is reflected in the depressed melting points of these 1,5-disubstituted tetrazoles. For example, while 5-methyltetrazole has a melting point of 148°C, 1,5-trimethylenetetrazole (**1**) melts at 110°C. Although other factors may influence molecular packing and intermolecular forces, the effect of hydrogen bonding appears to be most dominant. The melting point of trimethylenetetrazole and some pyrrolotetrazole derivatives are given in Table 5.

8.06.2.2.2 Tautomerism

The azidoazomethine tetrazole isomerism in tetrazoles fused with five-membered rings has been reviewed ⟨73CI(L)371, 77AHC(21)404⟩. For trimethylenetetrazole (**1**), IR studies have established that tetrazole ring destabilization as a result of fusion to another five-membered ring is insufficient for isomerization of this molecule to its less stable azide tautomer (**4**) (Equation (1)), and both in the solid state and in solution only absorption bands arising from the tetrazole ring are observed and bands expected for the azide moiety are not found ⟨59JA4671⟩. While, in principle, 5*H*-pyrrolo[1,2-*d*]tetrazoles (**2**) could equilibrate to an open-chain azido tautomer, such compounds have been noted to exhibit good thermal stability ⟨90JOC571⟩.



(1) (4) (1)

Table 5 Melting points of some fused tetrazoles.

Structure	R^1	R^2	R^3	R^4	*m.p.* (°C)	*Ref.*
(1)					109–110	91JA7261
					109–110	71T1281
					109–110	59JA4671
					110	35GEP611692
					110	68JA6476
					110	69BSF3704
(2)	Me	H	H		113	90JOC571
	H	Me	H		104	90JOC571
	Me	Me	H		95	90JOC571
	Me	H	CO_2Et		58–59	90JOC571
(3)	Me	COPh	Me	Ac	210	92JCS(P1)1483
	Me	Ac	Me	Ac	130–131	92JCS(P1)1483
	Me	H	Ph	CO_2Me	128–129	94H(37)683
	Me	H	4-BrC_6H_4	CO_2Me	114–116	94H(37)683
	Ph	H	Ph	Ac	95	94H(37)683
	Me	H	Me	Ac	152–154	94H(37)683
	Me	H	Ph	Ac	92–94	94H(37)683
	Me	H	Ph	H	140–142	94H(37)683
	Me	H	4-BrC_6H_4	H	201–203 (d)	94H(37)683
	Ph	H	Ph	H	127–129	94H(37)683
	Me	H	Me	H	oil	94H(37)683
	Me	NO	Ph	CO_2Me	138–140	94H(37)683
	Me	NO	4-BrC_6H_4	CO_2Me	128–130 (d)	94H(37)683
	Me	NO	Ph	Ac	141–143 (d)	94H(37)683
	Me	N_2Ph	Ph	H	168–170 (d)	94H(37)683
	Me	N_2Ph	Me	H	128–131	94H(37)683
	Me	N_2Ph	Ph	CO_2Me	240–242 (d)	94H(37)683

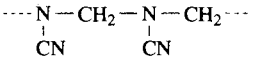
8.06.2.2.3 Gas chromatography

Gas chromatographic characteristics of several cyclopolymethylenetetrazoles and the conditions for their routine analyses by gas–liquid chromatography (GLC) have been determined ⟨77MI 806-01⟩. At a He flow rate of 60 ml min^{-1} and oven temperature of 210 °C on a 6 ft × $\frac{1}{8}$ in. stainless-steel tubing packed with 3% Hi-Eff 8-BP on 100/120 mesh Gas-Chrom Q, the retention time of pentamethylenetetrazole (PMT) is 210 s. With PMT as the standard, the retention time and sensitivity for (**1**) were found to be 0.99 and 0.16, respectively. The relatively low sensitivity for (**1**) was found to be due to decomposition at 210 °C. By lowering the injection port temperature to 175 °C, decomposition was reduced but not completely eliminated. While the plot of average detector response time versus the concentration of tetrazoles was linear from 10^{-3} to 10^{-1} M, deviation from linearity was observed at concentrations greater than 10^{-1}M.

8.06.3 REACTIVITY

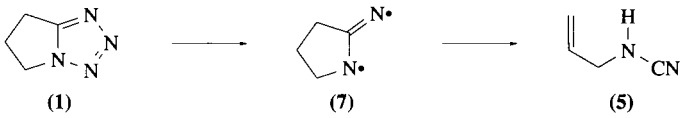
8.06.3.1 Gas-phase Pyrolysis

Trimethylenetetrazole (**1**) undergoes pyrolysis at 500 °C/10^{-1} torr to afford a 1% yield of 3-propenylcyanamide (**5**) with IR absorption at 2130, 2224, and 3200 cm^{-1}. The main product is a hard, transparent polymer whose IR and elemental analysis are consistent with poly-*N*-cyanomethanimine (**6**). Wentrup has implicated the nitrene intermediate (**7**), formed by ring opening of the tetrazole ring upon loss of N_2, in the formation of these compounds (Scheme 1) ⟨71T1281⟩.



(**6**)

In 1991, Wentrup and co-workers ⟨91JA7261⟩ showed that flash vacuum pyrolysis (FVP) of (**1**) at 300–450 °C with product isolation at 77K yields azide (**4**) having a band of medium stretch at about 2130 cm^{-1}; this band gradually disappears and the spectrum becomes identical to that for (**1**). While (**1**) is the stable form in the crystalline state at room temperature, the azide form (**4**) is more favored



(1) (7) (5)

Scheme 1

in the gas phase. FVP of **1** at 500–800 °C causes loss of N_2 and ethylene and leads to almost quantitative formation of *N*-cyanomethanimine which polymerizes above −100 °C. In a related study, Bock and co-workers obtained the PE spectrum of (**1**) and showed that in a low pressure flow system this compound decomposes above 730K with elimination of N_2, ethylene, and $H_2C{=}NCN$ ⟨90ZN(B)59⟩.

8.06.3.2 Coordination with iodine

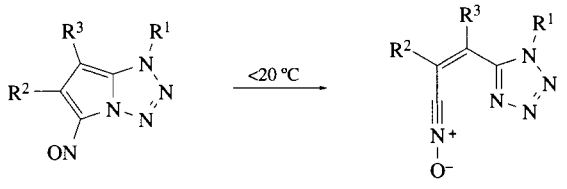
The donor ability of (**1**) has been investigated spectrophotochemically in the tetrazole-iodine charge-transfer complex formation reaction (**1**) + $I_2 \rightleftharpoons$ (**1** · I_2) in 1,2-dichloroethane solutions at several temperatures ⟨68JA6476⟩. Formation constants, K_f, of the complex have been calculated using the Ketelaar equation by measuring absorbances at 430, 420, 410 and 400 nm (near the complex absorption maximum). Thermodynamic constants for this reaction are given in Table 6. These results indicate that the donor properties of **1** are rather weak and are comparable to those of an aromatic ring although such interactions do not involve the *p* electrons of tetrazole.

Table 6 Thermodynamic constants for the reaction (**1**) + $I_2 \rightleftharpoons$ (**1** · I_2).

Temperature (°C)	K_f (M^{-1})	$\Delta G°$ (cal mol^{-1})	$\Delta S°$ *(e.u.)*	ΔH (kcal mol^{-1})
35.0	1.16 + 0.06	−91	−10.8	−3.4
25.0	1.42 + 0.09	−215		
15.0	1.63 + 0.04	−299		
5.0	2.10 + 0.03	−454		

8.06.3.3 Valence isomerism

In a 1994 study by Moderhack and Decker, using IR, ^{13}C and ^{15}N NMR analyses, it was demonstrated that below 20 °C, certain 1,6-disubstituted 5-nitroso-1*H*-pyrrolotetrazoles (**8**), generated by nitrosation of the corresponding 5-unsubstituted pyrrolotetrazoles, ring open to give the isomeric acrylonitrile oxides (**9**) (Equation (2)) ⟨94H(37)683⟩. Chemical characterization of the nitrile oxides was achieved by deoxygenation to the corresponding acrylonitriles as well as [3 + 2] cycloaddition with DMAD. In contrast, the 5-nitroso derivatives in which R^3 is acyl or carbomethoxyl, are stable under ordinary conditions but smoothly undergo cycloaddition with DMAD at elevated temperature to produce isoxazoles. Similarly 5-phenylazo analogs are stable, but prolonged heating of these compounds at 110 °C with DMAD affords pyrazole cycloadducts.



(8) (9) (2)

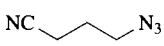
R^1 = Me, R^2 = Ph, R^3 = H
R^1 = Me, R^2 = 4-BrC_6H_4, R^3 = H
R^1 = Ph, R^2 = Ph, R^3 = H

8.06.4 SYNTHESIS

8.06.4.1 Synthesis of trimethylenetetrazole

8.06.4.1.1 Acid-catalyzed cyclization of 4-azidobutyronitrile

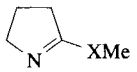
The chlorosulfonic acid-catalyzed intramolecular cyclization of 4-azidobutyronitrile yielding (**1**), originally reported by von Kereszty and Wolf remains the most important route to this compound ⟨35GEP611692⟩. Popov and co-workers, for example, obtained (**1**) in 74% yield using von Kereszty's method ⟨68JA6476⟩. Nitrosation of 4-azidobutyronitrile with $NO^+BF_4^-$ has also been noted to produce a 28% yield of (**1**), possibly through a carbenium intermediate ⟨79JOC2923⟩.



(**1**) (3)

8.06.4.1.2 Reaction of 2-methylpyrrolinethiol or 2-methoxypyrroline with hydrazoic acid

Boyer and Miller prepared (**1**) by treating 2-methylthiol Δ^1-pyrroline (**10a**), with hydrazoic acid affording a 20% yield ⟨59JA4671⟩. Compound (**10a**), in turn, may be made from 2-thiopyrrolidine upon methylation with iodomethane. Wentrup obtained a 55.8% yield of (**1**) by a slight modification of this procedure ⟨71T1281⟩. In an analogous fashion, reaction of 2-methoxy Δ^1-pyrroline (**10b**) with hydrazoic acid produces (**1**) in 30% yield (Equation (4)) ⟨69BSF3704⟩.

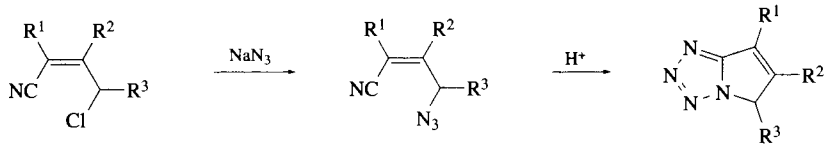


(**10a**) X = S
(**10b**) X = O

(**1**) (4)

8.06.4.2 Synthesis of 5H-pyrrolo[1,2-d]tetrazoles

Chlorosulfonic acid-catalyzed thermal cyclization of 4-azido-2-butenenitriles (**11**) in chloroform, affords moderate to good yields of substituted pyrrolotetrazoles (**2**) (Scheme 2) ⟨90JOC571⟩. Treatment of (**2b**) with NaH in DMSO followed by reaction with ethyl chloroformate leads to exclusive acylation at C(5) in high yield. Compounds (**11**) are prepared by substitution with sodium azide of chlorobutenenitriles (**12**).



(**12a–e**) (**11a–e**) (**2a–e**)

a: $R^1 = R^2 = R^3 = H$
b: $R^1 = Me$; $R^2 = R^3 = H$
c: $R^2 = Me$; $R^1 = R^3 = H$
d: $R^3 = Me$; $R^1 = R^2 = H$
e: $R^1 = R^2 = Me$; $R^3 = H$

Scheme 2

8.06.4.3 Synthesis of 1H-pyrrolotetrazoles

Treatment of salts (**13a**) and (**13b**) with triethylamine in the presence of acetic anhydride affords pyrrolotetrazoles (**3a**) and (**3b**) in 14% and 6% yields, respectively. The reaction presumably proceeds via a tetrazolium-*N*-phenacylide (Equation (5)) ⟨92JCS(P1)1483⟩.

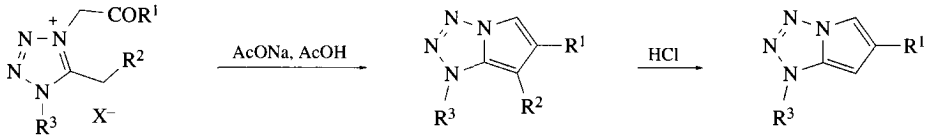


(5)

(13a) R^1 = Ph, R^2 = Ac, X = BF_4
(13b) R^1 = Me, R^2 = H, X = Br

(3a) R = Ph
(3b) R = Me

In a similar manner, reaction of salts (**13c–g**) with sodium acetate in acetic acid at 110 °C affords pyrrolotetrazoles **3**(**c–g**) which upon treatment with concentrated HCl at 100 °C yield the corresponding 7-unsubstituted pyrrolotetrazoles (**3h–k**) (Scheme 3) ⟨94H(37)683⟩.



(13c) R^1 = Ph, R^2 = CO_2Me, R^3 = Me
(13d) R^1 = 4-BrC_6H_4, R^2 = CO_2Me, R^3 = Me
(13e) R^1 = Ph, R^2 = COMe, R^3 = Ph
(13f) R^1 = Me, R^2 = COMe, R^3 = Me
(13g) R^1 = Ph, R^2 = COMe, R^3 = Me

(3c–g)

(3h) R^1 = Ph, R^3 = Me
(3i) R^1 = 4-BrC_6H_4, R^3 = Me
(3j) R^1 = Ph, R^3 = Ph
(3k) R^1 = Me, R^3 = Me

Scheme 3

8.06.5 MISCELLANEOUS PROPERTIES

8.06.5.1 Biological Activity

Cyclopolymethylenetetrazoles (**1**) and a number of their derivatives are noted for their stimulating action on the central nervous system and can cause convulsions. The convulsant activity varies and depends on the exact molecular structure of the compound. The convulsant potencies of numerous tetrazole derivatives has been estimated for white mice. The approximate minimum convulsant dose (injected intraperitoneally in physiological saline solution) for (**1**) is 1000 mg/kg^{-1} body weight ⟨70MI 806-01⟩.

The ability of a series of cyclopolymethylenetetrazoles (**1**) to inhibit [^{3}H]diazepam binding to benzodoazepine receptors *in vitro* has been investigated. There is an excellent correlation between their *in vitro* potencies in displacing [^{3}H]diazepam binding and their *in vivo* potencies in producing seizures ⟨82MI 806-01⟩. A series of cyclopolymethylenetetrazoles have also been examined for their potencies in displacing [^{35}S]-*t*-butylbicyclophosphorothionate (TBPS) from the picrotoxin site on the benzodiazepine–GABA–chloride ionophore receptor complex. A very high correlation has been observed between the potencies of these compounds in displacing [^{35}S]-TBPS binding *in vitro* and their convulsant potencies *in vivo*. The displacement potency increases with the number of methylene groups up to seven and then decreases. For (**1**), the IC_{50} for inhibition of specific [^{35}S]-TBPS binding to rat brain membrane is 43000 ± 3000 mM ⟨84LS1439⟩.

8.06.5.2 Photography

Pyrrolotetrazoles (**3**) have found use in the photographic industry as components in color photographic materials ⟨94JAP06102639, 94JAP06175315, 954AP061867080⟩.

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8.07
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 2 : 2

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Universität Innsbruck, Austria

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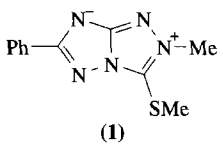
8.07.1 INTRODUCTION

The 5,5-fused ring system with one fusion nitrogen atom and two additional heteroatoms in each five-membered ring (2N2) gives rise to a large number of conceivable structural combinations. Considering the elements of nitrogen, oxygen, and sulfur for the four peripheral heteroatom positions reduces the number of possible combinations. In reality, only 16 ring systems of this type of (5,5) (2N2)-fused rings have substantiated, as listed in Table 1. The topology gives the positions of the heteroatoms, the position of the fusion nitrogen atom being put in parentheses. Thus, the quotation of the heteroatoms is in this order and includes a slash to indicate the fusion nitrogen atom in either the 4- or 7-position. The naming of the parent fused heterocycles follows the "Recommendations for the Nomenclature of Fused and Bridged Fused Ring Systems" ⟨B-94MI 807-01⟩. The last two columns of Table 1 survey the (5,5) (2N2) systems covered in *CHEC-I* and *CHEC-II.*

There is one major review in two parts on the synthesis of fused heterocycles ⟨B-87MI 807-01, B-92MI 807-01⟩; the approach focuses on the type of functional group(s) and/or ring atom(s) of the first ring involved in the formation of the second heterocyclic ring.

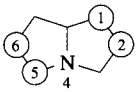
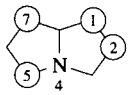
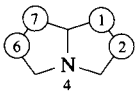
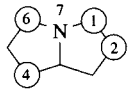
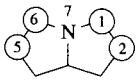
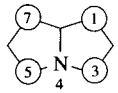
8.07.2 THEORETICAL METHODS

In a series of 5,5-fused heterocycles the inner salt (**1**) displays a substantial aromatic character as indicated by the aromaticity index $I_{(5,5)}$ of 82 ⟨87T4725⟩.



(**1**)

Table 1 5,5-Fused ring systems (2N2): one fusion nitrogen atom and two heteroatoms in each fused ring.

Topology of heteroatom positions	*Heteroatoms in positional order*	*Name of (5,5) (2N2) system*	*CHEC-I*	*CHEC-II*
 12{4}56	NN/NN	[1,2,4]triazolo[4,3-*c*][1,2,3]triazole	–	+
 12{4}57	NN/NN	[1,2,4]triazolo[4,3-*b*][1,2,4]triazole	+	+
	NO/NN	[1,2,4]triazolo[5,1-*c*][1,2,4]oxadiazole	–	+
	NN/NO	[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole	+	+
	NN/NS	[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole	+	+
	NS/NS	[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole	+	+
	NS/NO	[1,2,4]thiazolo[3,4-*b*][1,3,4]oxadiazole	+	–
 12{4}67	NN/NN	[1,2,4]triazolo[3,4-*c*][1,2,4]triazole	–	+
	ON/NN	[1,2,4]triazolo[4,3-*d*][1,2,4]oxadiazole	–	+
	SN/NN	[1,2,4]triazolo[4,3-*d*][1,2,4]thiadiazole	–	+
	SS/NN	[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazole	–	+
	SN/SN	[1,2,4]thiadiazolo[5,4-*c*][1,2,4]thiadiazole	+	–
 1246{7}	NNSN/	[1,2,3]triazolo[5,1-*b*][1,3,4]thiadiazole	–	+
 1256{7}	n.a.		–	–
 13{4}57	SN/NN	[1,2,4]triazolo[5,1-*b*][1,3,4]thiadiazole	–	+
	NS/NS	[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazole	+	+
	ON/SN	[1,2,4]thiadiazolo[3,2-*b*][1,3,4]oxadiazole	–	+

8.07.3 STRUCTURE

8.07.3.1 X-ray

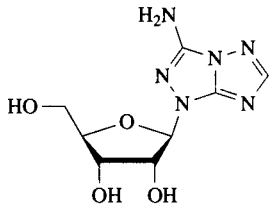
X-ray analyses of azapentalenes have been used to determine the structures of products from reactions with ambiguous reaction sites or with concomitant rearrangements. Thus, the x-ray structure of the β-D-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole (**2**) establishes that glycosylation has occurred at the N-1 position; furthermore, it also shows that the compound is the β-anomer. In addition to intermolecular hydrogen bonds in the crystal structure an intramolecular hydrogen bond is extended from OH-5 to N-7 ⟨84MI 807-01⟩.

The x-ray structure of the inner salt of compound (**1**) has been determined and proves its mesoionic character ⟨85BCJ735⟩.

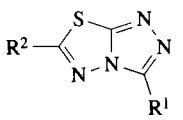
The structure of 3-(2-aminophenyl)-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**3**) is based on its determination by x-ray crystallography; it indicates that in the course of its formation (cf. 8.07.8.3.1) a thioaroyl group has migrated and has been incorporated into the thiadiazole ring of the product ⟨89LA1055⟩.

The structure of the 1*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]triazole (**4**) has been established from its x-ray analysis ⟨87CB965⟩, as has the unexpected product structure of the 3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole (**5**) ⟨94T7019⟩.

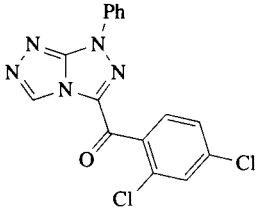
The x-ray analyses of crystal structures also reveal the interplanar angle of the fused heterocycles, which varies only slightly. In keeping with its aromatic character the mesoionic system (**1**) is planar ⟨85BCJ735⟩. As in other fully conjugated azapentalene systems the dihedral angle of the fused five-membered rings does not strongly deviate from co-planarity; in (**3**) the dihedral angle is 1.9° ⟨89LA1055⟩ which is close to the angle reported in other studies of fused five-membered rings ⟨78AHC(22)183⟩ (cf. literature cited in ⟨84MI 807-01, 85BCJ735⟩). Only in (**2**) is the dihedral angle of 3.6° between the planes of the two fused triazole rings significantly larger ⟨84MI 807-01⟩.



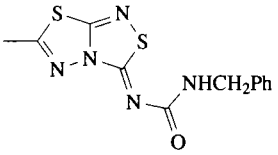
(2)



(3) $R^1 = C_6H_4\text{-}NH_2\text{-}2$
$R^2 = Ph$



(4)



(5)

8.07.3.2 NMR Data

The (5,5) (2N2)-fused heterocyclic system contains three ring carbon atoms, one fusion carbon atom, and one additional nonfusion carbon atom in each five-membered ring. Only scattered ^1H and ^{13}C NMR data are available for this system.

8.07.3.2.1 ^1H NMR data

Most ^1H NMR data refer to the substituents attached to the fused heterocyclic rings and very little is reported on C-unsubstituted compounds.

Methine groups are generally part of a ring azomethine moiety and are either linked to a fusion atom (C or N) or to a nonfusion atom (N or S) (Table 2).

Table 2 ^1H NMR data for ring methine groups in (5,5) (2N2) systems.

X—CH=N	*Solvent*	*δ (range)*	*Ref.*
X (fusion atom): C	$DMSO\text{-}d_6$	7.86	92JHC713
X (fusion atom): N	$DMSO\text{-}d_6$	7.2–7.9 (under arom. H)	93MI 807-01
	$DMSO\text{-}d_6$	5.5	92IJC(B)467
	$CDCl_3$	7.86	87CB965
X (nonfusion atom): N	$DMSO\text{-}d_6$	8.02	84MI 807-01, 93JHC1289
X (nonfusion atom): S	$DMSO\text{-}d_6$	6.2	92IJC(B)714
	$DMSO\text{-}d_6$	7.7–8.14 (under arom. H)	90IJC(B)135

The resonance range of protons attached to a saturated ring carbon atom is at higher field, as would be expected for aminal-type protons; there are two reports on signals at even higher field which do not conform with this assignment (Table 3).

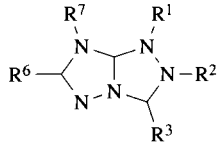
Table 3 ^1H NMR data for hydrogen attached to saturated ring carbon atoms in (5,5) (2N2) systems.

Structural Unit	*Solvent*	*δ (range)*	*Ref.*
 N, S nonfusion atoms	$DMSO\text{-}d_6$	7.86	93MI 807-01
	$DMSO\text{-}d_6$	1.3–1.6	90IJC(B)176, 90H(31)2147
	$CDCl_3$	6.3	90IJC(B)135
 N fusion atom X nonfusion atom			
X = N	$CDCl_3$	5.55–5.9	92PS(70)99
X = O	$CDCl_3$	5.82, 5.89	92PS(70)99

8.07.3.2.2 ^{13}C NMR data

Most ^{13}C NMR data on ring carbon atoms are reported for [1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (Table 4).

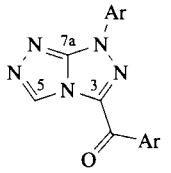
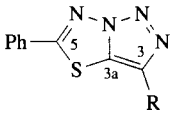
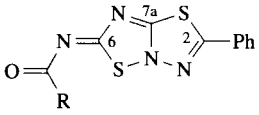
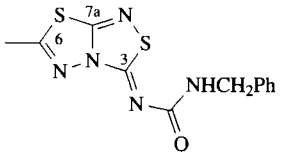
Table 4 Carbon-13 NMR data for [1,2,4]-triazolo[4,3-*b*]triazoles (with maximum unsaturation).



R^1	R^2	R^3	R^6	R^7	*Solvent*	*C-3*	*C-6*	*C-7a*	*Ref.*
1′,2′,5′-$(Bn)_3$-β-ribose		NH_2			$CDCl_3$	140.9	158.3	156.0	93JHC1289
1′,2′,5′-$(Bn)_3$-α-ribose		NH_2			DMSO-d_6	139.9	158.4	155.9	93JHC1289
H	1′,2′,5′-$(Bn)_3$-β-ribose	=NH			DMSO-d_6	138.3	160.3	160.1	93JHC1289
		1′,2′,5′-$(Bn)_3$-α-ribose		H	DMSO-d_6	139.5	158.2	156.7	93JHC1289
		1′,2′,5′-$(Bn)_3$-β-ribose		H	DMSO-d_6	139.1	158.5	156.7	93JHC1289
H						126.7	158.9	156.8	77OMR(9)508, 85BCJ735
Me						127.7	159.0	156.0	77OMR(9)508, 85BCJ735
				Me		130.5	149.0	153.8	77OMR(9)508, 85BCJ735
(−)	Me	=O	Ph		D_2O-dioxane	159.0	168.0	146.6	85BCJ735
H	Me	=O	Ph		DMSO-d_6	145.2	155.2	146.5	85BCJ735
(−)	Me	=S	Ph		D_2O-dioxane	160.1	168.4	147.8	85BCJ735
H	Me	=S	Ph		DMSO-d_6	154.2	156.2	149.0	85BCJ735
H		SMe	Ph		DMSO-d_6	134.7	157.9	157.4	85BCJ735
(−)	Me (+)	SMe	Ph		DMSO-d_6	159.4	168.3	161.9	85BCJ735
Me		SMe	4-tolyl		DMSO-d_6	134.1	168.3	156.7	85BCJ735
COMe		SMe	Ph		DMSO-d_6	140.4	164.4	155.0	85BCJ735
		SMe	Ph	Me	DMSO-d_6	135.2	157.7	155.8	85BCJ735
Me		Me	4-tolyl			135.84	169.57	156.48	85H(23)2613
Me		SMe	$S^{(-)}$	Ph	DMSO-d_6	136.3	175.9	144.6	84TL5427, 86T2121
Me		SMe	SMe	Ph	DMSO-d_6	138.6	162.3	146.1	84TL5427, 86T2121

The scarce data available for other (5,5) (2N2)-systems (Table 5) do not allow any systematic correlation.

Table 5 Carbon-13 NMR data for (5,5) (2N2) fused systems.

Structure	*Solvent*	*Ring C atoms*			*Ref.*
	$DMSO-d_6$	C-3 134.31	C-5 133.43	C-7a 156.57	87CB965
	$CDCl_3$	C-3 123.1[a] n.a.[b]	C-3a 131.5[a] 136.1[b]	C-5 167.3[a] 168.9[b]	92JHC713
	TFA	C-2 137.83	C-6 133.40	C-7a 134.95	91IJC(B)435
	$DMSO-d_6$	C-3 165.7	C-6 162.5	C-7a 153.7	94T7019

[a]R = H; [b]R = CO_2Et.

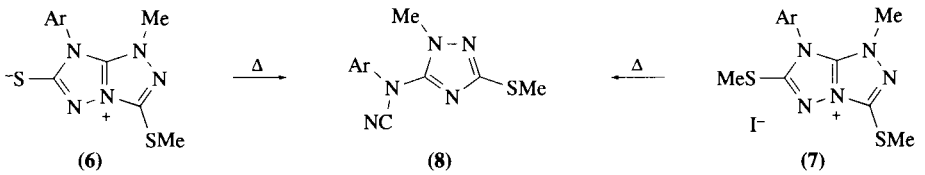
8.07.4 THERMODYNAMIC ASPECTS

The ring-chain equilibrium position of substituted diazoalkylthiadiazoles is influenced by substituents and solvents and has been determined by NMR spectroscopy ⟨92JHC713⟩ (cf. 8.07.2.1.1 and 8.07.8.1.3).

8.07.5 REACTIVITY OF FULLY CONJUGATED RINGS

8.07.5.1 Thermally Induced Ring Opening

Both the inner salts (**6**) of anhydro 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium hydroxides and their methylation products (**7**), when heated above the melting points suffer loss of sulfur or loss of methyl iodide and sulfur, respectively. Under concomitant ring opening transformation into 1-methyl-3-methylthio-5-(arylcyanamino)[1,2,4]triazoles (**8**) takes place (Scheme 1) ⟨84TL5427, 86T2121⟩.



(6) (8) (7)

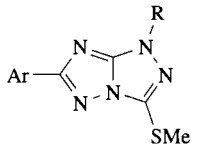
Scheme 1

8.07.5.2 Electrophilic Attack at Ring Nitrogen

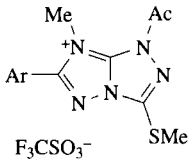
8.07.5.2.1 N-*Methylation and* N-*acetylation*

Direct methylation of the 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**9**) is achieved by treatment of the potassium salt with methyl iodide, yielding the 1-methyl derivatives (**10**) ⟨83S415⟩. The 7-methyl

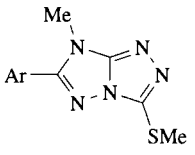
isomers (**13**) are obtained after conversion of compound (**9**) into the 1-acetyl derivatives (**11**) followed by methylation with methyl trifluoromethanesulfonate gives the 1-acetyl-6-aryl-7-methyl-3-methylthio-1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-7-ium-trifluoromethanesulfonates (**12**), which upon treatment with aqueous sodium carbonate afford the 7-methyl derivatives (**13**) ⟨85BCJ735⟩.



(**9**) R = H
(**10**) R = Me
(**11**) R = Ac



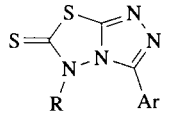
(**12**)



(**13**)

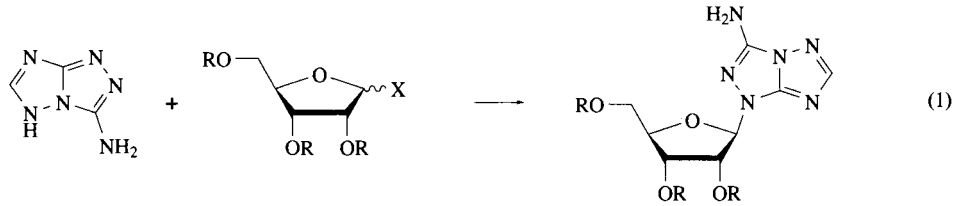
8.07.5.2.2 N-*Hydroxymethylation and* N-*glycosylation*

The reaction of 3-(2-benzofuranyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione (**14**) with formaldehyde in ethanol gives the 5-(hydroxymethyl) derivative (**15**). The same reaction in the presence of a primary or secondary amine in ethanol affords the corresponding Mannich base, e.g. (**16**) ⟨92IJC(B)167⟩.



(**14**) R = H
(**15**) R = CH_2OH
(**16**) R = $CH_2NR^1R^2$

Direct glycosylation of 3-amino-5(7)*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole (**17**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**18**) in the presence of trimethylsilyl triflate gives the 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl) derivative (**20**). The same product (**20**) results from the high temperature glycosylation with boron trifluoride etherate in nitromethane as well as from the reaction of the triazolotriazole sodium salt with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**19**) (Equation (1)) ⟨87MI 801-01⟩. When 3-amino-5(7)*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole (**17**) is treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**19**) and stannic chloride a mixture of four products is obtained. In addition to (**20**), the 1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl) derivative (**21**), the 3-imino-2,3-dihydro-7*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl) derivative (**22**), and the 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino) derivative (**23**) are isolated (Equation (1)) ⟨93JHC1289⟩.



(1)

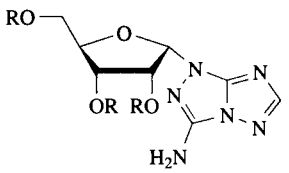
(**17**)

(**18**) X = OAc, R = COPh
(**19**) X = Br, R = COPh

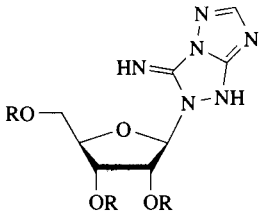
(**20**) R = COPh

8.07.5.2.3 *Exchange of a functionalized ring carbon with carbonic acid derivatives*

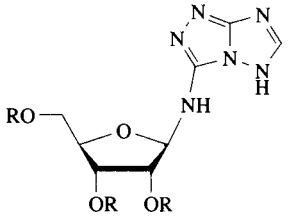
The 3-arylimino and 3-thione functions of the 5-aryl-3*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazoles (**24**) and (**25**) are formally interchanged upon heating (**25**) with carbon disulfide and (**24**) with arylisothiocyanates, respectively ⟨83ABC1017⟩.



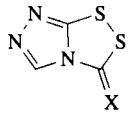
(21)



(22) R = COPh



(23)

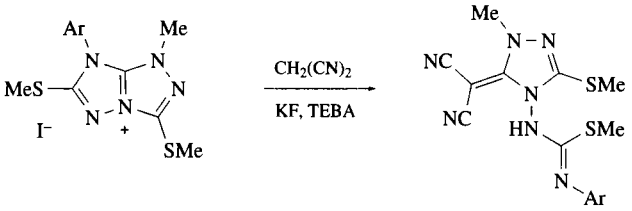


(24) X = S
(25) X = N–Ar

8.07.5.3 Nucleophilic Attack at Carbon

8.07.5.3.1 Attack of C*-nucleophile at fusion carbon inducing ring opening*

Malononitrile under hydrolytic solid-liquid phase transfer catalysis attacks the methiodides (**26**) at the fusion carbon atom, thereby inducing ring opening and the formation of 4-(*N*-aryl-*S*-methylisothioureido)-5-(dicyanomethylene)-1-methyl-3-methylthio-4,5-dihydro-1*H*-[1,2,4]triazoles (**27**) (Equation (2)) ⟨86T2121⟩.



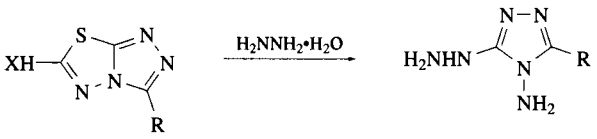
(2)

(26) (27)

TEBA = benzyltriethyl ammonium chloride

8.07.5.3.2 Attack of N*-nucleophiles at fusion carbon inducing ring opening*

The 3-hetaryl substituted 6-hydroxy- and 6-sulfonyl[1,2,4]triazolo[3,4-*b*][1,2,4]thiadiazoles (**28**) and (**29**) on treatment with hydrazine hydrate gave the 3-hetaryl-substituted 4-amino-5-hydrazino-[1,2,4]triazoles (**30**). Obviously, ring opening is induced by nucleophilic attack at the fusion carbon atom (Equation (3)) ⟨90IJC(B)135⟩.

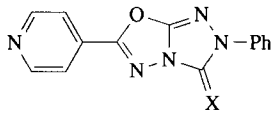


(3)

(28) X = O
(29) X = S

(30)

On the other hand the thione (**31**) was converted into the corresponding hydrazone (**32**) with hydrazine ⟨84MI 807-02⟩.



(31) X = S
(32) X = NNH_2

8.07.5.3.3 Hydrolysis

Hydrolysis of the inner salts (**33**) of anhydro 6-aryl-2-methyl-3-methylthio[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium hydroxides with alkali results in the displacement of the methylthio group and the formation of the 7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-3(2*H*)-ones (**34**) (Equation (4)) ⟨85BCJ735⟩.



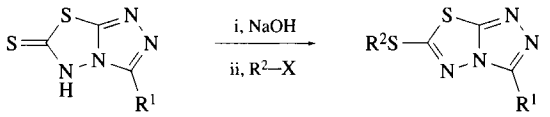
(4)

(33) **(34)**

8.07.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING C-ATOMS

8.07.6.1 *S*-Alkylation

Thioxo (or thiol) derivatives (as part of a thiourea function incorporated into the heterocyclic system) are effectively *S*-alkylated by treatment of the anion with alkyl halides. Thus, the 3-heteroaryl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thiones (**35**) dissolved in sodium hydroxide solution react with alkyl halides yielding the corresponding 6-alkylthio derivatives (**36**) (Equation (5)) ⟨92IJC(B)167⟩.

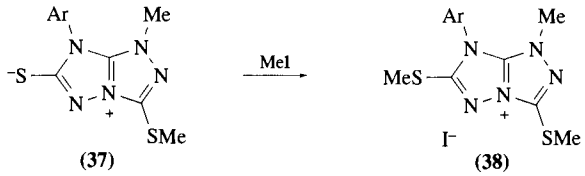


(5)

(35) **(36)**

R^1 = hetaryl
R^2 = Me, Et, cyclopentyl
X = Br, I

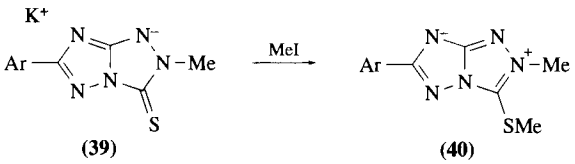
The mesoionic compounds (**37**), inner salts of anhydro 7-aryl-1-methyl-3-methylthio-6-sulfonyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium hydroxides are methylated with methyl iodide to give the corresponding quaternary salts (**38**) (Equation (6)) ⟨84TL5427, 86T2121⟩.



(6)

(37) **(38)**

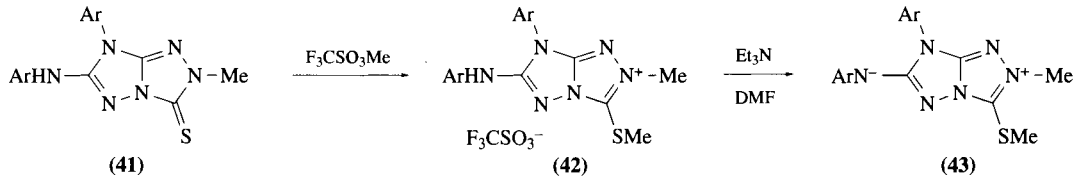
Similarly, the potassium salts of 6-aryl-2-methyl-1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**39**) are methylated affording betaines (**40**) Equation (7) ⟨85BCJ735⟩.



(7)

(39) **(40)**

The 7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4]triazole-3(2*H*)-thiones (**41**) are *S*-methylated with methyl trifluoromethanesulfonate to give the trifluoromethanesulfonates (**42**). These salts (**42**), in turn, when treated with triethylamine are converted into the betaines (**43**) (Scheme 2) ⟨87JCS(P1)2667⟩.



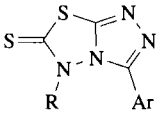
(41) (42) (43)

Scheme 2

8.07.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

8.07.7.1 Conversion of *N*-Hydroxymethyl Groups

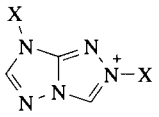
The reaction of 3-(2-benzofuranyl)-5-(hydroxymethyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione (**44**) with thionyl chloride provides the 5-chloromethyl derivative (**45**). This compound (**45**) upon treatment with 4-chloroaniline is converted into the 5-(4-chloroanilinomethyl) derivative (**46**) which is also obtained via a direct route (cf. 8.07.5.2.2) ⟨92IJC(B)167⟩.



(**44**) R = CH_2OH
(**45**) R = CH_2Cl
(**46**) R = CH_2NH–C_6H_4Cl-4
Ar = 2-benzofuranyl

8.07.7.2 Nitration of *N*-Amino Groups

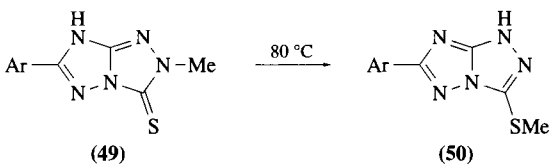
The nitration of the 2,7-diamino-7*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]triazolium ion (**47**) with nitronium tetrafluoroborate affords after work-up with base the corresponding potassium bis(*N*-nitroimides) (**48**) ⟨91IZV1239⟩.



(**47**) X = NH_2
(**48**) X = ^-N–NO_2 K^+

8.07.7.3 *N* to *S* Methyl-Migration

On heating 6-aryl-2-methyl-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole-3(2*H*)-thiones (**49**) undergoes *N* to *S* migration of the methyl group, yielding the rearrangement products (**50**) (Equation (8)) ⟨85BCJ735⟩.



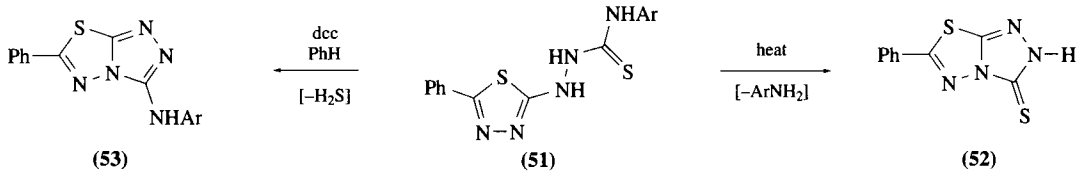
(49) (50) (8)

8.07.8 RING SYNTHESES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

8.07.8.1 Ring Closure of a Substituent Providing Three Ring Atoms: (5)3 → (5,5)

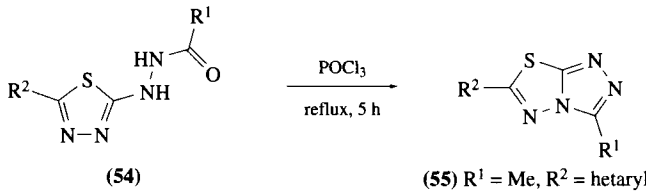
8.07.8.1.1 (5)N1N2C3 → 12{4}57 NN/NS: [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole

The 2-[4-aryl(thiocarbamoylhydrazino)]-5-phenyl[1,3,4]thiadiazoles (**51**) are sensitive to heat; they undergo cyclization to 6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3(2*H*)-thiones (**52**) when heated during their preparation or on recrystallization at elevated temperature. On the other hand, the thiosemicarbazides (**51**) upon treatment with dicyclohexylcarbodiimide undergo cyclodesulfurization affording [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**53**) (Scheme 3) ⟨86JHC1339⟩.



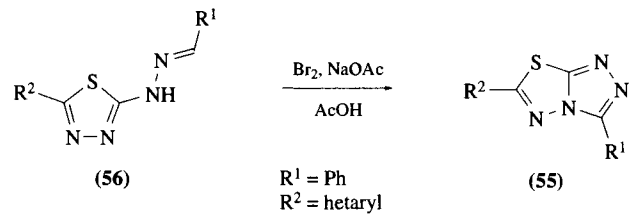
Scheme 3

The 5-substituted 2-acetyl- or 2-benzoylhydrazino[1,3,4]thiadiazoles (**54**) are cyclized with $POCl_3$ to give the corresponding 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**55**) (Equation (9)) ⟨90IJC(B)135⟩.



(9)

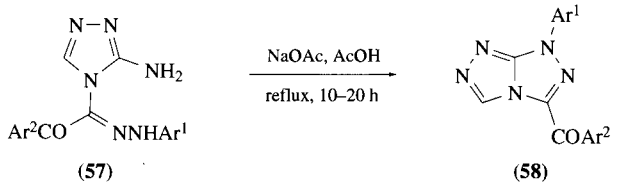
The identical [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**55**) are obtained from 5-substituted 2-benzylidenehydrazino[1,3,4]thiadiazoles (**56**) upon oxidative cyclization with bromine in the presence of sodium acetate in acetic acid (Equation (10)) ⟨90IJC(B)135⟩.



(10)

8.07.8.1.2 (5)C3N2N1 → 12{4}67 NN/NN: [1,2,4]Triazolo[3,4-c][1,2,4]triazole

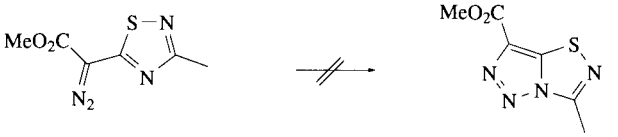
In the presence of sodium acetate in acetic acid the arylhydrazones (**57**) (available from the reaction of ω-halogen-ω-(arylhydrazono)acetophenones with 3-amino[1,2,4]triazole) undergo cyclization to yield 3-aroyl-1-aryl-1*H*-[1,2,4]-triazolo[3,4-*c*][1,2,4]triazoles (**58**) (Equation (11)) ⟨87CB965⟩.



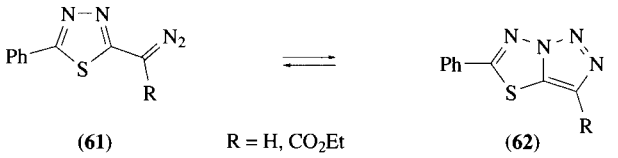
(57) (58) (11)

8.07.8.1.3 (5)C3N2N1 → 1246{7} NN/NS: [1,2,3]Triazolo[5,1-b][1,3,4]thiadiazole

Whereas methyl 5-(3-methyl[1,2,4]thiadiazolyl)diazoacetate (**59**) shows no tendency to cyclize to 7-methoxycarbonyl-3-methyl[1,2,3]triazolo[3,4-*d*][1,2,4]thiadiazole (**60**), the 5-(1-diazoalkyl) substituted [1,3,4]thiadiazoles (**61**) are in equilibrium with the fused bicyclic form, the [1,2,3]triazolo[5,1-*b*][1,3,4]thiadiazoles (**62**) ⟨88BSB795, 92JHC713⟩. The latter ring-closed form (**62**) prevails in the solid state as indicated by IR (KBr disk). The chain/ring equilibrium of the diazoimine/triazole forms is shifted toward the open-chain diazo form (**61**) by raising the temperature and by using less polar solvents (Equations (12) and (13)).



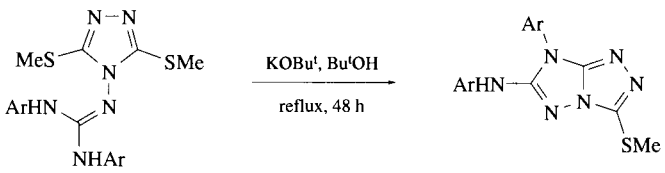
(59) (60) (12)



(61) (62) (13)

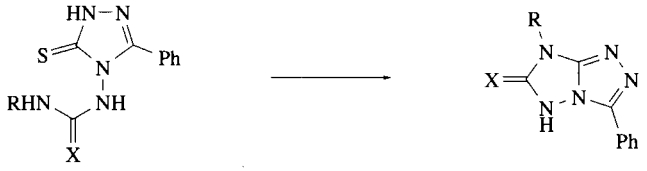
8.07.8.1.4 (5)N5C6N7 → 12{4}67 NN/NN: [1,2,4]Triazolo[4,3-b][1,2,4]triazole

4-(*N*,*N*′-Diarylguanidino)-3,5-bis(methylthio)[1,2,4]triazoles (**63**) undergo base-induced cyclization to give 7-aryl-6-arylamino-3-methylthio-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**64**) (Equation (14)) ⟨88H(27)161⟩.



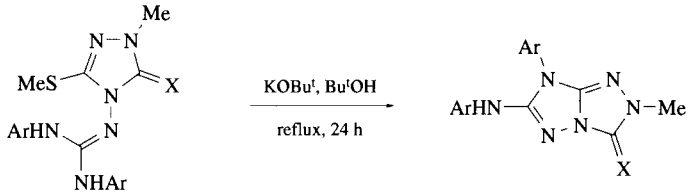
(63) (64) (14)

Similarly, the cyclization of the *N*-substituted 4-ureido and 4-thioureido derivatives of 3-phenyl-4,5-dihydro-1*H*-[1,2,4]triazole-5-thiones (**65**) affords 7-substituted 5*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-6(7*H*)-one (**66**) and -triazole-6(7*H*)-thiones (**67**), respectively (Equation (15)) ⟨91RRC619⟩.



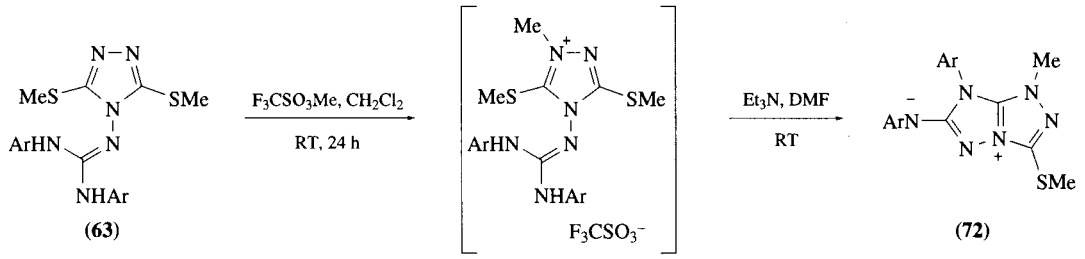
(65) R = Me, Ph (66) X = O (67) X = S (15)

4-(*N*,*N*′-Diaryl)guanidines (**68**) and (**69**) undergo base-induced cyclization to give the corresponding 7-aryl-6-arylamino-2-methyl-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-3(2*H*)-ones (**70**) ⟨87JCS(P1)2667⟩ and 3(2*H*)-thiones (**71**) (Equation (16)) ⟨86H(24)363, 87JCS(P1)2667⟩.



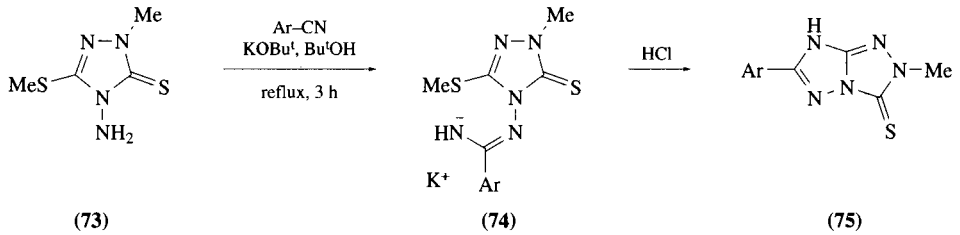
(68) X = O (69) X = S (70) X = O (71) X = S (16)

The sequential treatment of 4-(*N*,*N*′-diaryl)guanidines (**63**) with methyl trifluoromethanesulfonate and subsequently with triethylamine leads to 7-aryl-6-arylamido-2-methyl-3-methylthio-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium inner salts (**72**) (Scheme 4) ⟨87JCS(P1)2667⟩.



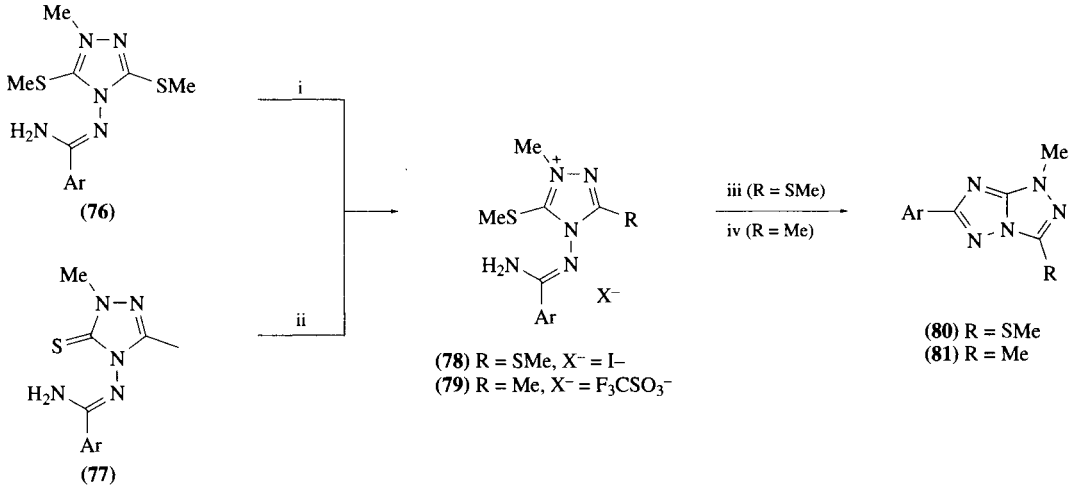
Scheme 4

The isolable potassium salts (**74**) (available from the nucleophilic addition of 4-amino-1-methyl-3-methylthio-1*H*-1,2,4-triazole-5(4*H*)-thiones (**73**) to aromatic nitriles in the presence of base) upon acidification with hydrochloric acid cyclize to give 7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole-3(2*H*)-thiones (**75**) (Scheme 5) ⟨85BCJ735⟩.



Scheme 5

N-Methylation of 4-(arylamidino)-3,5-bis(methylthio)-4*H*-[1,2,4]triazoles (**76**) with methyl iodide, or *S*-methylation of 4-(arylamidino)-1,3-dimethyl-1*H*-[1,2,4]triazole-5(4*H*)-thiones (**77**) with methyl trifluoromethanesulfonate lead to the respective 3-substituted 4-(arylamidino)-1-methyl-5-methylthio-4*H*-[1,2,4]triazolium salts (**78**) and (**79**). These salts (**78**) upon treatment with base, and (**79**) on heating in ethanol followed by work-up with base undergo cyclization to the corresponding 3-substituted 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**80**) and (**81**) (Scheme 6) ⟨83S415, 85H(23)2613⟩.



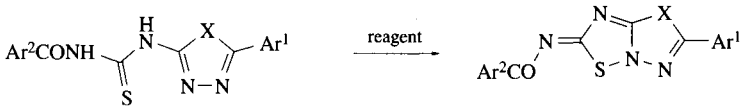
Reagents: i, MeI, reflux, 7 h; iii, KOBu^t, Bu^{t}OH, reflux, 20 h
Reagents: ii, F_3CSO_3Me, CH_2Cl_2, RT, 24 h; iv, EtOH, reflux, 14 h, then KOH

Scheme 6

8.07.8.1.5 (5)N7C6N5→13{4}57

(i,ii) ON/SN: [1,2,4]Thiadiazolo[3,2-b][1,2,4]oxadiazole; SN/SN: [1,2,4]Thiadiazolo[3,2-b][1,2,4]thiadiazole

Dehydrogenative cyclization of 2-(*N*-aroylthioureido)-5-aryl[1,3,4]oxadiazoles (**82**) and -thiadiazoles (**83**) affords 6-(aroylimino)-2-aryl-6*H*-[1,2,4]thiadiazolo[3,2-*b*][1,3,4]oxadiazoles (**84**) and -[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazoles (**85**), respectively (Table 6 and Equation (17)).



(**82**) X = O
(**83**) X = S

(**84**) X = O
(**85**) X = S

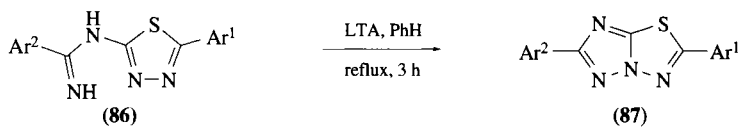
(17)

Table 6 6-(Aroylimino)-2-aryl-6*H*-[1,2,4]thiadiazolo[3,2-*b*][1,3,4]oxadiazoles (**84**) and 6-(aroylimino)-2-aryl-6*H*-[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazoles (**85**).

X	*Reagent and reaction condition*	*Ref.*
O, S	PCl_5, $POCl_3$, reflux, 3 h	88IJC(B)185, 88IJC(B)997
O, S	Br_2, $CHCl_3$	88IJC(B)185, 88IJC(B)997
S	Br_2, AcOH, 2 h	88IJC(B)997
S	LTA, C_6H_6, reflux, 2 h	88IJC(B)997

(iii) SN/NN: [1,2,4]Triazolo[5,1-b][1,3,4]thiadiazole

Oxidative cyclization of 2-aryl-5-(arylamidino)[1,3,4]thiadiazoles (**86**) gives 2,6-diaryl[1,2,4]-triazolo[5,1-*b*][1,3,4]thiadiazoles (**87**) (Equation (18)) ⟨91IJC(B)435⟩, which are also obtained upon thermolysis of 1-[1,3,4]thiadiazol-2-yl)tetrazoles (**163**) (cf. 8.07.9.1) ⟨85IJC(B)908⟩.



(**86**)

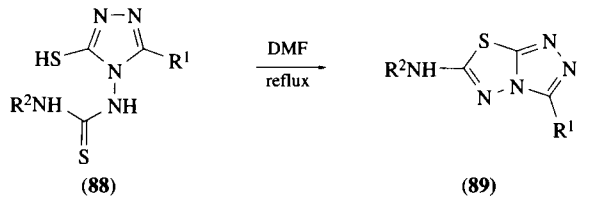
(**87**)

(18)

8.07.8.2 Ring-Closure of Two Adjacent Substituents Providing Two and One Ring Atoms: (5)2,1 → (5,5)

8.07.8.2.1 (5)N5C6,S7 → 12{4}57 NN/NS: [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole

Upon heating in DMF at reflux temperature the 4-thioureido-5-sulfonyl[1,2,4]triazoles (**88**) undergo cyclization to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**89**) (Equation (19) and Table 7).

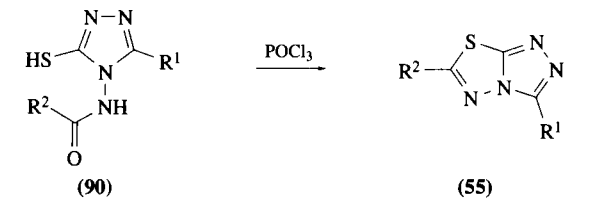


(88) (89) (19)

Table 7 3-Substituted 6-(*N*-substituted)amino[1,2,4]triazolo[3,4-*b*]thiadiazoles (**89**).

R^1	R^2	*Ref.*
methyl	aryl, aroyl	83S411
aryloxymethyl	aryl,	88IJC(B)576
alkyl	aryl	88ABC1229

Treatment of 4-aroylamino-5-thiol[1,2,4]triazoles (**90**) with $POCl_3$ induces cyclization to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**55**) (Equation (20) and Table 8). The same fused heterocycles (**55**) can be obtained from the cyclization of 5-substituted 2-acetyl- or 2-benzoylhydrazino[1,3,4]thiadiazoles (**54**) (cf. 8.07.8.1.1(i)).

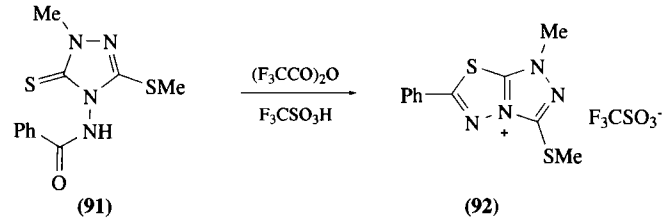


(90) (55) (20)

Table 8 3,6-Disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**55**).

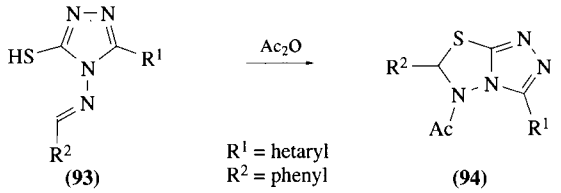
R^1	R^2	*Ref.*
alkyl	hetaryl	90IJC(B)135
aryl	aryl, hetaryl	84JHC1689, 90IJC(B)135
hetaryl	aryl	88MI 807-01, 93PS(82)171

4-(*N*-benzoylamino)-4,5-dihydro-1-methyl-3-methylthio-1*H*-[1,2,4]triazole-5-thione (**91**) upon treatment with trifluoracetic anhydride and trifluoromethanesulfonic acid is converted into the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolium trifluoromethanesulfonate (**92**) (Equation (21)) ⟨86LA1540⟩.



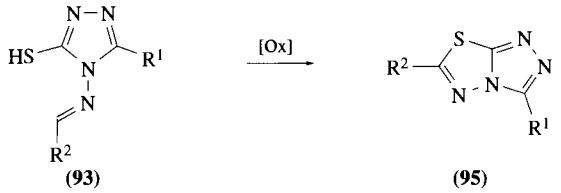
(91) (92) (21)

The benzylidene derivatives (**93**) of the 3-hetaryl substituted 4-amino-3-thiol-1,2,4-triazoles, on treatment with acetic anhydride, undergo cyclization to give the corresponding 3-substituted 5-acetyl-5,6-dihydro-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**94**) (Equation (22)) ⟨90IJC(B)135⟩.



(93) (94) (22)

Hydrazones (**93**) derived from the condensation of various aldehydes and 3-substituted 4-amino-3-sulfonyl[1,2,4]triazoles, on oxidative cyclization, afford the corresponding fully conjugated heterocycles (**95**) (Table 9 and Equation (23)).

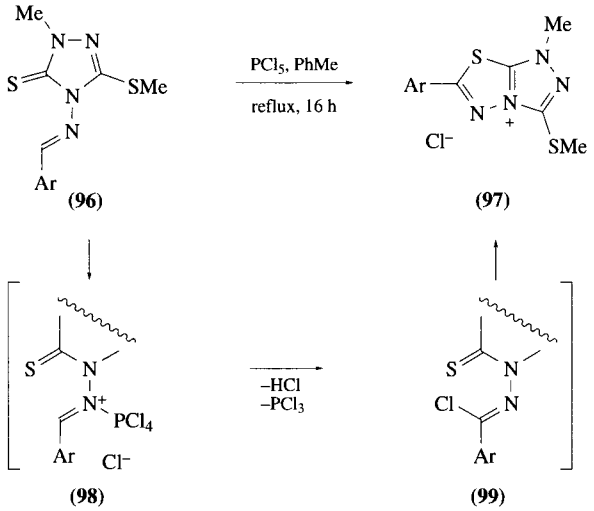


(93) (95) (23)

Table 9 3,6-Disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**95**).

[Ox]	*R^1*	*R^2*	*Ref.*
$SOCl_2$	alkyl, aryl	hetaryl	91JIC341
	arylaminomethyl	aryl	92MI 807-02
Br_2, AcOH	alkyl, aryl	hetaryl	91JIC341
Br_2, NaOAc, AcOH,	hetarylmethyl	alkyl, aryl	90IJC(B)135
$PhNO_2$	aryl	aryl, hetaryl	90M221

The *N*-arylidene derivatives (**96**) of 4-amino-4,5-dihydro-1-methyl-3-methylthio-1*H*-[1,2,4]triazole-5-thione, when treated with phosphorus pentachloride, are cyclized to give the 3-methylthio[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolium chlorides (**97**). This conversion is envisaged to involve the initial formation of an iminium salt (**98**) which by attack of the chloride ion gives the intermediate imidoyl chloride (**99**); subsequent cyclization by intramolecular nucleophilic attack of the thiocarbonyl sulfur atom turns it into the fused bicyclic product (**97**) (Scheme 7) ⟨86LA1540⟩.

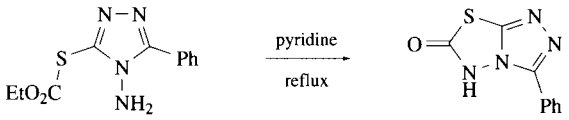


(96) (97) (98) (99)

Scheme 7

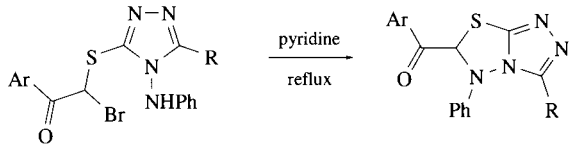
8.07.8.2.2 (5)C6S7,N5 → 12{4}57 NN/NS: [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole

Refluxing the 4-amino-3-ethoxycarbonylthio-5-phenyl-4*H*-[1,2,4]triazole (**100**) in pyridine induces cyclization to 3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6(5*H*)-one (**101**) (Equation (24)) ⟨91RRC619⟩.



(100) (101) (24)

The 3-substituted 5-(1-aroyl-1-bromo)methylthio-4-phenylamino-4*H*-[1,2,4]triazoles (**102**) (available from the corresponding 1,2,4-triazoles with phenacyl bromides and subsequent UV light-induced bromination), on heating under reflux in pyridine, afford 3-substituted 6-aroyl-5,6-dihydro-5-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**103**) (Equation (25)) ⟨93MI 807-01⟩.



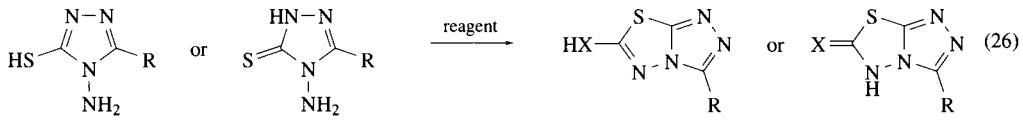
(102) (103) (25)

8.07.8.3 Formation of the Second Ring by Insertion of a One-Atom Ring Member between Two Adjacent Substituents at the First Ring Each Providing One Atom for the Second Ring: (5)1,1 + 1 → (5,5)

8.07.8.3.1 (5)N5,S7 + C6 → 12{4}57 NN/NN: [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole

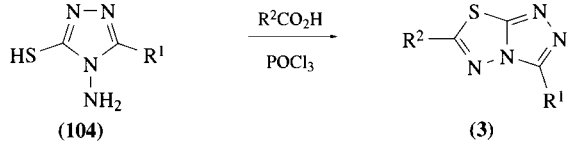
The most widely used method for the preparation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**106**) and (**107**) (see below) employs 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**104**) or 4-amino[1,2,4]-triazole-5(4*H*)-thiones (**105**) as starting materials.

The reaction of the triazoles (**104**) or (**105**) with carbonic acid derivatives furnishes [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles with a heteroatom substituent (N, O, S) in position 6; the O- and S-functions are formulated as 6-hydroxy and 6-sulfonyl derivatives (**106a**) or as thiadiazol-(5*H*)6-ones and -thiadiazole-(5*H*)6-thiones (**106b**), respectively (Table 10 and Equation (26)).



(104) (105) (106a) (106b) (26)

The reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**104**) with carboxylic acids and phosphorus trichloride has been widely applied for the preparation of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**3**) (Equation (27) and Table 11).



(104) (3) (27)

The reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**104**) with carboxylic acids as well as with carboxylic acid derivatives provides 6-substituted or 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazoles (**3**) (Equation (28) and Table 12).

Table 10 Formation of 6-heterosubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**106**), [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-(5*H*)6-ones and corresponding 6-hetero derivatives (**107**) from the reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazole (**104**) with carbonic acid derivatives.

Reagent	*Structure*	*X*	*R*	*Ref.*
CS_2, KOH	(**106**)	S	aryloxymethyl	89MI 807-01, 92IJC(B)714
	(**106**)		hetaryl	88MI 807-02, 90SUL239, 91POL1297
	(**107**)	S	hetarymethyl	93MI 807-02
	(**107**)	S	aryl	92IJC(B)167, 92MI 807-03
CS_2, pyridine	(**106**)	S	aryl	88IJC(B)128, 89JIC330
	(**107**)	S	aryl	87JHC1173, 91JIC474
	(**107**)	S	hetaryl	88JIC49
BrCN	(**106**)	NH	aryl	86JHC1339, 87JHC1173, 86MI 807-01, 91MI 807-01, 91H(32)1897
R—N=C=S	(**106**)	R—N	methyl	83S411
	(**106**)		aryloxymethyl	86MI 807-01, 92IJC(B)714
	(**106**)		aryl	87JHC1173, 91MI 807-01, 91H(32)1897
R—CO—N=C=S	(**106**)	R—CO—N	aryl	91MI 807-01, 91SUL167, 91H(32)1897, 94MI 807-02
	(**106**)		hetaryl	88JIC49, 92MI 807-04, 94MI 807-02
$ClCO_2Et$, Et_3N	(**106**)	O	aryl	90IJC(B)135
$ClCO_2Et$, MeONa	(**107**)	O	hetaryl	91SUL167

Table 11 Preparation of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**3**) from the reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazole (**104**) with carboxylic acids and phosphorus trichloride.

R^1	R^2	*Ref.*
alkyl	alkyl	84IJC(B)793
	arylmethyl	84IJC(B)793, 94MI 807-03
	aryl	93MI 807-03, 93MI 807-04
	aryl–hetaryl	91JIC341
arylmethyl	alkyl, aryl	93MI 807-02
hetarylmethyl	H, alkyl, aryl, hetaryl	83IJC(B)712, 89JHC177, 90SUL239
aryloxymethyl	H, alkyl, aryl, hetaryl	89MI 807-01, 92IJC(B)714
arylaminomethyl	aryl	92MI 807-02
	aryloxymethyl	91JIC250
aryl	alkyl	90IJC(B)135
	arylmethyl	93MI 807-04
	aryloxymethyl	86IJC(B)566
	arylthiomethyl	92IJC(B)673
	aryl	87JHC1173, 90IJC(B)135, 90IJC(B)176, 90H(31)2147, 91JIC474, 92MI 807-03
	hetarylaryl	91JIC341
hetaryl	H	91MI 807-02, 91SUL167, 93MI 807-05
	alkyl	89JHC177, 89MI 807-01, 90MI 807-01, 91SUL167, 91MI 807-02, 93MI 807-05, 93MI 807-06
	vinyl	93MI 807-05
	aryl	88MI 807-01, 89JHC177, 90MI 807-01, 90SUL239, 91MI 807-02, 93MI 807-05, 93MI 807-06, 93MI 807-07
	hetaryl	89JHC177, 90MI 807-01, 91MI 807-02, 91SUL167, 93MI 807-05
hetaryl-aryl	alkyl, aryl	93PS(82)171



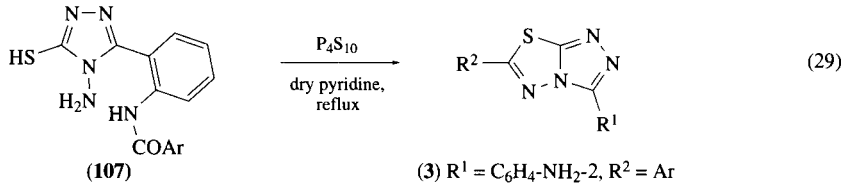
(**104**) (**3**) (28)

On treatment with phosphorus pentasulfide 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**107**; R^1 = 2-ArCONHC$_6$H$_4$) are converted into 6-aryl-3-(2-aminophenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**3**). This conversion is presumed to involve the transformation of the amide into the thioamide and a subsequent transfer of the thioaroyl group from the phenylamino side chain to the *N*-amino

Table 12 6-Substituted and 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**3**) from the reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazole (**104**) with carboxylic acids or carboxylic acid derivatives.

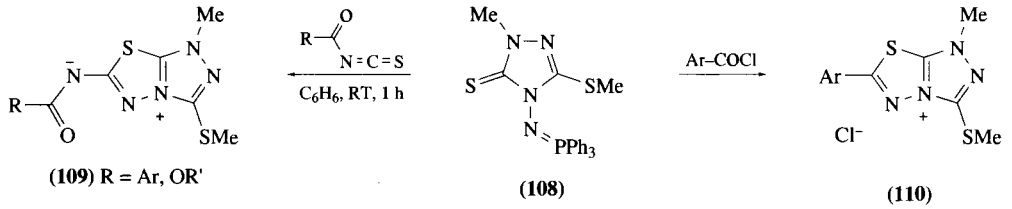
R^1	R^2	X	*Ref.*
alkyl	alkyl, aryl	CO_2H	93MI 807-08
	hetaryl		92MI 807-04
aryloxyaryl	H		92IJC(B)467
aryl	H, alkyl		89MI 807-01, 91RRC619
	aryl		86MI 807-01, 89MI 807-02, 89MI 807-03
	hetaryl		92MI 807-05
hetaryl	H, alkyl, aryl, hetaryl		89MI 807-04, 91MI 807-03, 91MI 807-04
aryloxymethyl	aryl	COCl	87MI 807-02
aryl	alkyl, aryl		92IJC(B)167
hetaryl	aryl		88MI 807-01, 91POL1297
aryloxymethyl	alkyl	CO—O—CO—R^2	87MI 807-02
hetaryl	alkyl		89MI 807-04, 91POL1297
hetaryl–aryl	alkyl		93PS(82)171
alkyl	ethoxycarbonylmethyl	CN	94KGS137
hetaryl	H	CO—NMe_2	90IJC(B)135

group of the triazole ring. Eventually, cyclodehydrosulfurization furnishes the bicyclic product (**3**) (Equation (29)) ⟨89LA1055⟩.



(**107**) (**3**) $R^1 = C_6H_4\text{-}NH_2\text{-}2$, R^2 = Ar (29)

4-(Triphenylphosphoranylidenamino)-1*H*-[1,2,4]triazole-5(4*H*)-thione (**108**) reacts with acylisothiocyanates to give the mesoionic compounds (**109**) ⟨86LA1540⟩, and with aroyl chlorides gives 6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolium chlorides (**110**) (Scheme 8) ⟨86LA1540⟩.



(**109**) R = Ar, OR' (**108**) (**110**)

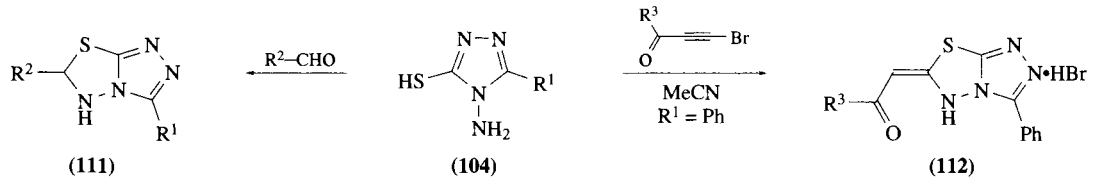
Scheme 8

The condensation of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**104**) with aldehydes in the presence of an acid catalyst affords 3-substituted and 3,6-disubstituted 5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles (**111**) (Scheme 9 and Table 13).

Table 13 3,6-Disubstituted 5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**111**) from the reaction of 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**105**) with aldehydes.

R^1	R^2	*Ref.*
aryl	H, alkyl	91RRC619
	aryl	88MI 807-02, 90IJC(B)176, 90H(31)2147
	hetaryl	88MI 807-02
hetaryl	aryl, hetaryl	92IJC(B)167

Treatment of 4-amino-3-phenyl-5-sulfonyl-4*H*-[1,2,4]triazole (**104**) with bromoacylacetylenes gives the corresponding 6-(acylmethylene)-5,6-dihydro-3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazohydrobromides (**112**) (Scheme 9) ⟨88ZOR2151⟩.



(111) (104) (112)

Scheme 9

8.07.8.4 Formation of the Second Ring by Insertion of a One-Atom Ring Member between a Substituent at the First Ring Providing Two Atoms and the Adjacent Ring Atom: (5)2 + 1 → (5,5)

8.07.8.4.1 (5)N1N2 + C3 → 12{4}57

*(i) NN/NO: [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazole*

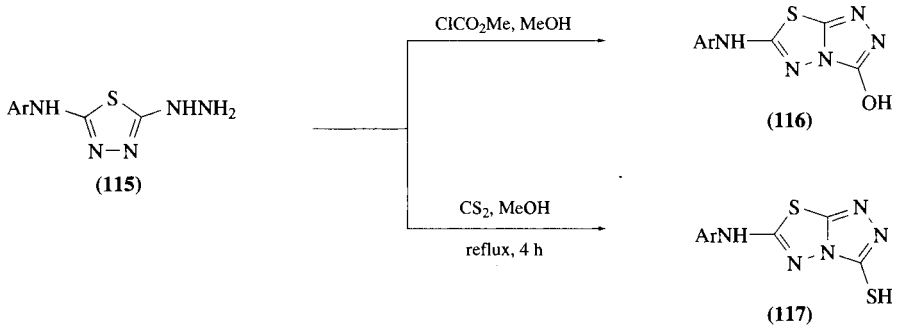
Cyclization of 2-hydrazino[1,3,4]oxadiazoles (**113**) with carbon disulfide in potassium hydroxide gives [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole-3(2*H*)-thiones (**114**) (Equation (30)) ⟨84MI 807-02⟩.



(113) R^1 = H, Ph; R^2 = hetaryl (114) (30)

*(ii) NN/NS: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole*

The reaction of 2-arylamino-5-hydrazino[1,2,4]thiadiazoles (**115**) with methyl chloroformate gives 6-arylamino-3-hydroxy[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**116**); with carbon disulfide the corresponding 3-sulfonyl derivatives (**117**) are formed (Scheme 10) ⟨92IJC(B)467⟩.

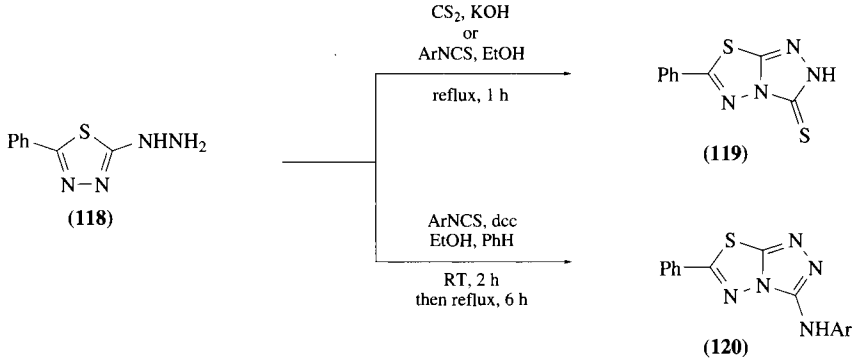


(115) (116) (117)

Scheme 10

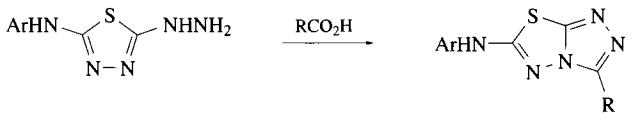
Similarly, 2-hydrazino-5-phenyl[1,3,4]thiadiazole (**118**) and carbon disulfide in the presence of potassium hydroxide give 6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3(2*H*)-thione (**119**) ⟨86JHC1339⟩. The same product (**119**) is obtained from the reaction with arylisothiocyanates on reflux in ethanol (Scheme 11) ⟨66JOC3528⟩.

When the reaction of (**118**) with arylisothiocyanates is carried out in the presence of dicyclocarbodiimide 3-arylamino-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**120**) are formed instead (Scheme 11) ⟨86JHC1339⟩.



Scheme 11

The reaction of the hydrazine (**115**) and aryloxyacetic acids affords 3-substituted 6-arylamino[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**121**); with formic acid the corresponding 3-unsubstituted products (**122**) are formed (Equation (31)) ⟨92IJC(B)467⟩.

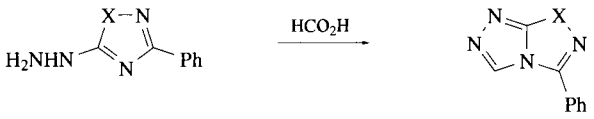


(31)

8.07.8.4.2 (5)N7N6 + C5 → 12{4}67

*(i) ON/NN: [1,2,4]Triazolo[4,3-*d*][1,2,4]oxadiazole*
*SN/NN: [1,2,4]Triazolo[4,3-*d*][1,2,4]thiadiazole*

5-Hydrazino-3-phenyl[1,2,4]oxadiazole (**123**) and -thiadiazole (**124**) react with formic acid to give 3-phenyl[1,2,4]triazolo[4,3-*d*][1,2,4]oxadiazole (**125**) and -thiadiazole (**126**), respectively (Equation (32)) ⟨91MI 807-05⟩.



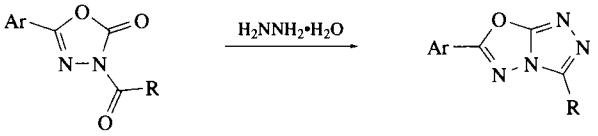
(32)

8.07.8.5 Formation of the Second Ring by Insertion of a Two-Atom Ring Member between a Substituent at the First Ring Providing One Atom and the Adjacent Ring Atom: (5)1 + 2 → (5,5)

8.07.8.5.1 (5)C3 + N1N2 → 12{4}57

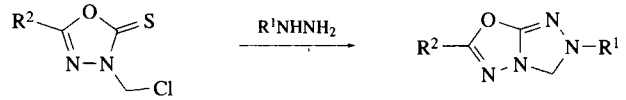
*(i) NN/NO: [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazole*

The cyclocondensation of 3-acyl/3-aroyl-5-aryl[1,3,4]oxadiazol-2(3*H*)-ones (**127**) with hydrazine hydrate gives the corresponding 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles (**128**) (Equation (33)) ⟨91H(32)237⟩.



(127) R = alkyl, aryl (128) (33)

The reaction of 5-aryl-3-(chloromethyl)[1,3,4]oxadiazole-2(3*H*)-thiones (**129**) with hydrazine or methylhydrazine yields the corresponding 2,3-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole derivatives (**130**) (Equation (34)) ⟨84JCED477⟩.



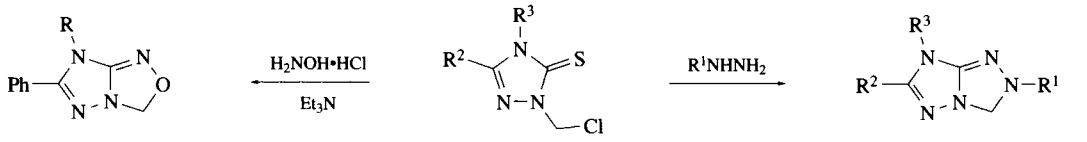
(129) R^1 = H, Me; R^2 = Ar (130) (34)

(ii) NO/NN: [1,2,4]Triazolo[3,2-c][1,2,4]oxadiazole

By analogy, the azole-2(3*H*)-thiones (**131**) react with hydroxylamine to form the 3,7-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]oxadiazoles (**133**) (Scheme 12) ⟨92PS(70)99⟩.

(iii) NN/NN: [1,2,4]Triazolo[4,3-b][1,2,4]triazole

Hydrazine and phenylhydrazine convert the [1,2,4]triazole-2(3*H*)-thiones (**131**) into 3,7-dihydro-2*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**132**) (Scheme 12) ⟨92PS(70)99⟩.

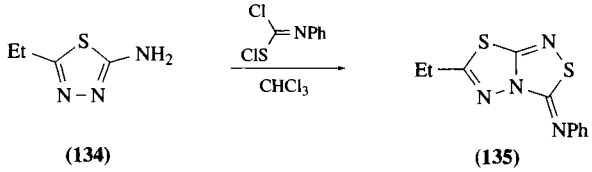


(132) R = Me, Ph (131) R^2 = Ph, R^3 = Me, Ph (132) R^1 = H, Ph; R^2 = Ar; R^3 = Me, Ph

Scheme 12

8.07.8.5.2 (5)N1 + S2C3 → 12{4}57 NS/NS: [1,3,4]Thiadiazolo[2,3-c][1,2,4]thiadiazole

2-Amino-5-ethyl[1,3,4]thiadiazole (**134**) upon reaction with 1-chloro-1-phenyliminomethanesulfenyl chloride yields 6-ethyl-3-phenylimino-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole (**135**) (Equation (35)) ⟨86S1027⟩.

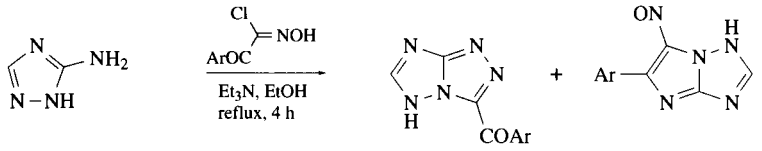


(134) (135) (35)

For another synthesis of a compound of structure (**135**) see 8.07.9.2 ⟨94T7019⟩.

8.07.8.5.3 (5)N1 + N2C3 → 12{4}57 NN/NN: [1,2,4]Triazolo[4,3-b][1,2,4]triazole

The treatment of arylglyoxylhydroximoyl chlorides with two equivalents of 3-amino-2*H*-[1,2,4]-triazole (**136**) in the presence of triethylamine produces 3-aroyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole (**137**) and 5-aryl-6-nitroso-1*H*-imidazo[1,5-*a*][1,2,4]triazole (**138**) (Equation (36)) ⟨84JHC1029⟩.



(136) (137) (138) (36)

8.07.8.5.4 (5)N5 + C6N7 → 12{4}57 NN/NN: [1,2,4]Triazolo[4,3-b][1,2,4]triazole

Contrasting with the reported formation of fused [1,3,4]thiadiazole rings in the course of the reaction of 3-substituted 4-amino-5-sulfonyl-4*H*-[1,2,4]triazoles (**104**) with various isothiocyanates (cf. 8.07.8.3.1, Table 10) there are reports that the reactions with methylisothiocyanate and similarly with phenylisocyanate afford 3,7-disubstituted 6,7-dihydro-5*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole-6-thiones (**139**) and -triazol-6-ones (**140**), respectively (Equation (37) and Table 14).



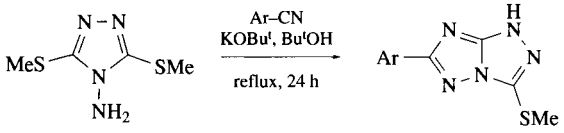
(104) (37)

(139) X = S
(140) X = O

Table 14 3,7-Disubstituted 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,2,4] triazolo-6-ones (**140**) and 6,7-dihydro-5*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]tri-azole-6-thiones (**139**).

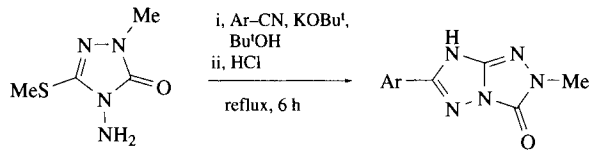
R^1	R^2	*X*	*Ref.*
aryl	phenyl	O	86MI 807-01
hetaryl	phenyl	O	92IJC(B)167
hetaryl	methyl	S	92IJC(B)167

4-Amino-3,5-bis(methylthio)[1,2,4]triazole (**141**) reacts with aromatic nitriles under basic conditions furnishing the 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**142**) (Equation (38)) ⟨83S415, 85BCJ735⟩.



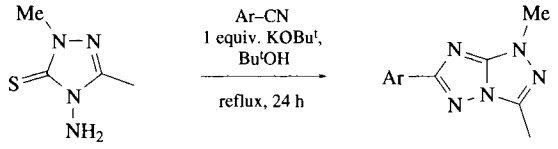
(141) (142) (38)

The reaction of 4-amino-1-methyl-3-methylthio-1*H*-[1,2,4]triazol-5(4*H*)-one (**143**) with aromatic nitriles under basic conditions furnishes 6-aryl-2-methyl-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-3(2*H*)-ones (**144**) (Equation (39)) ⟨85BCJ735⟩.



(143) (144) (39)

The reaction of the 4-amino[1,2,4]triazole-5(4*H*)-thione (**145**) with aromatic nitriles (but not with aliphatic nitriles) under basic conditions furnishes 6-aryl-1,3-dimethyl-1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**146**) (Equation (40)) ⟨85H(23)2613⟩.



(145) (146) (40)

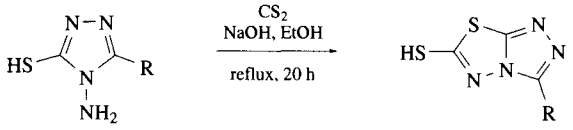
The reaction of 4-amino-1-methyl-3,5-bis(methylthio)[1,2,4]triazolium iodide (**147**) with aryl isothiocyanates yields the mesoionic compounds (**148**) (Equation (41)) ⟨84TL5427, 86T2121⟩.



(147) (148) (41)

8.07.8.5.5 (5)N5 + C6S7 → 12{4}57 NN/NS: [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole

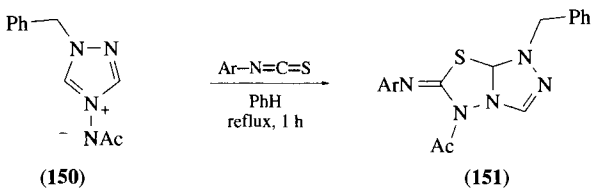
The 3-hetarylmethyl substituted 4-amino-5-sulfonyl-4*H*-[1,2,4]triazole (**105**) upon reaction with carbon disulfide in ethanol and NaOH yields the 6-sulfonyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**149**) (Equation (42)) ⟨90IJC(B)135⟩.



(105) (149) (42)

R = [3,4-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]methyl

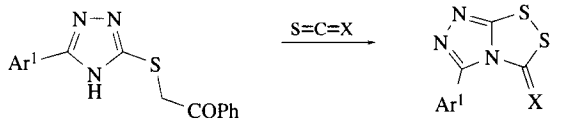
The reaction of 1-benzyl-4-(acetylimido)-1*H*-[1,2,4]triazolium inner salt (**150**) (an azomethine imine) with aromatic isothiocyanates yields among other products 5-acetyl-6-(arylimino)-1,5,6,7a-hydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**151**). The formation of the cycloadducts (**152**) is preferred in nonpolar solvents (Equation (43)) ⟨84CCC1713⟩.



(150) (151) (43)

8.07.8.5.6 (5)S1 + S2C3 → 12{4}67 SS/NN: [1,2,4]Triazolo[3,4-c][1,2,4]dithiazole

5-Aryl-3-phenacylthio-1,2,4-triazoles (**152**) react with carbon disulfide and with arylisothiocyanates to give 5-aryl-3*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazole-3-thiones (**153**) and the 3-arylimino derivatives (**154**), respectively (Equation (44)) ⟨83ABC1017⟩.



(44)

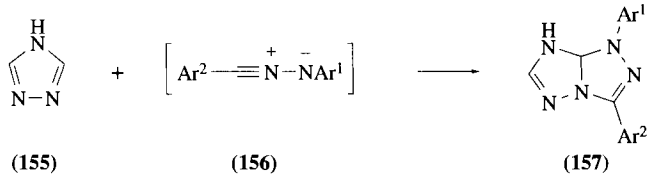
(**152**)

(**153**) X = S
(**154**) X = N–Ar^2

8.07.8.6 Formation of the Second Ring by Addition of a Three-Atom Ring Member to Two Adjacent Ring Positions of the First Ring: (5) + 3 → (5,5)

8.07.8.6.1 (5)[N4,C7a] + N1N2C3 → 12{4}57 NN/NN: [1,2,4]Triazolo[4,3-b][1,3,4]triazole

The electrolysis of the 4-nitrophenylhydrazone of 4-dimethylaminobenzaldehyde generates the corresponding diarylnitrilimine intermediate (**156**) which in the presence of [1,2,4]triazole (**155**) undergoes 1,3-dipolar cycloaddition to give the 7,7a-dihydro-1*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4]triazole (**157**) (Equation (45)) ⟨85ZC443⟩.

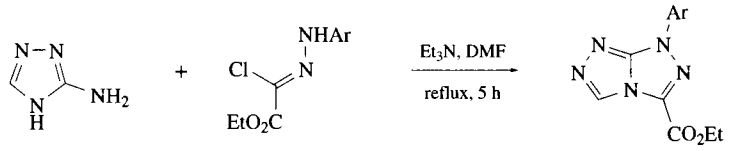


(45)

(**155**) (**156**) (**157**)

Ar^1 = 4-$O_2NC_6H_4$
Ar^2 = 4-$Me_2NC_6H_4$

3-Amino[1,2,4]triazole (**158**) reacts with the 4-tolylhydrazone of ethyl chloroglyoxalate (**159**) in the presence of triethylamine. Presumably, the [3 + 2] cycloaddition of the 1,3-dipolar nitrilimine intermediate is followed by the elimination of ammonia to furnish ethyl 1-(4-methylphenyl)-1*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]triazole-3-carboxylate (**160**) (Equation (46)) ⟨88JIC194⟩.



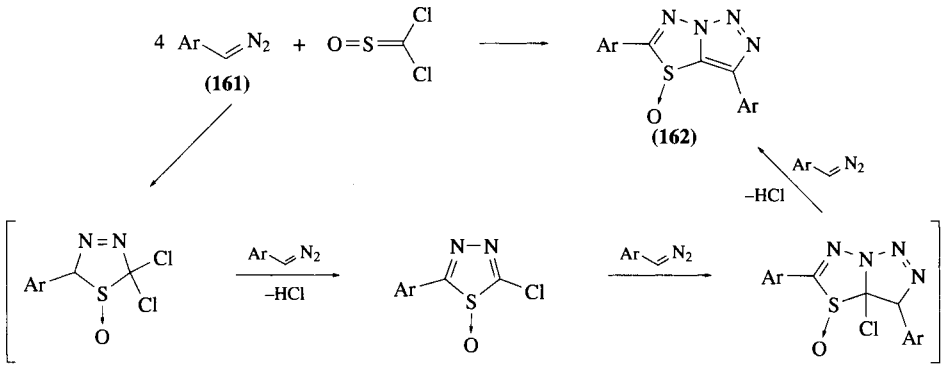
(46)

(**158**) (**159**) Ar = 4-MeC_6H_4 (**160**)

8.07.8.7 Formation of the 5,5-Fused Rings from Three Fragments Providing Two, Three, and Three Ring Atoms: 2 + 3 + 3 → (5,5)

8.07.8.7.1 C3aS4 + C5N6N7 + C3N2N1 → 1246{7} NNSN: [1,2,3]Triazolo[5,1-b][1,3,4]thiadiazole

The reaction of a fourfold excess of aryldiazomethanes (**161**) with dichlorosulfine leads to 3,5-diaryl[1,2,4]triazolo[5,1-*b*][1,3,4]thiadiazole-4-oxides (**162**). The formation of the fused heterocycles (**162**) is rationalized on the basis of two consecutive cycloaddition steps each followed by elimination of hydrogen chloride promoted by the excess of aryldiazomethane (Scheme 13) ⟨84JCR(S)175⟩.

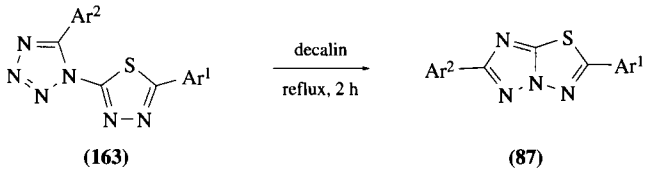


Scheme 13

8.07.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

8.07.9.1 Thermolysis with Extrusion of Dinitrogen

The thermolysis of 1-([1,3,4]thiadiazol-2-yl)tetrazoles (**163**) gives rise to the loss of dinitrogen from the tetrazole ring and the formation of 2,6-diaryl[1,2,4]triazolo[5,1-*b*][1,3,4]thiadiazoles (**87**) (Equation (47)) ⟨85IJC(B)908, 90MI 807-02⟩. (For another synthesis of compounds with structure (**87**) see 8.07.8.1.4.2).

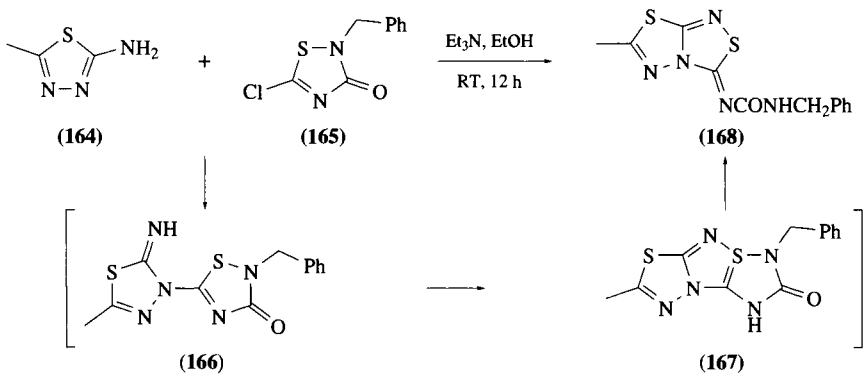


(47)

(163) **(87)**

8.07.9.2 Ring-Closure and Ring-Opening by Displacement of N by N at S

In the presence of triethylamine the reaction of 2-amino-5-methyl[1,3,4]thiadiazole (**164**) with 2-benzyl-5-chloro[1,2,4]thiadiazol-2-one (**165**) gives 3-(benzylcarbamoylimino)-6-methyl-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole (**168**). Presumably, the first-formed intermediate (**166**) rearranges through the thiapentalene intermediate (**167**) to the fused thiadiazole product (**168**) (Scheme 14) ⟨94T7019⟩.



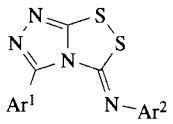
(164) **(165)** **(168)** **(166)** **(167)**

Scheme 14

8.07.10 APPLICATIONS

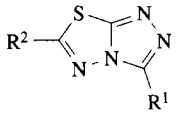
8.07.10.1 Agrobiological Activity

5-Aryl-3-arylimino[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazoles (**169**) have been compared with Dithane M-45 for their fungitoxicity against *Helmintosporium oryzae* and *Fusarium oxysporium* ⟨83ABC1017⟩.



(**169**)

A number of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) with a wide variety of substituents R^1 and R^2 (Table 15) have been screened and tested for their activity against fungi (e.g., *Helmintosporium oryzae* and others).



(**170**)

Table 15 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) with fungitoxic activity.

R^1	R^2	*Ref.*
H, alkyl, aryl	CH_2—hetaryl	83IJC(B)712
Me, Et	cycloC_6H_{11}, aryl	88ABC1229
H, OH, OCH_2Ar, SH	NH—Ar	92IJC(B)467
hetaryl	Me, Ph	93PS(82)171

For many [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) both fungicidal and herbicidal activities have been found (Table 16).

Table 16 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) with fungicidal and herbicidal activities.

R^1	R^2	*Ref.*
Me	hetaryl	93MI 807-06
alkyl, aryl	CH_2Ar	93MI 807-04
H, alkyl, aryl, hetaryl	hetaryl	93MI 807-05
alkyl	CH_2OAr	94MI 807-03
aryl, hetaryl	NHCOPh	94MI 807-04

8.07.10.2 Pharmacological Activity

In many cases fused heterocycles have been synthesized with the primary goal of investigating their pharmacological activity. A large number of them have been found to exhibit antimicrobial activity, but apparently none of them shows any outstanding activity.

8.07.10.2.1 Bactericidal Activity

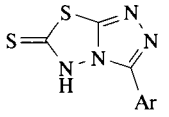
Mainly [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) have been tested for their activity against various bacteria (Table 17). Many more systems of this type including 5,6-dihydro derivatives ⟨90IJC(B)135, 91RRC619⟩ and 6(5*H*)-thiones ⟨87JHC1173, 88JIC(B)576, 89JIC330, 91JIC474⟩ have been screened or found active but no specific data have been released.

Table 17 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) with bactericidal activity.

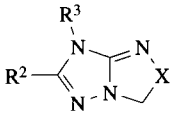
R^1	R^2	*Ref.*
H	aryl	91RRC619
aryl	aryl	89MI 807-03, 92MI 807-03
aryl	SH	90IJC(B)135
aryl	NHPh	87JHC1173
4-pyridyl	alkyl	91MI 807-02, 91MI 807-03
4-pyridyl	aryl	91MI 807-03, 91MI 807-06
4-pyridyl	H, hetaryl	91MI 807-03
4-pyridyl	ArCONH	92MI 807-04

8.07.10.2.2 Fungicidal activity

Some fused heterocyclic systems such as 3-aryl[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thiones (**171**) ⟨88IJC(B)128, 89JIC330⟩, 2,7-dihydro-3*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (**172**), and 3*H*,7*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]oxadiazoles (**173**) ⟨92PS(70)99⟩ have been found to be active against pathogenic fungi (e.g., *Candida albicans*).



(**171**)



(**172**) X = NR^1
(**173**) X = O

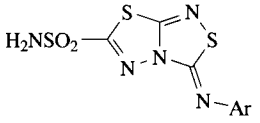
8.07.10.2.3 Various pharmacological activities

Numerous 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**170**) have been found to be pharmacologically active (Table 18).

Table 18 Pharmacological activities of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**171**).

R^1	R^2		*Ref.*
arylmethyl	arylmethyl	antiinflammatory	84IJC(B)793
		CNS depressant	84IJC(B)793
aryl	aryloxymethyl	antiinflammatory	86IJC(B)566
		analgesic	86IJC(B)566
Me, aryl	aryloxymethyl	antihypertensive	87MI 807-02
benzyl	aryloxymethyl	anthelmintic	89MI 807-01
hetarylthiomethyl	aryl	anthelmintic	92IJC(B)673

A series of 3-arylimino-6-sulfamoyl-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazoles (**174**) due to their corneal permeability and ocular hypotensive effect were suggested to be active against glaucoma ⟨93MI 807-09, 93MI 807-10⟩.



(**174**)

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8.08
Bicyclic 5-5 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 3 : 1

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8.08.1 INTRODUCTION

No specific review of the field has been produced. Pertinent material has been dealt with in reviews apart from the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I): (i) general reviews of fused 5-5 ring systems ⟨61HC(15)63, 77HC(30)1, 78AHC(22)183⟩; (ii) articles on fused tetrazoles ⟨76RCR183⟩, on tetrazole chemistry as a whole ⟨77AHC(21)323⟩, and on fused imidazoles of type 5-5 with three additional heteroatoms ⟨86HC(46)384⟩; (iii) surveys of the azolotetrazole (**T**)/azidoazole (**A**) valence bond tautomerism ⟨73CI(L)371, 73S123, 75RCR481, 79CRV181⟩. Care should be exercised when consulting the literature on azole-fused tetrazoles (fully conjugated systems); quite a number of examples shown as bicycles (**T**) are in fact the monocyclic azidoazoles (**A**).

Figure 1 gives an outline of the general systems mentioned in this survey. These include the pyrazolo[1,5-*d*]tetrazoles (**1**)–(**4**), (**6**)–(**8**); isoxazolo[2,3-*d*]tetrazole (**5**); the imidazo[1,5-*d*]- and imidazo[1,2-*d*]tetrazoles (**9**)–(**11**) and (**12**)–(**14**), (**16**), (**18**), (**19**), respectively; the thiazolo[3,2-*d*]tetrazoles (**15**), (**17**), (**20**)–(**23**); the tetrazolo[1,5-*b*]indazole (**24**) and tetrazolo[1,5-*b*][1,2]benzisothiazole (**25**); the tetrazolo[1,5-*a*]benzimidazole (**26**); tetrazolo[5,1-*b*]benzoxazole (**27**), -benzothiazole (**28**)

(also quaternary salts analogous to (**22**), (**23**)) and -benzoselenazole (**29**); imidazo[1,2-*c*][1,2,3,5]-thiatriazole (**30**) and -[1,2,3,5]selenatriazole (**31**); [1,2,3,5]thiatriazolo[3,4-*a*]- and [1,2,3,5]selenatriazolo[3,4-*a*]benzimidazole, (**32**) and (**33**), respectively. The parent bicycles have been isolated only in the case of (**15**), (**16**; R = H), (**28**), (**29**), (**32**), and (**33**), while the majority are known in derivatized form. Efforts to obtain derivatives of (**11**)–(**13**) have failed, and of the types (**4**), (**5**), (**8**), (**20**), (**21**), (**24**), (**25**; $n = 2$), and (**27**), only monocyclic valence tautomers have been found.

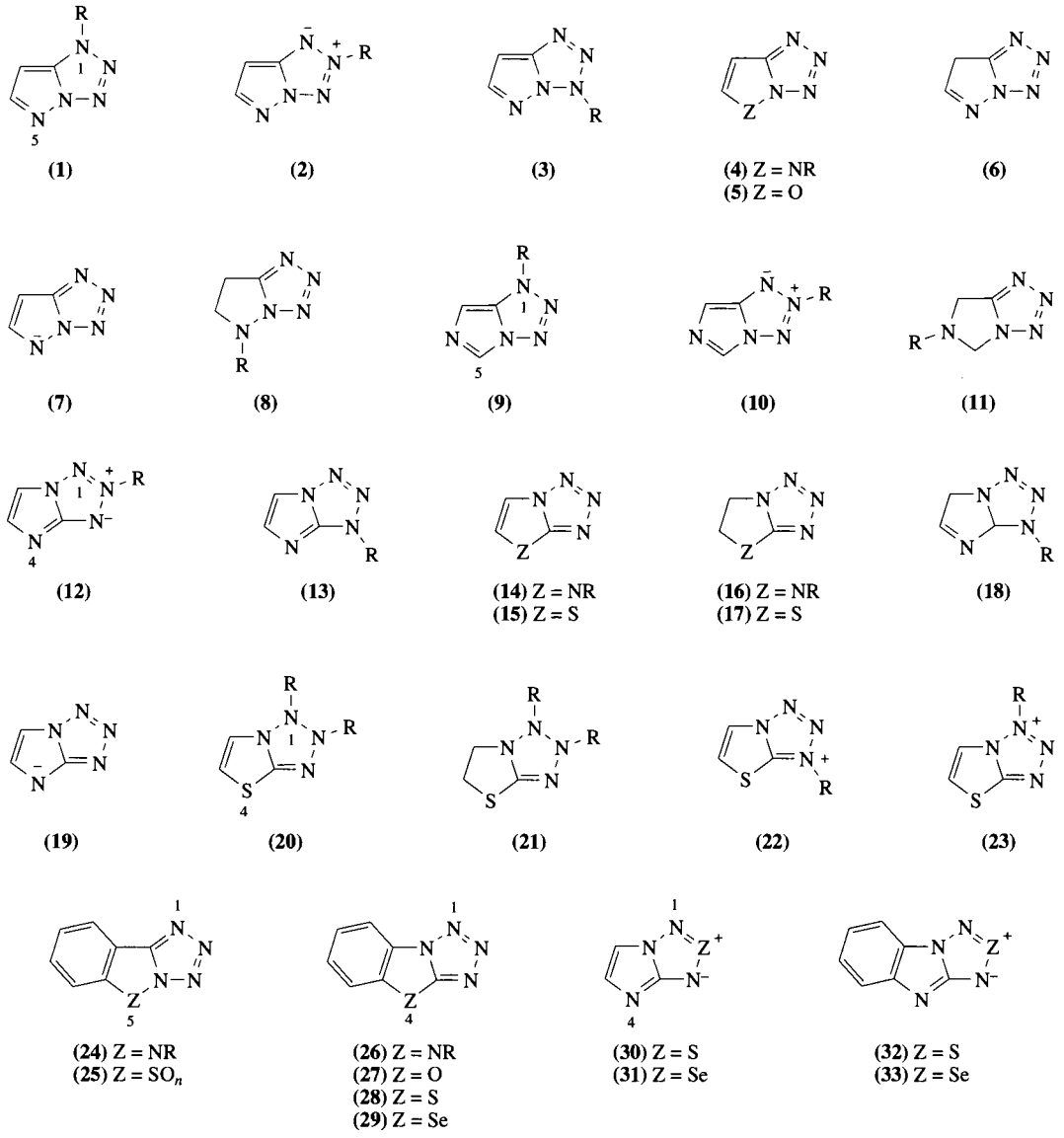


Figure 1 Overview of title systems.

Where appropriate, attention will be drawn to 5-5 systems having five and six extra heteroatoms (3 : 2 and 3 : 3).

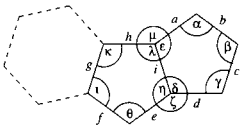
8.08.2 THEORETICAL METHODS

Theoretical interest has been directed essentially to fully conjugated ring systems and here most of the work is associated with the study of the azolotetrazole (**T**)/azidoazole (**A**) valence bond tautomerism (cf. Section 8.08.4).

Semiempirically calculated bond lengths and π-bond orders for (**14**; R = H) (MNDO) and (**15**)

(CNDO/S) show that the imidazole and thiazole moieties in these bicycles are less "aromatic" than in the respective azidoazoles (**A**) ⟨75BSB1189, 78CJC46, 79JHC685⟩. This is reflected by an increase of the vicinal coupling constants $^3J_{H,H}$ on cyclization of the azides (**A**) (Table 2). A substituted tetrazolic half-ring makes the counterpart more "aromatic" as shown for (**1**; R = H) by CNDO/2 approximation and confirmed by experimental bond lengths of (**1d**) (Table 1) ⟨78JHC395⟩. To understand the observation that only the *anion* of 2-azidoimidazole is capable of cyclizing (i.e., to (**19**)), MNDO calculations have been performed which predict the latter to be 16.9 kcal mol^{-1} (70.7 kJ mol^{-1}) more stable than (**14**; R = H); another argument was provided by computation of formal charge distribution, which is most efficiently delocalized in (**19**) ⟨79JHC685⟩.

Table 1 Bond distances (pm) and angles (deg) from x-ray diffraction.[a]



Compound	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*				*Ref.*
(**1d**)	134.3	137.0	128.9	135.5	135.8	133.9	142.6	139.7	134.3				78JHC395
(**2b**)	134.4	132.8	132.1	133.7	135.0	135.0	140.5	140.3	136.0				83JHC1629
(**3b**)[b]	135.8	130.8	133.6	132.5	132.9	136.3	138.8	140.0	134.0				83JHC1629
(**18a**)[c]	143.5	125.0	136.0	145.6	148.0	127.3	152.6	146.1	146.5				93CB129
(**28**)	135.2	130.9	137.2	132.2	172.8	177.1	138.9	140.3	134.4				74CSC335
(**34**)	135.6	132.9	129.6	138.4	137.5	132.9	139.7	133.1	135.9				86JCR(S)38; 86JCR(M)501
	α	*β*	*γ*	*δ*	*ε*	*ζ*	*η*	*θ*	*ι*	*κ*	*λ*	*μ*	
(**1d**)	109.2	109.3	105.9	112.0	103.7	132.8	115.1	102.1	113.4	103.1	106.2	150.1	78JHC395
(**2b**)	102.3	118.0	100.0	112.2	107.5	132.6	115.2	100.7	115.8	101.9	106.3	146.1	83JHC1629
(**3b**)[b]	106.8	110.1	107.3	108.2	107.8	135.7	116.2	100.1	115.6	101.8	106.5	145.8	83JHC1629
(**18a**)[c]	109.6	111.6	107.9	99.7	105.2	113.2	107.0	107.5	113.7	102.0	105.6	109.9	93CB129
(**28**)	104.5	112.6	104.2	109.3	109.4	138.2	112.5	89.0	113.3	109.0	116.3	134.3	74CSC335
(**34**)	101.5	120.3	99.1	111.1	108.0	142.0	106.9	105.6	112.6	102.5	112.4	139.6	86JCR(S)38; 86JCR(M)501

[a]Generalized formula is orientated according to structures shown in Figures 1 and 2. [b]Averaged bond distances and angles of two independent molecules observed. [c]With addition of supplementary material.

Estimates have also been made of

(i) dipole moments of (**5**), (**15**), (**27**), and (**28**) (parents and/or derivatives) by INDO, CNDO/2, and CNDO/S methods ⟨77CJC1728⟩;

(ii) HMO energies of all fully conjugated NH species possible, including their anions and azido-azole valence tautomers (**A**) (the data, however, were largely in disagreement with experimental findings) ⟨77MI 808-01⟩;

(iii) π-charge densities for (**14**; R = H) and (**19**) by MNDO ⟨79JHC685⟩ and for (**15**; 6-Ph-) by HMO calculations ⟨76UKZ1298⟩;

(iv) formal charge densities for (**7**) and the heats of formation of *N*-methyl derivatives of (**1**)–(**4**) (R = Me), both by MINDO/3, showing that methylation of (**7**) in position 3 (as erroneously assumed earlier ⟨78JHC395⟩) is thermodynamically disfavored ⟨83JHC1629⟩;

(v) ^{15}N shieldings of (**15**) by the INDO/S-SOS method ⟨84OMR(22)209⟩;

(vi) aromaticity indices for (**1d**), (**2b**), and (**3b**) by statistical evaluation of the deviations in peripheral bond orders (values 78, 85 and 82, respectively; higher than in the case of tetrazolo[1,5-*b*]pyridazine) ⟨87T4725⟩ (in the cited literature there is a misprint regarding the 7-substituent of (**1d**)) (see Figure 2).

8.08.3 EXPERIMENTAL STRUCTURAL METHODS

Literature data on bond lengths and angles is available for only a limited number of classes (Table 1). Apart from (**18a**), the examples listed are planar aromatic molecules. The observed bond

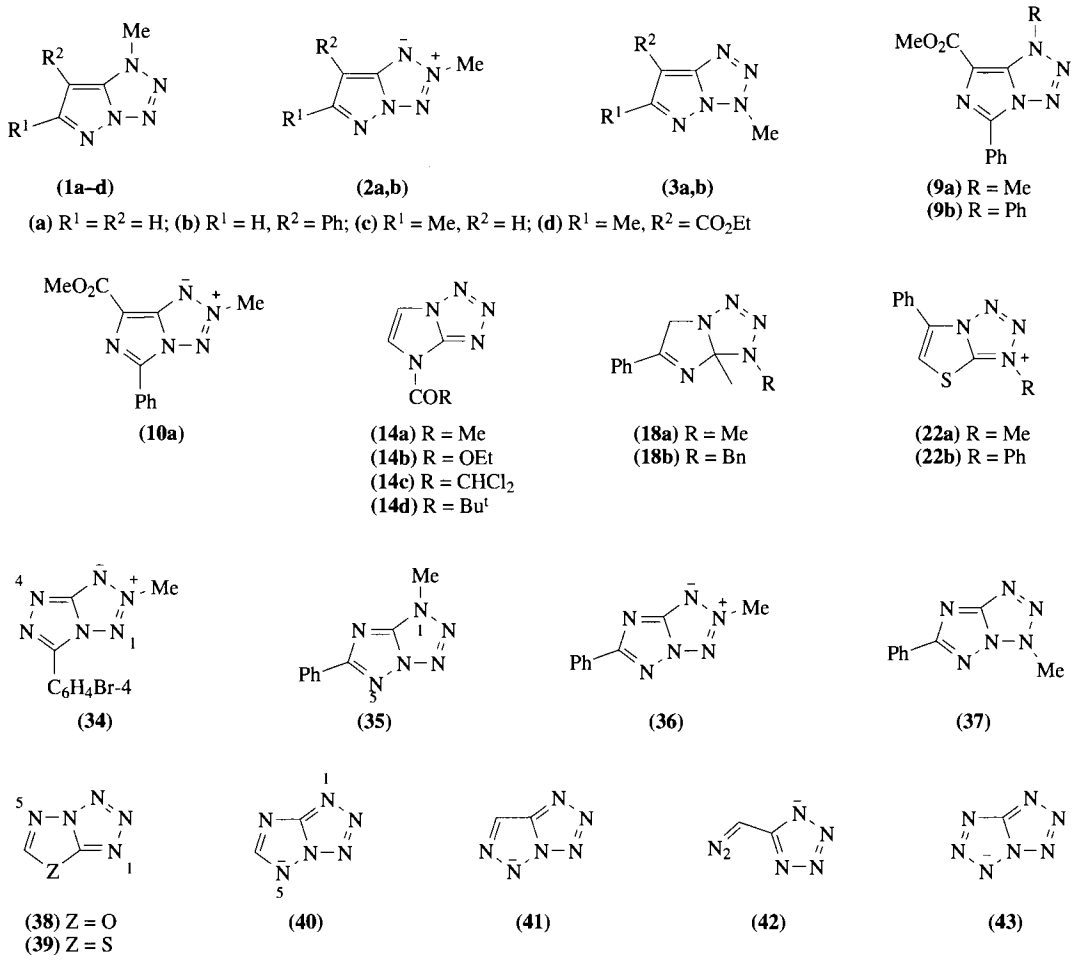


Figure 2 Selected title compounds and bicyclic 5-5 systems having additional heteroatoms.

distances of (**1d**) are in reasonable agreement with the CNDO/2 calculated ones of the parent bicycle (**1**; R = H) ⟨78JHC395⟩.

NMR chemical shifts of ring hydrogens, carbons, and nitrogens are recorded in Tables 2–4. Every class measured is represented by at least one example. Of the types (**9**) and (**10**) which are missing in Table 2, only fully substituted derivatives are known. An interesting feature of ^{13}C NMR chemical shifts concerns the progressive deshielding of the bridgehead carbon atom on passing from (**1**) through (**2**) to (**3**). The same trend applies to the triad (**35**)–(**36**)–(**37**) and has a parallel in the 1*H*-/2*H*-pyrrolotetrazole couple ⟨94UP 808-01⟩.

UV absorption maxima are shown in Table 5. Mesoionic 2*H*-structures such as (**2b**) are characterized by a pronounced bathochromic shift of the longest wavelength compared to 1*H*- and 3*H*-isomers; the same holds for the 2*H*-pyrrolotetrazole series ⟨94UP 808-01⟩. UV spectra of (**15**), (**28**), and (**29**) and substituted derivatives (all determined in methanol) have also been reported but must be regarded with care because of the presence of the azidoazole valence bond tautomer (**A**) ⟨59JOC1478, 62UKZ511⟩.

IR spectroscopic data pertaining to ring vibration modes is available from studies of the azolotetrazole (**T**)/azidoazole (**A**) tautomerism: (**16**; R = H) ⟨59JA4671⟩ and both (**15**) ⟨59JOC1205, 68KGS423⟩ and (**28**) ⟨59JA4671, 61DOK(141)1388, 62MI 808-01, 63JGU968⟩ (including substituted examples). In addition, IR spectra of (**1b–d**) and (**2b**) ⟨76JHC379⟩ and of quaternary salts of (**15**) and (**28**) are known ⟨64JGU275, 73JHC5⟩.

Mass spectra (EI) has been reported for (**1b**) and (**2b**) ⟨78JHC395⟩, (**9b**) ⟨85T4621⟩, (**17**; 5-MeO-) ⟨91MI 808-01⟩, (**18a**) ⟨93CB129⟩, 6-aryl substituted (**22**; R = Ar; anion: ClO_4^-) ⟨73JHC5, 78MI 808-01⟩ as well as for (**30**, **31**; each 5-Ph- and 5,6-Ph_2-), (**32**) and (**33**) ⟨81JOC4065⟩; in three of the last cases, the molecular ion only was given.

Table 2 Proton NMR spectral data for ring hydrogens.

Compound	*Chemical shift* (δ, ppm) *H-5*	*H-6*	*H-7*	*Coupling constant J* (Hz)	*Solvent*	*Ref.*
(**1a**)[a]		7.76	5.80	2.4	$CDCl_3$	78JHC395
(**1b**)		7.93			$CDCl_3$	78JHC395
(**2a**)[b,c]		7.86	6.05	2.8	$CDCl_3$	78JHC395
(**2b**)[c]		8.22			$CDCl_3$	78JHC395[d]
(**3a**)[e]		7.75	6.27	2.6	$CDCl_3$	83JHC1629
(**3b**)		8.06			$CDCl_3$	83JHC1629
(**7**; 7-Ph-)		8.16[f]			KOD/D_2O	74JHC921
(**14a**)	8.32[g]	8.06[g]		2.8[g]	DMSO-d_6	75TL1523[h]
(**14b**)	8.32[i]	7.97[i]		2.8[i]	DMSO-d_6	77JHC33
(**14c**)	8.49[j]	8.35[j]		2.8[j]	DMSO-d_6	77JHC33
(**15**)	7.96[k]	8.75[k]		4.35[k]	DMSO-d_6	75BSB1189
(**15**; 6-Ph-)	8.83[l]				HMPA	76UKZ1298
(**16**; R = H)[m]	4.19[n]	4.39[n]			DMSO-d_6	84CS195
(**16**; R = Me)	4.11[o]	4.39[o]			DMSO-d_6	84CS195
(**17**; 5-MeO-)	6.28	3.73		3.0	DMSO-d_6	91MI 808-01
(**18a**)		4.29		17	$CDCl_3$	93CB129
		5.04				
(**19**)	7.21[p]	7.43[p]		1.5	DMSO-d_6	76JHC281[d]
(**22b**)[q]	8.63				DMSO-d_6	73JHC5
(**30**; 5-Ph-)		8.27			$CDCl_3$	81JOC4065
(**31**; 5-Ph-)		8.22			$CDCl_3$	81JOC4065

[a] *N*-Me: 4.11. [b] *N*-Me: 4.43. [c] In cited literature viewed as (**3a**) and (**3b**), respectively; revision in ⟨83JHC1629⟩. [d] See also ⟨76JHC379⟩. [e] *N*-Me: 4.44. [f] Azidoazole tautomer [(**A**); Equation (1)]: 7.95. [g] (**A**) tautomer: 6.89, 7.51; 2.0 (H-4, H-5; *J*). [h] See also ⟨76JHC281⟩. [i] (**A**) tautomer: 6.89, 7.37; 1.8. [j] (**A**) tautomer: 7.00, 7.67; 1.9. [k] (**A**) tautomer: 7.60, 7.49; 3.55. [l] (**A**) tautomer: 8.30. [m] *N*-H: 3.8. [n] (**A**) tautomer: 4.76 (TFA). [o] (**A**) tautomer: 4.73 (TFA). [p] No assignment. (**A**) tautomer: 6.89. [q] Anion: ClO_4^-.

Table 3 Carbon-13 NMR chemical shifts (δ, ppm) for ring carbons and *N*-methyls.

Compound	*C-3a*	*C-4*	*C-5*[a]	*C-6*[a]	*C-7*	*C-7a*	N-*Me*	*Solvent*	*Ref.*
(**1a**)				146.9	78.2	138.4	35.7	$CDCl_3$	78JHC395
(**1b**)				144.9	96.7	134.9	37.2	$CDCl_3$	78JHC395
(**2b**)				143.26	98.94	147.81	42.47	$CDCl_3$	83JHC1629
(**3b**)				141.17	104.05	149.33	35.85	$CDCl_3$	83JHC1629
(**9a**)			128.8		101.1	139.4	36.5	$CDCl_3$	89JHC729
(**10a**)			127.0		105.4	150.4	43.1	$CDCl_3$	89JHC729
(**15**)	159.35[b]		123.2[b]	118.5[b]				DMSO-d_6	78CJC46
(**16**; R = H)	165.9		43.2	51.5				DMSO-d_6	84CS195
(**18a**)	109.7		166.9	60.8			33.2	$CDCl_3$	93CB129
(**22a**)[c]	154.6		122.8	125.0			37.9	DMSO-d_6	78OMR(11)507
(**23**; R = Me)[c,d]	160.8		124.3	125.0			44.8	DMSO-d_6	78OMR(11)507
(**28**)	158.1[e]		132.8[e]	128.1[e]				DMSO-d_6	78CJC46
(**28**)	159.0		132.2	127.9				Solid	87H(26)333
(**35**)				168.4		150.2	35.1	DMSO-d_6	79JCS(P1)2886
(**36**)[f]				169.0		156.2	43.2[g]	DMSO-d_6	79JCS(P1)2886
(**37**)				167.98		161.94	37.92	DMSO-d_6	83JHC1629

[a] In case of (**28**): C-4a and C-8a, respectively. [b] Azidoazole tautomer [(**A**); Equation (1)]: 161.8 (C-2), 140.4 (C-4), 117.6 (C-5). [c] Anion not specified ($MeOSO_3^-$, ClO_4^-, I^-). [d] 6-Ph substituted. For assumption of this unusual structure, see Section 8.08.5.1. [e] (**A**) tautomer: 163.2 (C-2), 148.8 (C-3a), 131.3 (C-7a). [f] In cited literature viewed as (**37**), revision in ⟨83JHC1629⟩. [g] Cf. 43.7 in case of (**34**) ⟨86JCR(S)38, 86JCR(M)501⟩.

8.08.4 THERMODYNAMIC ASPECTS

Bicycles (both fully conjugated, i.e., 10 π aromatic, and nonconjugated species) whose tetrazolic half-ring bears *one* R substituent are stable, often high-melting solids (examples are shown in Figure 2); the same applies to the thia- and selenatriazole derivatives (**30**)–(**33**). By contrast, the structural units (**20**) and (**21**), which occur in the (3 + 2) cycloadducts from dehydrodithizone and electron-poor alkynes, alkenes, and also benzyne ⟨71CC490, 76JCS(P1)1673, 77JCS(P1)965, 77JCS(P1)1612, 81JCS(P1)2692⟩, undergo spontaneous N-1—N-7 bond cleavage after their formation. Fully conjugated azolotetrazoles having an NH ring grouping (any position) exist as monocyclic azidoazoles (**A**) (see below);

Table 4 Nitrogen-15 NMR chemical shifts (δ, ppm) for ring nitrogens.[a]

Compound	*N-1*	*N-2*	*N-3*	*N-4*	*N-6*	*N-7*	*Solvent*	*Ref.*
(**9a**)	186.2	375.4	325.4	255.7	269.3		$CDCl_3$	89JHC729
(**9b**)	204.8	374.9	326.9	255.9	271.5		$CDCl_3$	85T4621
(**10a**)	280.8	276.4	311.3	242.5	277.3		$CDCl_3$	89JHC729
(**15**)	351.8[b]	409.5[b]	306.8[b]			265.8[b]	DMSO-d_6	84OMR(22)209

[a]All chemical shifts expressed in ppm from liquid ammonia, determined by means of external $MeNO_2$/Cr(acac)$_3$. [b]Calculated shifts (INDO/S-SOS method): 401.6, 409.7, 374.8 and 338.7, respectively ⟨84OMR(22)209⟩.

Table 5 UV absorption maxima.

Compound	λ_{max} (nm) (log ε)	*Ref.*
(**1b**)[a]	298sh (3.46), 257 (4.15)	78JHC395
(**2b**)[a,b]	346 (3.15), 268 (3.85), 264 (2.86), 258 (3.85)	78JHC395
(**2b**)[c]	353 (3.56), 268 (4.23)	83JHC1629
(**3b**)[c]	319 (3.81), 267sh (3.97), 258sh (4.02), 249 (4.09)	83JHC1629
(**16**; R = H)[a]	232 (3.25)	59JA4671
(**22**; R = Me)[a,d]	242 (3.74)	78OMR(11)507
(**22a**)[a,d]	248 (4.13)	78OMR(11)507
(**30**; 5-Ph-)[e]	401 (4.02), 315 (4.05), 223 (4.16), 212 (4.16)	81JOC4065
(**31**; 5-Ph-)[e]	442 (3.91), 345 (4.03), 263 (3.44), 229 (4.09)	81JOC4065
(**32**)[e]	438 (3.96), 335 (3.91), 232 (4.28)	81JOC4065
(**33**)[e]	505 (3.30), 364 (4.33), 251 (4.46), 229 (4.30)	81JOC4065
(**37**)[c]	266 (4.18), 244 (4.23)	83JHC1629

[a]Measured in ethanol. [b]In cited literature viewed as (**3b**), revision in ⟨83JHC1629⟩. [c]Measured in dichloromethane. [d]Anion: $MeOSO_3^-$. [e]Measured in methanol.

therefore, annular tautomerism, while an object of theoretical calculations (cf. Section 8.08.2), is meaningless from the practical point of view. Regarding functional tautomerism, 6-oxo-substituted (**17**) exists as such in both the solid state and DMSO solution ⟨87MI 808-01⟩.

Most importantly, all bicycles having a tetrazolic half-ring with three unsubstituted pyridine-like nitrogens are subject to the azolotetrazole (**T**)/azidoazole (**A**) valence bond tautomerism (Equation (1)). The position of this equilibrium is governed by several factors (physical state of sample (solid or solution); solvent polarity; temperature; substituents; nature, number and location of heteroatoms in the second half-ring). The ample material has been reviewed and commented on previously ⟨75RCR481, 77AHC(21)323, 78AHC(22)183, 79CRV181⟩; for a condensed picture see Table 6 and the ensuing list of the "extreme" cases:



(T) (A) (1)

This equilibrium is entirely on the azide side (**A**) with the following systems (C-substituents, if any, not given): (**4**; R = H, Me, Ph, Ac) ⟨59JOC1205, 74CC411, 74JHC921, 84CS195⟩; (**5**) ⟨77CJC1728, 77JHC1299⟩; (**8**; R = Ac, Ts) ⟨84CS195⟩; 3*H*-tautomer of (**9**; R = H) ⟨73KGS94⟩; (**14**; R = H, Me, 2,4-dinitrophenyl) ⟨75TL1523, 76JHC281⟩; (**24**; R = H) ⟨77MI 808-01⟩, (**25**; $n = 2$) ⟨59JA4671⟩ ($n = 0$ not reported); (**26**; R = H, alkyl) ⟨59JA1478, 59JOC1205, 75TL1523⟩; (**27**) ⟨59JA1478, 59JOC1205, 77CJC1728, 77JHC1299⟩; and (**28**, 4,4-dioxide) ⟨59JOC1205⟩. Conversely, the equilibrium is completely shifted to the tetrazole side (**T**) with the neutral systems (**16**; R = H, Me, Bn, Ac, NO_2) ⟨59JA4671, 84CS195, 88JOC5371, 91MI 808-02⟩, (**17**) ⟨87MI 808-01, 91MI 808-01⟩, and (**28**, 4a,5,6,7,8,8a-hexahydro-) ⟨82MI 808-01⟩, and with the anions (**7**) ⟨74CC411, 74JHC921⟩, (**19**) ⟨75TL1523, 76JHC281, 79JHC685⟩, and (**24**, **26**; R = minus charge) ⟨75TL1523, 77MI 808-01⟩; for system (**6**) see Section 8.08.8. A unique case is compound (**16**; R = H), of which also the (**A**) tautomer can be obtained pure ⟨84CS195⟩. Likewise, (**T**) and (**A**) forms have been isolated with the tricyclic tetrazolo[1′,5′:1,5]pyrazolo[3,4-*d*]pyrimidine system ⟨92JCS(P1)239⟩.

In marked contrast to the anion (**40**), which equilibrates with its (**A**) tautomer (Table 6), the *v*-triazole congener (**41**), once formed by cyclization of the respective azide (**A**), undergoes rapid

Table 6 Azolotetrazole (**T**) ⇌ azidoazole (**A**) valence bond tautomerism.[a]

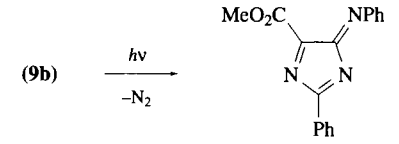
Compound	*K*[(**T**)] : [(**A**)]	*Solvent*[b]	*Temperature* (°C)	*Ref.*
(**14a**)	0.59 / 0.53 / 0.48 / 0.42	A[c]	15 / 25 / 35 / 45	76JHC281[d]
(**14b**) // (**14c**)	0.16 // 0.24	A	35 // 20	77JHC33
(**14d**)	1.7[e]	A	35	76TL4175
(**15**)	4.76 / 0.83 / 0.45[f] / 0.18	A / B / C / D	30 / 30 / 28 / 30	75BSB1189, 77CJC1728, 77JHC1299
(**15**; 5-Me- // 6-Me- // 6-Ph-)	20 / 1.47 // 33 // 0.77[g]	A / D // A // A	28 / 28 // 30 // 20	75BSB1189, 77JHC1299
(**26**; R = Ac)	0.67 / 0.1	A / D	Unspecified	75TL1523
(**28**)	12.5[h] / 1.0[h]	A / D	28	77JHC1299
(**39**; 6-Me-)	6.67 / 0.26[i]	A / D	28	77JHC1299
(**40**) // (**40**; 6-Ph-)	2.22 / 0.70 // 1.28 / 0.63	A // A	27 / 90 // 23 / 80	77MI 808-01, 79JCS(P1)2886

[a]Studied by ^{1}H NMR spectroscopy. In the solid state, the nonionic azolotetrazoles listed (except (**14a**)) exist as such (no azide band in the IR spectra); no IR data on neat (**14b**) and (**14c**) which are liquids. [b]A = DMSO-d_6, B = CD_3OD, C = dioxane-d_8, D = $CDCl_3$. [c]In $CDCl_3$, tautomer (**T**) not observed. [d]See also ⟨75TL1523, 77JHC33⟩. [e]High value entropy-controlled (bulky substituent) ($\Delta S^\circ = -20.1 \pm 4.2$ JK^{-1} mol^{-1}; cf (**14a**): $\Delta S^\circ = -33.5 \pm 2.5$ JK^{-1} mol^{-1}). [f]$K = 0.43$ (25 °C) by dipolarometry (calculation of $\mu_{(T)}$ and $\mu_{(A)}$ by CNDO/S approximation) ⟨77CJC1728⟩. [g]In the case of the 6-(4-$NO_2C_6H_4$) derivative, form (**T**) not observed. [h]In the case of the 7-NO_2 derivative, form (**T**) not observed. [i]Both tautomeric forms also observed with the oxalogue (**38**; 6-Ph-), but the *K* value not reported ⟨84CS90⟩.

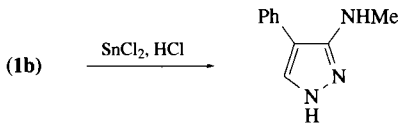
v-triazole cleavage to give (**42**) ⟨88CC1144⟩; the bicycle (**41**) remains unobservable, as does the azalogue (**43**), which is the putative intermediate in the topomerization of 5-azidotetrazolide ⟨86CC959⟩.

8.08.5 REACTIVITY OF FULLY CONJUGATED RINGS

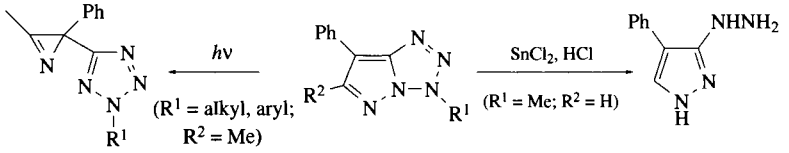
A major thermal reaction constitutes the tetrazole ring-opening already treated in Section 8.08.4 (Equation (1)). A photochemical reaction which proceeds with loss of molecular nitrogen from the tetrazolic half-ring has been reported for compound (**9b**) and its 5-Me analogue (Equation (2)) ⟨85T4621⟩, while photolysis of (**3**) affects the pyrazole ring, giving tetrazolyl-substituted 2*H*-azirines as final products (Scheme 1) ⟨90MI 808-01⟩. Reductive tetrazole degradation is known of the bicycles (**1b**) and (**3**; R^1 = Me, R^2 = H) ⟨83JHC1629⟩. Also, removal of 3-Me and 3-Bn substituents from class (**3**) (by ethoxide and sodium/liquid ammonia, respectively) has been mentioned, leading ultimately to azidopyrazoles ⟨83JHC1629, 85JAP8533552⟩.



(2)



(3)



Scheme 1

8.08.5.1 Electrophilic Attack at Nitrogen

(i) Action of proton acids such as TFA has been investigated with the series (**15**) and (**28**) and derivatives, showing that protonation occurs at N-3. Stable salts are not obtained; moreover, ^{1}H

NMR ⟨76UKZ1298, 77OMR(10)249⟩ as well as ^{13}C NMR spectroscopy ⟨86AQ(C)61⟩ demonstrates that the bicyclic cations formed slowly ring-open to give azidinium ions which then predominate.

(ii) Quaternization studies (effected with dimethyl sulfate at 100 °C) are also limited to the classes (**15**) and (**28**) ⟨64JGU275, 78OMR(11)507⟩; two series of tetrazolium salts ((**22**) (major component)/(**23**) and their benzo-fused analogues) are reported (the earlier reference mentions only one without specifying the type). Structure (**23**) has been based upon a nuclear Overhauser effect observed with benzo-fused (**23**) and explained as arising from ring-closure of the azidothiazole species methylated at the terminal N of the functional group ⟨78OMR(11)507⟩.

(iii) Interaction with salts of transition metals has been studied with (**28**) and its 6-Me derivative. Part of the complexes formed contain the ring-open tautomers (**A**); a specific binding site of the ligand is not known ⟨75UKZ1238⟩.

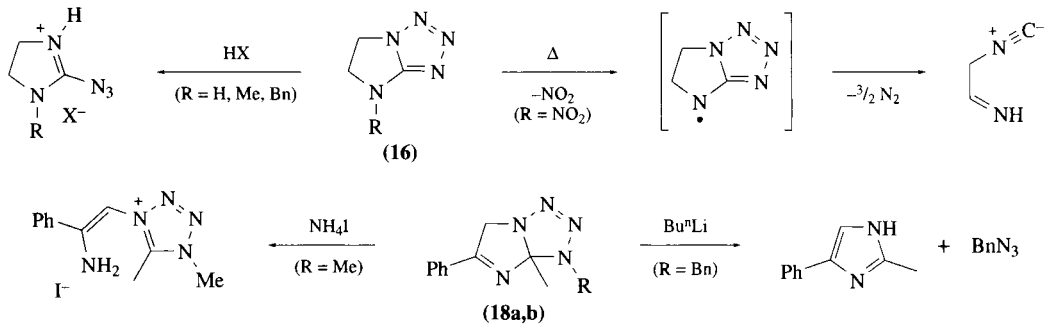
(iv) The bicyclic anions (**7**) and (**19**) have been reacted with methyl iodide: the products obtained from (**7**) are (**1**) and (**2**) where R = Me (the latter structure according to revision) and 3-azido-1-methylpyrazole ⟨76JHC379, 78JHC395, 83JHC1629⟩. In contrast, (**19**) is attacked exclusively at N-4 to give, after ring-opening, 2-azido-1-methylimidazole ⟨76JHC379⟩.

8.08.5.2 Electrophilic Attack at Carbon

This has been attempted with (**15**) and its 6-Me and 6-Ph derivatives to include (i) bromination, (ii) thiocyanation, (iii) sulfonation, (iv) sulfochlorination, and (v) nitration ⟨68KGS423, 73UKZ60, 76UKZ1298⟩. Substitution of (**15**; 6-Ph-) in acidic media, i.e., with (iii)–(v), occurred at the phenyl ring only (C-4) and the products were isolated as azides (**A**) (cf. Equation (1)); accordingly, (**15**) and (**15**; 6-Me-) were found unreactive. In case of the reactions (i) and (ii), carried out in chloroform, (**15**; 6-Me-) gave the 5-Br and 5-SCN derivatives, respectively (isolated in bicyclic form (T)). However, there is doubt that these reactions proceed with the (**T**) tautomer of the educt: in chloroform the (**A**) form predominates which, in addition, shows a much higher electron density at C-5 compared to (**T**) ⟨76UKZ1298⟩.

8.08.6 REACTIVITY OF NONCONJUGATED RINGS

The dihydro compound (**16**; R = H) can easily be alkylated and acylated at N-4 to give stable derivatives (**16**; R = Me, Bn, Ac) ⟨84CS195⟩; nitration (effected with nitric acid/acetic anhydride) affords (**16**; R = NO_2) ⟨88JOC5371⟩. Ring-opening reactions caused by (i) proton acids or (ii) butyllithium, or (iii) thermally have been reported for the following species: (i) (**16**; R = H, Me, Bn) ⟨84CS195⟩; (**18a**) ⟨93CB129⟩; (ii) (**18b**) ⟨93CB129⟩; (iii) (**16**; R = NO_2) ⟨91MI 808-02⟩ (Scheme 2). For the behavior of the structural types (**20**) and (**21**), see Section 8.08.4.



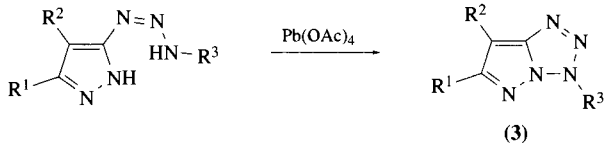
Scheme 2

8.08.7 RING SYNTHESES

8.08.7.1 Starting from Functionalized Monocycles Having Two Heteroatoms

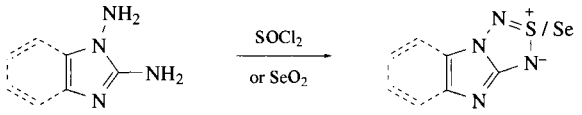
Compounds of type (**3**) are readily available by intramolecular dehydrogenation of appropriate triazenopyrazoles (Scheme 3) ⟨82AG(E)698, 83JHC1629, 85JAP8533552, 87CB1375⟩. Species having a tetra-

zolic half-ring with three unsubstituted pyridine-like nitrogens arise by cyclization of the respective azides (**A**) (see Section 8.08.4); in case of (**7**) and C-substituted derivatives, this process has been studied kinetically ⟨74CC411, 74JHC921⟩. For the synthesis of (**30**)–(**33**), two adjacent functional groups in the educt are required ⟨81JOC4065⟩.



(**3**)

R^1 = H, alkyl; R^2 = H, aryl, CO_2R, Br;
R^3 = alkyl, aryl, pento/hexopyranosyl



(**30**)–(**33**)

Scheme 3

8.08.7.2 Starting from Functionalized Monocycles Having Four Heteroatoms

This section refers to tetrazoles throughout. Thermolysis of certain tetrazol-5-yl substituted diazo compounds in aceto- or benzonitrile gives rise to derivatives of class (**9**) (Scheme 3) ⟨85T4621, 88JHC1741, 89BSB421, 89JHC729, 89T749⟩. Type (**10**) is obtained similarly, but in lower yield because of a competing nitrile to acylcarbene cycloaddition ⟨89JHC729⟩. Cyclonucleosides having the dihydroimidazo[1,2-*d*]tetrazole moiety (**16**) readily result from ring closure of suitably functionalized 5-(alkylamino)tetrazole nucleosides ⟨86LA1736⟩. Easy approach to (**17a**) is given by linking a potential SH group to the acetal carbon of the open-chain precursor ⟨91MI 808-01⟩. Concentrated ammonia converts certain *N*-phenacyltetrazolium salts into the bicycle (**18**) (unless R^1 = H and/or R^2 = Ar); with R^2 becoming bulkier, the formation of (**18**) is increasingly hampered ⟨93CB129⟩. As an alternative to the quaternization of (**15**) (see Section 8.08.5.1), cyclization of 1-substituted 5-[(acylmethyl)-thio]tetrazoles with mineral acid is an efficient entry to class (**22**) ⟨68TL6287, 71PHA463, 73JHC5, 78MI 808-01⟩.

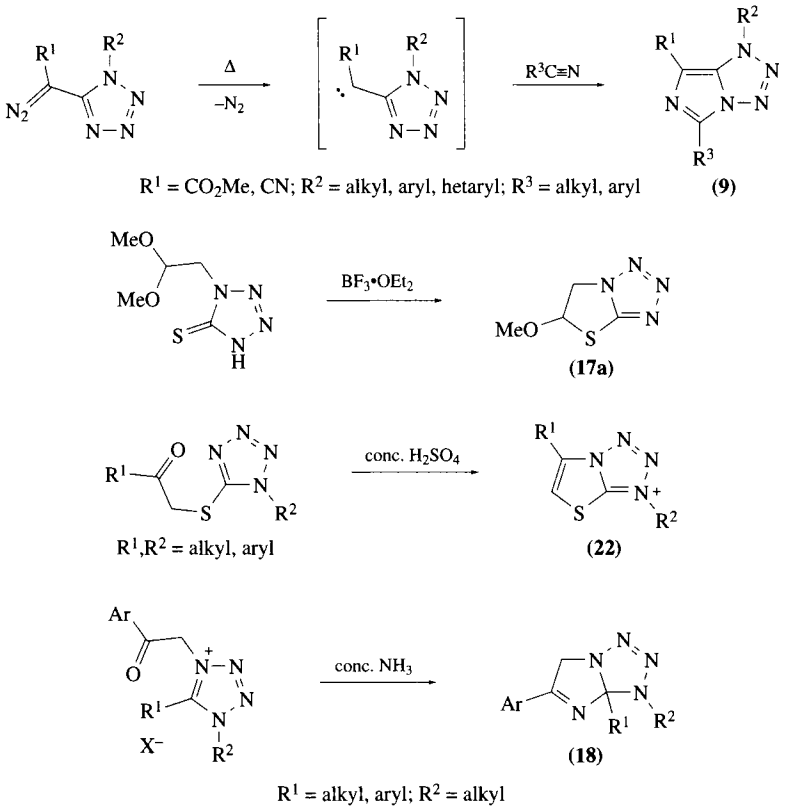
The following cyclizations could not be accomplished: reaction of either 5-(aminomethyl)tetrazole with formaldehyde or 5-(chloromethyl)tetrazole with hexamine to give (**11**; R = H), a methano-ditetrazolo-[1,3,6,8]tetrazecine derivative being obtained in both cases ⟨89LA689⟩; treatment of 1,4-diphenacyl-1*H*-tetrazol-5(4*H*)-imine with bases to give 5-phenyl-substituted (**13**; R = CH_2COPh) ⟨73BSF1854⟩; heating of the sodium and silver salts of 2-bromo-2-ethyl-*N*-(tetrazol-5-yl)butyramide to give 6,6-diethyl-5-oxo substituted (**16**; R = H) ⟨33JPR314⟩. The compound claimed to be the 1*H*-tautomer of (**13**; R = H) having at C-5 a 4-(methylsulfonyl)phenyl substituent ⟨66JMC29⟩ has been shown to be the 1-phenacylated 5-aminotetrazole ⟨73BSF1854⟩.

8.08.7.3 *N*-Substitution of the Corresponding Bicycles

As already mentioned in Sections 8.08.5.1 and 8.08.6, this is an entry to the classes (**1**), (**2**), (**16**), and (**22**), including the benzothiazolium analogue, while (**12**) and (**13**) are not accessible in this manner.

8.08.8 IMPORTANT COMPOUNDS AND APPLICATIONS

The patent literature on color photography abounds in pyrazolotetrazole dyes showing the 7-[(4-aminophenyl)imino] substituted unit (**6**) (e.g., ⟨85JAP8533552, 89JAP8948862, 90JAP90297539, 92JAP92112089⟩); but, as in the case of 7,7-dihalogenated derivatives of (**6**) which are used as couplers ⟨88JAP8877055⟩, the bicyclic nature (**T**) (cf. Equation (1)) does not seem to have been proved. The



Scheme 4

(5,6-dihydrothiazolo[3,2-*d*]tetrazol-5-yl)oxy unit (derived from (**17**)) linked to a coupler is split off by the oxidized developer and then acts as a development inhibitor ⟨85JAP85232549⟩. Materials known for their improving effects on emulsions and image quality include (**15**) and (**28**) and/or derivatives ⟨59USP2891862, 70MI 808-01⟩ as well as quaternary salts of (**17**) ⟨84JAP8415240⟩. Anthelmintic activity has been reported for (**22b**; anion: ClO_4^-) ⟨78MI 808-01⟩. Compound (**15**; 5-Pr^n-, 6-Bu^n-) and/or its azide tautomer (**A**) show affinity for the bovine odorant-binding protein ⟨92BMC1603⟩. The nitro compound (**16**; R = NO_2) has attracted interest as a potential propellant and explosive ⟨91MI 808-02⟩.

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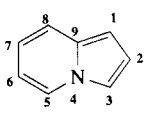
8.09
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: No Extra Heteroatom

WILHELM FLITSCH
Universität Münster, Germany

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8.09.1 INTRODUCTION

Chemical Abstracts uses the name indolizine for pyrrolo(1,2-*a*)pyridine as the author does in this chapter. Numbering of the system is shown in formula (**1**). The denomination of hetero derivatives follows the replacement nomenclature system, for example, 1-azaindolizine, etc. *Chemical Abstracts*, however, follows the systematic fusion nomenclature; for example, 1-azaindolizine is imidazolo(1,2-*a*)pyridine. This chapter expands on the review in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(4)443⟩.



(1)

8.09.2 THEORETICAL METHODS

Indolizine has a delocalized 10π-system. The nitrogen atom influences the properties of both rings differently, conferring on the five-membered ring characteristic features of electron rich pyrroles, and on the six-membered ring properties similar to those of electron deficient pyridines. Thus, electrophilic substitution takes place at the "pyrroloid" five-membered ring while condensation occurs on activated methyl groups of the "pyridinoid" six-membered ring.

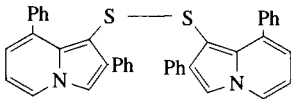
The aromaticity of indolizine was discussed with the aid of configuration analysis of matrices, the isoelectronic (9)annulenyl anion serving as aromatic reference compound ⟨81CCA427⟩. A new aromaticity index has been applied to indolizine and other bicyclic heterocycles ⟨87T4725⟩.

Indolizines failed to give chromium and molybdenum carbonyl π-complexes. This was discussed in terms of LCAOMO calculations at the MNDO level ⟨90JCR(S)64⟩.

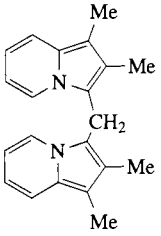
8.09.3 EXPERIMENTAL STRUCTURAL METHODS

8.09.3.1 X-Ray

X-ray data of indolizine (**2**) indicate contributions of C=S$^+$-bonds in the molecular structure ⟨85IZV2724⟩. An x-ray structural investigation of (**3**) reveals that it occupies a two-bladed propeller conformation with an anti relation between the methylene protons and the four methyl groups. In the crystal, the molecule lacks a C_2 symmetry and is asymmetric rather than helical. Since the indolizine ring carries no substituents which conjugate, the structural results supply information about the geometry of indolizine itself ⟨87CB231⟩.

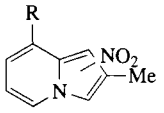


(2)



(3)

X-ray investigation of indolizines (**4**) showed that the NO_2-groups were coplanar with the rings. Contributions of charge-separated structures are indicated ⟨89MI 809-01⟩. The crystal and molecular structure of 1,2,3-tribenzoylindolizine was determined. The indolizine ring is conjugated only with the 1-benzoyl group ⟨93MI 809-01⟩.



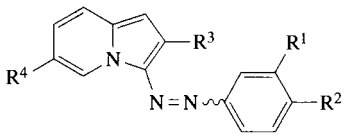
(4) R = H, Me

8.09.3.2 NMR Spectra

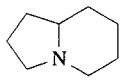
Detailed one- and two-dimensional NMR spectroscopic analysis of 2-substituted indolizines has facilitated interpretation of ^{1}H and ^{13}C NMR spectra ⟨93JCS(P1)1809⟩.

NMR spectroscopy can serve to detect the ratios of *syn*- and *anti*-conformers (**5**). For R^1 =

$R^2 = R^3 = H$, $R^4 = Me$ the *syn*-conformer is favored. *Anti*-conformers are stabilized by electron-withdrawing substituents R^2 and R^3 ⟨81UKZ1071⟩.



(5)



(6)

It has been deduced from NMR investigations that indolizidine (**6**) is *trans* fused with the piperidine ring in a chair conformation. The pyrrolidine ring forms an envelope with the nitrogen displaced out of the four ring atoms ⟨84JCS(P1)1⟩.

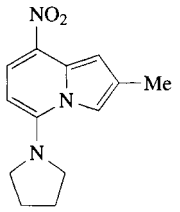
Carbon-13 NMR shifts of indolizine were correlated. The effect of *N*-substitution on both rings was studied ⟨87JHC805⟩.

A ^{15}N NMR investigation of azolopyridines including indolizines has been reported ⟨84OMR(22)209⟩. Solvent effects on the nitrogen shielding of indolizines were studied ⟨90MRC988⟩.

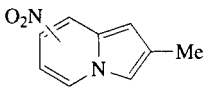
8.09.3.3 Mass Spectra

Mass spectra of indolizines have been reviewed ⟨90MI 809-01⟩. Fragmentation paths depend on the ability of the molecular ion to form a resonance-stabilized species containing a quaternary ring nitrogen ⟨81KGS1368⟩. Hydrogen cyanide elimination was proved by mass spectroscopic investigation of ^{13}C labeled indolizines ⟨83OMS(18)198⟩.

The fragmentation pattern of (**7**) was discussed ⟨82KGS765⟩. Collisional–activation spectra of (MOH^+) and (MNO^+) of 1-, 3-, 6- and 8-NO_2—(**8**) were analyzed. They can be used to establish the position of the NO_2-group ⟨88KGS1631⟩.



(7)



(8)

8.09.4 THERMODYNAMIC ASPECTS

Octanol–water partition coefficients were determined for indolizine and 2-phenylindolizine ⟨82JPS614⟩. The tendency of pyridinium substituted indolizines to aggregate in aqueous and acetonitrile solution is dominated by solute–solvent interactions. It is proposed that π-stacking of the indolizine residues results in weak electronic interactions which are sufficient to result in the delocalization of bound excitonic states over the aggregate ⟨93JPC1085⟩.

8.09.5 REACTIVITY OF FULLY CONJUGATED RINGS

8.09.5.1 Reduction, Oxidation

Half-wave oxidation potentials ($E_{1/2}$) in MeCN at a platinum electrode, and gas-phase ionization potentials (*P*) were measured for 15 indoles and 12 indolizines substituted at the 5-membered ring. Except for a few compounds, a linear correlation of $E_{1/2}$ and *P* was found. Deviations of linearity were discussed in terms of conformation differences between the two phases ⟨86JCS(P2)1229⟩.

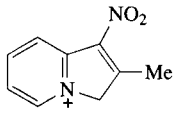
3-Unsubstituted indolizines undergo oxidative dimerization in the presence of catalytic amounts

of iron(III) and oxygen. A chain mechanism with reoxidation of iron(II) by oxygen cannot be envisaged ⟨88JCS(P1)3067⟩.

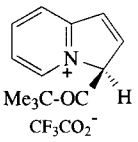
Indolizines were hydrogenated over Re_2S_7 catalysts. The pyridine ring was more easily hydrogenated than the pyrrole ring. Phenyl substitution did not prevent complete reduction while alkyl substituents made the reduction more difficult. Nitro groups were reduced to amino groups ⟨91IZV1413⟩.

8.09.5.2 Electrophilic Attack

Protonation of 2-methyl-1-nitroindolizine gave (**9**) as shown by ^{1}H NMR spectroscopy ⟨85ZOR673⟩. Compound (**10**) was obtained from the corresponding indolizine with trifluoroacetic acid ⟨87KGS1695⟩.



(**9**)

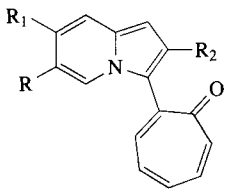


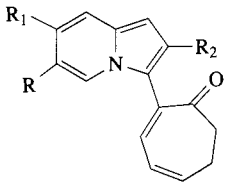
(**10**)

Partial rate factors of hydrogen exchange of azulene, cycl(2.2.3)azine, indolizine, *N*-methylisoindole, and indole have been compared ⟨87JCS(P2)591⟩.

Phosphorylation of indolizines with phosphorus(III)chloride originally results in formation of 1-phosphinoindolizines which then undergo isomerization into 3-phosphino isomers. One, two, or three indolizine substituents can be consecutively attached to the phosphorus atom. New methods of synthesis of 1,3-diphosphinoindolizines have been developed ⟨93HAC343⟩.

Addition reaction of indolizines with tropone yielded (**11**) and (**12**) ⟨81H(16)1697⟩.

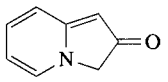




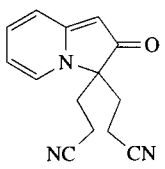
R = R_1 = H, Me; R_2 = Me, Ph

(**11**) (**12**)

Michael addition of unsaturated nitriles, esters and one amide to 2(3*H*)-indolizinones gave double adducts. The transformation of (**13**) into (**14**) may serve as an example ⟨82BCJ3590⟩.



(**13**)



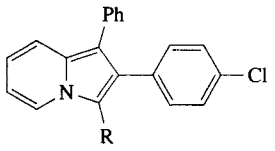
(**14**)

Compound (**3**) was prepared from 1,2-dimethylindolizine and aqueous formaldehyde ⟨87CB231⟩. Mannich reaction of (**15a**) with a series of secondary amines gave 72–92% (**15b**) ⟨86MI 809-01⟩.

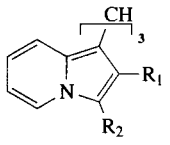
Tri(indolizinyl)methanes (**16**) and (**17**) were prepared from $HC(OEt)_3$ and indolizines. Structure (**17**) is a three-bladed propeller lacking local C_2-axes. Compounds of this type are chiral and eight stereomeric conformations are possible ⟨87CB(120)239⟩.

Two trifluoromethylsulfenyl groups were introduced into the 1,3-positions of indolizines by reaction of F_3CSO_2Cl with indolizine and 2-substituted indolizine derivatives ⟨81JFC(19)67⟩.

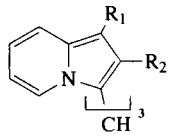
Reactions of 1- and 3-substituted indolizines with HNO_2 resulted in *ipso*-substitution products, essentially the corresponding nitro derivatives. An electron-transfer process is proposed for the



(15) a) R = H
b) R = $CH_2NR'_2$
R′ = CH_3, C_3H_7, C_6H_{11}, CH_2CH_2OH



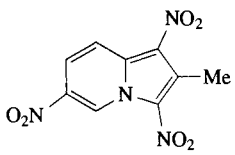
(16)



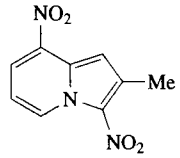
(17)

initial step, based on the reaction products, ESR evidence and substrate oxidation potentials ⟨84JCS(P2)165⟩.

Nitration of 2-methyl-6-nitroindolizine gave the tetrasubstituted indolizine (**18**), from the 8-nitroisomer only the monosubstitution product (**19**) was obtained ⟨89MI 809-01⟩.



(18)

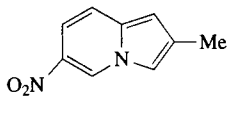


(19)

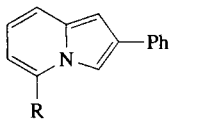
2-Methylindolizine was acetylated with Ac_2O—Et_3N to give mainly 3-acetyl-2-methylindolizine (87%, 1.5% 1-isomer). Carbomethoxylation with $ClCO_2Me$ resulted in 86% 3- and 1% 1-acylation ⟨89KGS1634⟩.

8.09.5.3 Nucleophilic Attack

Base-catalyzed D exchange of (**20**) with NaOD in MeOD took place only at the 5-position ⟨87KGS1285⟩. Regioselective metallation of 2-phenylindolizine occurred at C(5). Subsequent reaction with electrophiles led to 5-substituted indolizines (**21**) in 90–96% yields ⟨92TL4433⟩.



(20)



R = CO_2H,PhCHOH,D, PhCO, Me_3Si, Me

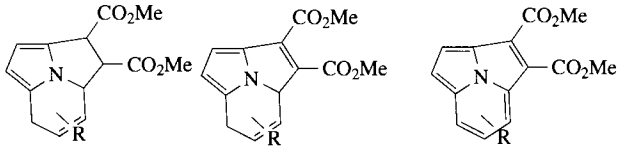
(21)

8.09.5.4 Cycloaddition and Cyclization

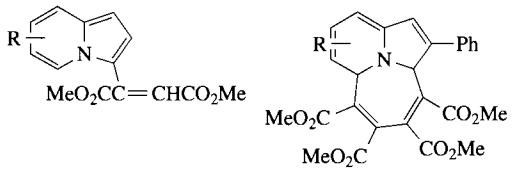
Reactions of indolizines with electron deficient alkenes and alkynes were studied. Cycloaddition reactions with dimethyl alkynedicarboxylate yield cycl(2.2.3)azine derivatives (**22**)–(**24**), adducts (**25**), and (2.3.4)cyclazines (**26**) ⟨84H(22)705⟩.

From a reaction with 1,2-dicyanocyclobutene cycl(2.3.4)azine (**27**) was formed, dimethyl maleate gave (**28**) ⟨87LA621⟩.

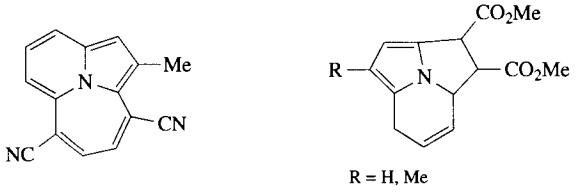
The photoreaction of indolizine with (*E*)-stilbene gave 1 : 1 (**29**) and 1 : 2 adducts (**30**) regio- and



(22) (23) (24)



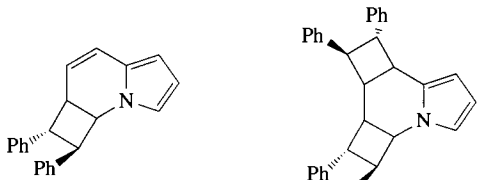
(25) (26)



R = H, Me

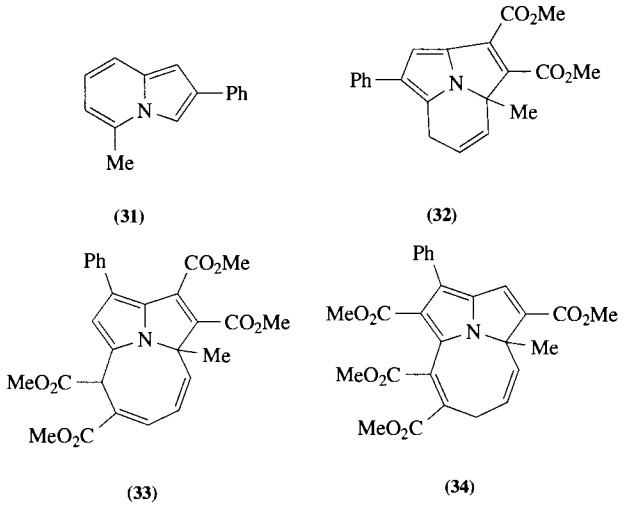
(27) (28)

stereoselectively. These together with other results were rationalized in terms of a biradical mechanism ⟨87TL6155⟩.



(29) (30)

Reaction of 2-phenyl-5-methylindolizine (**31**) with dimethyl acetylenedicarboxylate gave partially hydrogenated cyclazines (**32**)–(**34**) ⟨91JCS(P1)2991⟩.

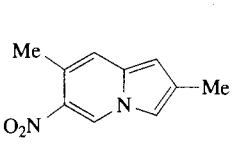


(31) (32)

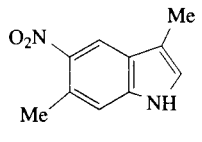
(33) (34)

8.09.5.5 Ring Opening Reactions

Isomerizations such as that of (**35**) into (**36**) have been described. Electron-withdrawing groups in the 6- and 8-positions are necessary; a nitro group in the 3-position hinders recyclization ⟨90IJC(B)1017, 90KGS758⟩.



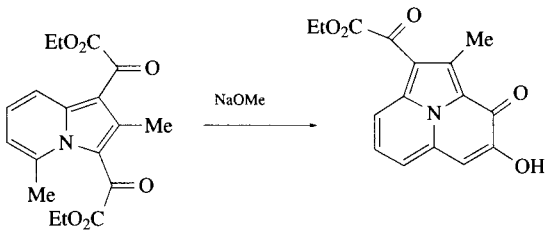
(**35**)



(**36**)

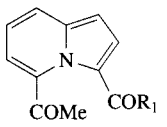
8.09.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Indolizine (**37**) has been transformed into cycl(2.3.3)azine (**38**) by an intramolecular condensation reaction (Equation (1)) ⟨81JCS(P1)3150⟩.

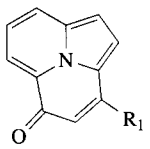


(**37**) (**38**) (1)

1,5-Diacylated indolizine (**39**) has been transformed into cycl(2.3.3)azine (**40**) by intramolecular aldol condensation ⟨84H(22)2467⟩.



(**39**)



(**40**)

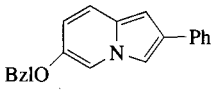
8.09.7 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPOUND

The synthesis of indolizines by 1,5-dipolar cyclization, the reaction of picolinium salts with ketene dithioacetals, the reaction of 2-pyridyl ketene dithioacetals with halogencarbonyls, and a reaction of *N*-imines or *S*-imines with ketene dithioacetals have been reviewed ⟨85YGK669⟩.

8.09.7.1 Formation of One Bond

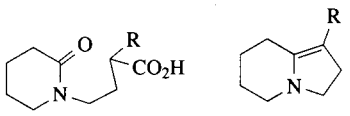
Compound (**41**) was prepared from 3-hydroxy-6-methylpyridine by sequential benzylation, N-quaternization with $PhCOCH_2Br$, and intramolecular cyclocondensation ⟨82JCR(S)245⟩. A series

of 6- and 8-nitroindolizines was obtained from $BrCH_2COMe$ and the corresponding pyridines ⟨87KGS203⟩. The method was applied in similar cases ⟨89JIC460⟩.



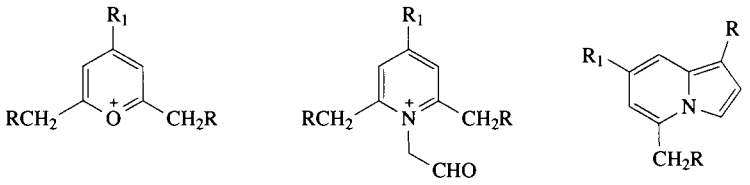
(41)

Dry distillation of (piperidinoyl)butyric acid (**42**) gave the hexahydro indolizine (**43**) ⟨82JHC1465⟩.



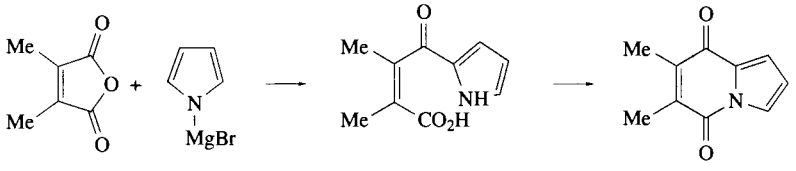
(42) (43)

N-Pyridinium aldehydes (**45**) obtained from pyrylium salts (**44**) were cyclized in KOH—MeOH to give indolizines (**46**) ⟨87TL3145⟩.



(44) (45) (46)

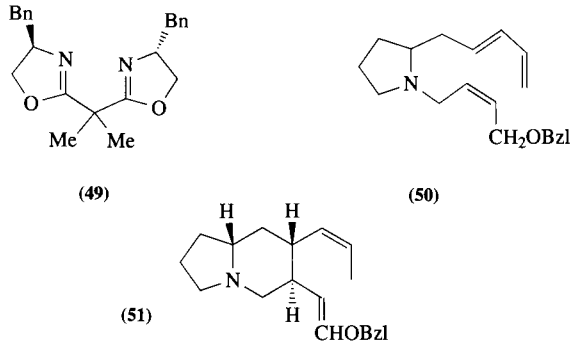
Indolizinedione (**48**) was obtained from pyrylmagnesium bromide and dimethylmaleic anhydride via (**47**) (Scheme 1) ⟨90JCS(P1)1463⟩.



(47) (48)

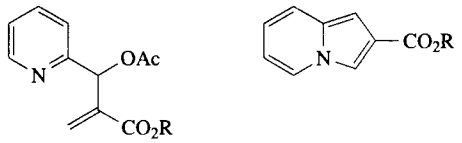
Scheme 1

Indolizidine ring systems were constructed in a stereoselective fashion using iron-catalyzed cyclization. The reduced iron catalyst tolerates trienes containing a basic nitrogen. Chemical efficiency and degree of 1,3-stereoinduction are dramatically influenced by the nature of the substrate (amine versus amide) and the nature of the ligand (2,2′-bipyridine versus bisoxazoline (**49**)) employed in the iron catalyst system. Thus, cyclization of the triene (**50**) in presence of Fe(acac)—3 Et_3Al—(**49**) gave 65% indolizine (**51**) ⟨93TL6219⟩.



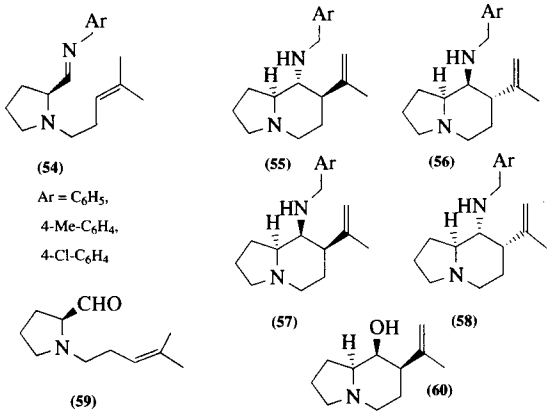
(49) (50) (51)

Thermal cyclization of (**52**) provided convenient access to indolizine (**53**) ⟨93JCS(P1)1809⟩.



(**52**) (**53**)

Lewis acid-catalyzed cyclization of prolinal benzylimines (**54**) results in a diastereoselective formation of α-amino-β-alkyl-substituted indolizidines (**55**), (**56**), (**57**), and (**58**). The diastereoselectivity depends on the Lewis acid; $FeCl_3$ gave predominantly (**55**), probably by cationic cyclization. In contrast, $TiCl_4$ yielded mainly (**57**) by a novel cyclization/intramolecular hydride transfer mechanism, which was supported by deuterium labeling studies. Analogous cyclization of (**59**) gave only the hydroxyindolizidine (**60**) ⟨94AG(E)458, 94CB2023⟩.

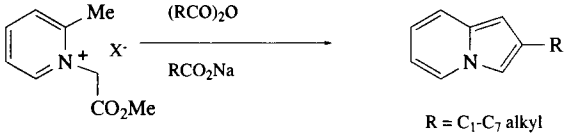


(**54**) Ar = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4

(**55**) (**56**) (**57**) (**58**) (**59**) (**60**)

8.09.7.2 Formation of Two Bonds

2-Substituted indolizines (**61**) were formed in a Chichibabin reaction of 1-(ethoxycarbonylmethyl)-2-methylpyridinium chloride (Equation (2)) ⟨81MI 809-01⟩.

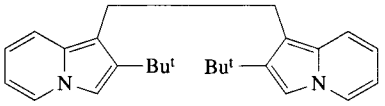


R = C_1-C_7 alkyl

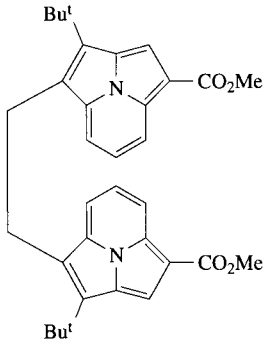
(**61**) (2)

From 1,4-di(2-pyridyl) butane with $BrCH_2$—$COBu^t$ (**62**) was obtained. Cycloaddition with methyl propiolate afforded (**63**) which was reduced by $LiAlH_4$ followed by dehydration to give the unstable cyclazinophane (**64**) ⟨82H(17)325⟩.

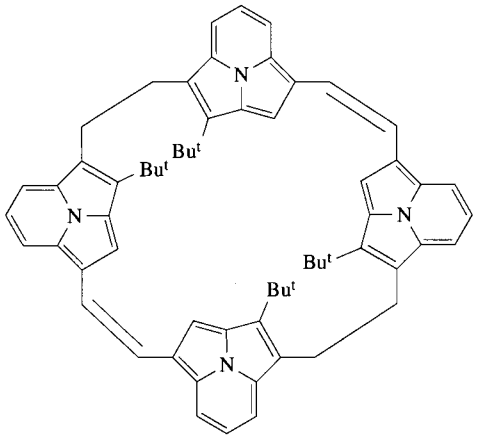
Compound (**66**) was prepared by one-pot successive 1,3-dipolar cycloadditions of pyridinium methylide (**65**) with benzyne ⟨82CL869⟩. Similar cycloadditions have been carried out with electron-deficient alkynes in a 2-phase system ⟨84JCR(S)202⟩; derivatives (**67**) were obtained with 1-nitro-2-(phenylthio)ethene ⟨88H(27)2345⟩ and a reaction of pyridinium salts (**68**) with $(MeS)_2C{=}CHNO_2$ gave indolizines (**69**) (Equation (3)) ⟨89JHC477⟩. Microwave irradiation induces a specific effect on the reaction, selectivity may be increased by using neutral bentonite as support ⟨94H(38)785⟩. A reaction in the presence of the new oxidant TPCD ($Py_4Co(HCrO_4)_2$) has been reported ⟨93JCS(P1)2487⟩.



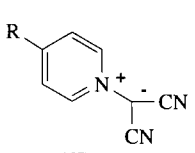
(62)



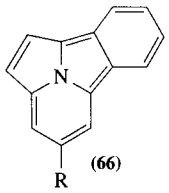
(63)



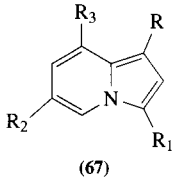
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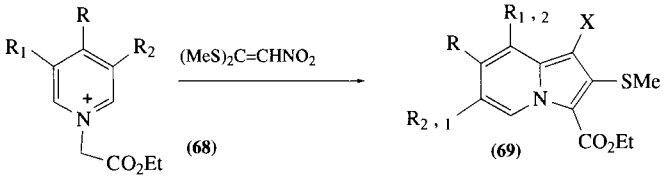
(65)



(66)

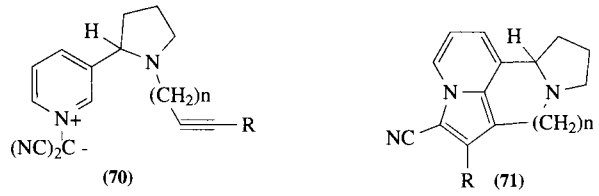


(67)



(68) (69) (3)

Thermally induced intramolecular cycloaddition reactions of nicotinium dicyanomethylides (**70**) led to novel, heterocyclically annulated indolizines (**71**) ⟨93AP(326)443⟩.



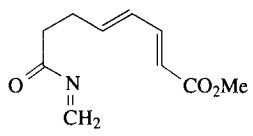
(70) (71)

Rhodium(II) catalyzed reaction of α-diazoazetophenone in the presence of 2-(methylthio)pyridine and DMAD gave 3-benzoyl-1,2-dicarbomethoxy-5-(methylthio)indolizine. The formation of the product proceeds via a pyridinium ylide formed by attack of the nitrogen lone pair on the electrophilic keto carbenoid ⟨93JOC1144⟩.

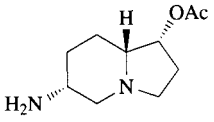
3-Substituted indolizines have been obtained from chlorocarbenes ClCR: with 2-vinylpyridine ⟨94CC509⟩.

8.09.7.3 Other Methods

An intramolecular Diels–Alder reaction of (**72**) was used to produce the indolizine skeleton and to establish the stereochemistry of slaframine (**73**) ⟨82JA7065⟩.

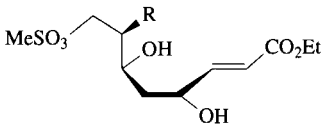


(72)

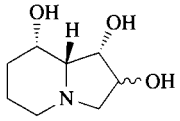


(73)

Two stereoisomers of swainsonine (**75**) were synthesized from D-glucose via (**74**) in a one-step cyclization ⟨85CL31⟩.

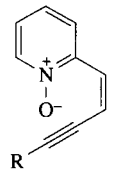


(74)

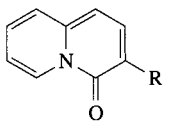


(75)

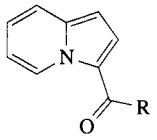
4-Oxo-4*H*-quinolizines (**77**) were formed together with 3-acylindolizines (**78**) on thermal activation of pyridine-*N*-oxide (**76**) ⟨89TL5591⟩.



(76)

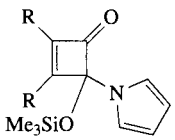


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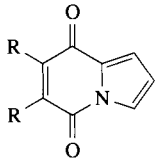


(78)

The key step of a synthesis of the alkaloid septicine involves ring expansion of the pyrrolylcylobutenone (**79**) to the corresponding indolizine-5-8-dione (**80**) ⟨94T6173⟩.

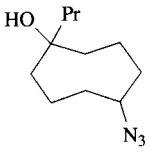


(79) R = 3,4(MeO)$_2$C$_6$H$_3$

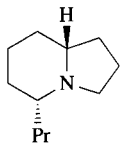


(80)

Under the conditions of the Schmidt reaction the azide group in (**81**) was captured intermolecularly by a carbocation, producing an aminodiazonium ion intermediate which subsequently rearranged yielding indolizidine 167B (**82**) ⟨93JA10183⟩.



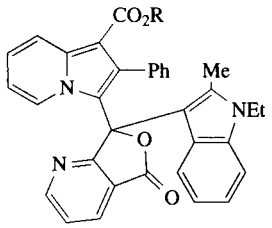
(81)



(82)

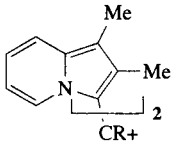
8.09.8 IMPORTANT COMPOUNDS AND APPLICATIONS

Indolizines are part of reversibly photochromic printing ink ⟨89EUP327788⟩. Chromogenic indolizines such as (**83**) have been prepared which may serve as pressure- or heat-sensitive mark forming systems ⟨81USP4275206⟩.



(83)

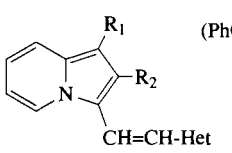
Carbenium ions (**84**) (R are heteroaryl substituents) are dyes showing halochromic properties ⟨83DP101⟩.



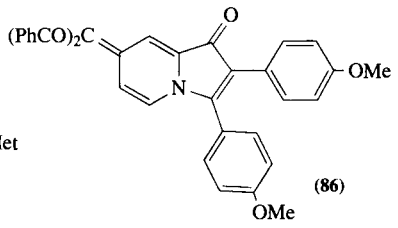
(84)

Indolizines (**85**) of cyanine and merocyanine type are dyes sensitizing silver halide emulsions in the red and orange region ⟨85EUP161789⟩.

Oxoindolizines such as (**86**) have a wide absorption range (visible-IR) and can be used in laser recording and reading and as image dyes ⟨83EUP68876⟩; 1,1- and 3,3-azoindolizines are useful for laser recording ⟨89JAP01260646⟩.



(85)



(86)

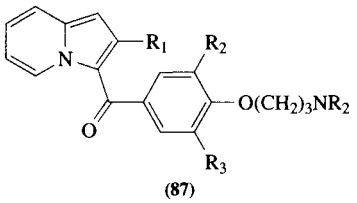
Indolizine alkaloids have been reviewed ⟨86MI 809-02, 88MI 809-01, 89MI 809-02, 93MI 809-02, 94MI 809-01⟩.

Chiral approaches to syntheses of bioactive indolizidine alkaloids have been reviewed ⟨92MI 809-01⟩.

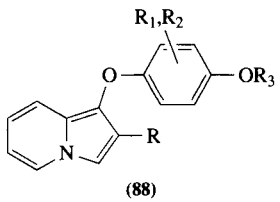
Indolizines were isolated from smoke condensate of cigarettes and shown to contribute to tobacco smoke flavor ⟨81MI 809-02⟩.

Indolizine esters containing electron-withdrawing groups in the 5-position are useful fluorophores which react with amines at the ester function to produce amides of use in the construction of biological probe compounds ⟨92JCR(S)362⟩.

Derivatives (**87**) showed effectiveness in the treatment of angina pectoris ⟨82EJM581, 83EJM339⟩ and indolizines (**88**) are cardiovascular agents ⟨88EUP235111⟩.



(87)



(88)

Indolizines are testosterone 3α-reductase inhibitors ⟨93EUP519353⟩ as well as 5-HT4 receptor antagonists ⟨93MIP9308187⟩ and calcium entry blockers ⟨93JMC1425⟩.

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8.10
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: One Extra Heteroatom 1 : 0

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Eastern Michigan University, Ypsilanti, MI, USA

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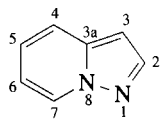
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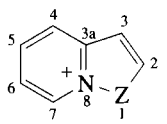
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8.10.1 INTRODUCTION

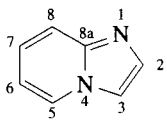
The subdivision of the heterocycles defined by the title of this chapter is based on the location of the heteroatom in the five-membered ring relative to the bridgehead nitrogen, and on the nature of the second heteroatom. In the first group, in which the heteroatoms are adjacent to one another, pyrazolo[1,5-*a*]pyridine (**1**) is treated separately, while isoxazolo [2,3-*a*]pyridine (**2**; Z = O) and isothiazolo[2,3-*a*]pyridine (**2**; Z = S) are treated together. Thereafter, the imidazopyridines, imidazo[1,2-*a*]pyridine (**3**) and imidazo[1,5-*a*]pyridine (**4**), are treated jointly, as are the oxazolopyridines, oxazolo[3,2-*a*] pyridine (**5**; Z = O) and oxazolo[3,4-*a*]pyridine (**6**; Z = O), and the thiazolopyridines, thiazolo[3,2-*a*]pyridine (**5**; Z = S) and thiazolo[3,4-*a*]pyridine (**6**; Z = S). The chapter concludes with a brief treatment of ring systems containing a heteroatom other than nitrogen, oxygen, or sulfur in the five-membered ring. The structures shown below are in all cases the fully conjugated systems, some of which are cationic.



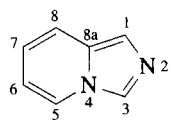
(1)



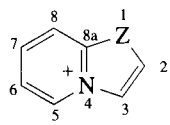
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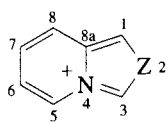
(3)



(4)



(5)



(6)

8.10.2 PYRAZOLO[1,5-*a*]PYRIDINE

Pyrazolo[1,5-*a*]pyridine was treated, along with many other fused pyrazoloazines, diazines and triazines, in Volume 5, Chapter 4.5 of the first edition of *Comprehensive Heterocyclic Chemistry*. In addition, a review of the chemistry of the five isomeric pyrazolopyridines, covering the literature through June 1982, has been published ⟨84AHC(36)343⟩. Although rare, the older names of 3-azaindolizine or pyrazolo[2,3-*a*]-pyridine occasionally still appear in the literature. The great majority of the published work concerns the fully conjugated systems. A brief treatment of perhydropyrazolo[1,5-*a*]pyridine may be found in a review of some saturated bicyclic 6/5 ring fused systems ⟨90AHC(49)193⟩.

8.10.2.1 Theoretical Methods

The results of a number of calculations of electron densities for pyrazolo [1,5-*a*]pyridine were collected in the first edition. A further set of values for π, σ, and total electron densities from an INDO MO calculation have been presented ⟨80JST(64)15⟩. No significant differences from the earlier values were found. An *ab initio* calculation of Mulliken net charges has also been carried out ⟨88JA2699⟩. An AM1 calculation of the total electron densities for the carbons of the six-membered ring of 3-bromo-2-isopropylpyrazolo[1,5-*a*]pyridine correctly predicted that C-6 would be the site of substitution of the second bromine ⟨92CPB639⟩. An *ab initio* calculation of the distribution of charge at the ring atoms of 3,5-dimethylpyrazolo[1,5-*a*]pyridine using the 6-31G* basis set was carried out on a supercomputer. Comparison of the results to those of other calculations showed that use of the ST03-G basis set or a MNDO calculation gave results qualitatively similar to those of the 6-31G* set, but that this was not the case when the AM1 or PM3 procedures were used ⟨94AP(327)435⟩.

8.10.2.2 Experimental Structural Methods

8.10.2.2.1 X-ray studies

The structures of several compounds containing the pyrazolo[1,5-*a*]pyridine ring system have been established by x-ray crystallography ⟨90CPB2667, 91TL4977, 94AJC991⟩.

8.10.2.2.2 NMR spectroscopy

(i) ^{1}H and ^{13}C NMR

Detailed assignments for both the ^{1}H spectrum (δ and J values) and the ^{13}C spectrum of pyrazolo[1,5-*a*]pyridine were reported in the first edition. Essentially identical absorption positions and assignments were made for the ^{13}C spectrum in two later investigations ⟨80JST(64)15, 87JHC805⟩. In the first of these a linear correlation was found between the ^{13}C chemical shifts and the total, rather than the π, charge densities as calculated by the INDO MO procedure. Data from substituted compounds have been routinely reported. ⟨81JHC1149, 87CPB156, 94AJC1009, 94H(38)1881⟩.

(ii) ^{14}N and ^{15}N NMR

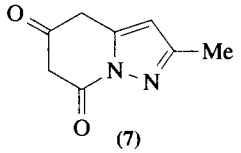
Both ^{14}N and ^{15}N NMR spectra have been recorded ⟨82OMR(18)87, 84OMR(22)209, 90MRC988⟩. In general, because of the difference in the extent of delocalization of the lone pair in "pyrrole-type" and "pyridine-type" nitrogens, differences in shielding and hence, in chemical shifts are to be expected. In azaindolizines the bridgehead nitrogen, a "pyrrole-type" nitrogen, generally gave a significantly sharper signal in the ^{14}N spectrum. This permitted easy assignment of the signal. For pyrazolo[1,5-*a*]pyridine in DMSO this signal was found shielded by 144.09 ppm relative to neat nitromethane, while that for N-1 was shielded by 93.23 ppm ⟨90MRC988⟩. As is typical for "pyridine-type" nitrogens, substantial solvent shifts were observed for the N-1 absorption while they were relatively insignificant for the bridgehead nitrogen. The differences between the shieldings for the

bridgehead and other nitrogens in some di- and triazaindolizines, including pyrazolo[1,5-*a*]pyridine, have been correlated with the differences in net electronic charge at the atoms concerned. It was, however, recognized that electronic charge differences between the nitrogen atoms were not the most important contributory factor to the generation of shielding differences ⟨89MRC88⟩.

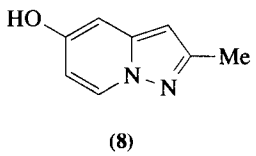
8.10.2.3 Thermodynamic Aspects

8.10.2.3.1 Tautomerism

It is commonly the case that compounds with oxygen substituted α or γ to a nitrogen in six-membered heteroaromatic rings favor the carbonyl tautomer. In agreement with this generalization, compound (**7**) exists entirely in the keto form ⟨85H(23)2251⟩. On the other hand compound (**8**) has been claimed, largely on the basis of ^{13}C NMR results, to exist as the hydroxy tautomer ⟨94AJC1009⟩. Substitution in five-membered rings is a different matter and, as reported in the first edition, the substituent at C-2 exists entirely as the hydroxy group. In parallel with this, the corresponding sulfur compound exists as the 2-thiol ⟨90CPB2662⟩.



(**7**)



(**8**)

8.10.2.4 Reactivity of Fully Conjugated Rings

Pyrazolo[1,5-*a*]pyridine can be considered as an aromatic system in which the bridgehead nitrogen is a "pyrrole-type" nitrogen, contributing a lone pair of electrons to complete the Hückel number of 10 π-electrons. Looking at its reactions the system is probably more appropriately considered a π-excessive (five-membered) ring fused to a π-deficient (six-membered) ring. The most common reactions are electrophilic substitutions. Compounds containing strongly activating substituents in the six-membered ring may direct some electrophilic substitutions into that ring ⟨94AJC1009⟩ but, if C-3 is open, reaction almost always occurs there. Examples of nitration, sulfonation, acylation, bromination, and nitrosation reactions were given in the first edition. Further examples of some of these and of other electrophilic substitutions are given below. Not surprisingly, nucleophilic substitution does not take place in the parent system, but halogens suitably positioned in the six-membered ring may be displaced. Oxidation and reduction do not occur readily, but, when they do, it is usually the six-membered ring that is affected.

8.10.2.4.1 Electrophilic attack at nitrogen

The "pyrrole-like" nature of the bridgehead nitrogen and "pyridine-like" nature of N-1 certainly suggest that reaction would be expected to occur at N-1. The first edition described UV data which indicated that N-1 was the site of protonation. Further experimental support for this has come from magnetic circular dichroism spectra ⟨85JOC302⟩, and from the measurement of the proton affinity in the gas phase using ICR spectroscopy ⟨88JA2699⟩.

8.10.2.4.2 Electrophilic attack at carbon

(i) Nitration

Reaction of (**8**) under carefully controlled conditions occurred first at C-4 and then at C-3. Under the same conditions the acetate of (**8**) reacted first at C-3 ⟨94AJC1009⟩.

(ii) Halogenation

Bromination of 2-isopropylpyrazolo[1,5-*a*]pyridine occurred as expected at C-3. This was followed by a synthetically useful selection for C-6 ⟨92CPB639⟩.

(iii) Acylation

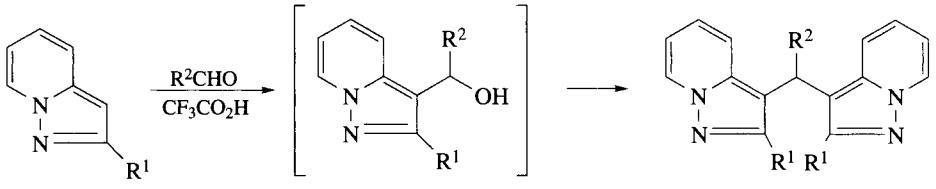
Numerous examples of acylation at C-3 have appeared. Reactions have been carried out with acid anhydrides ⟨92CPB631⟩, acid halides ⟨86CPB2833, 85MI 810-01⟩, aryl sulfonyl chlorides ⟨93JMC1425⟩ and under Vilsmeier–Haack conditions ⟨93H(35)915⟩. Yields were generally better, and the required conditions milder, when C-2 carried an electron-releasing group. No reaction occurred when ethyl 2-pyrazolo[1,5-*a*]pyridinecarboxylate was heated with benzoyl chloride ⟨93H(35)915⟩.

(iv) Alkylation

The parent compound failed to react with several activated alkenes, but the 3-substituted compound was formed, albeit in poor yield, on reaction with benzoylacetylene. 2-Phenylpyrazolo[1,5-*a*]pyridine was significantly more reactive ⟨94H(38)1881⟩.

(v) Reaction with aldehydes

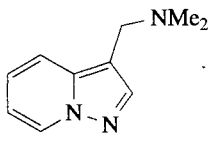
Reaction occurred at C-3, but in the presence of the acid catalyst, the first-formed product (**9**) reacted further to produce high yields of bispyrazolo[1,5-*a*]pyrid-3-ylmethanes (**10**) (Scheme 1) ⟨93JHC1045⟩.



Scheme 1

(vi) The Mannich reaction

Reaction of the parent compound with Eschenmoser's salt proceeded smoothly to yield (**11**) ⟨94H(38)1881⟩. The acetate of (**8**) reacted similarly ⟨94AJC1009⟩.

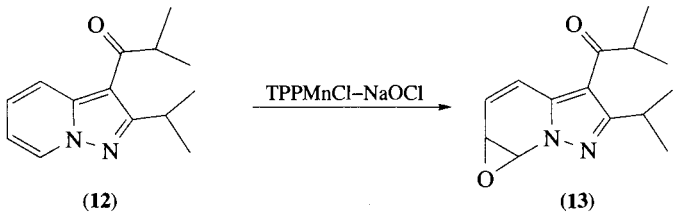


(**11**)

(vii) Oxidation

Attempts to oxidize (**12**) with hydrogen peroxide, MCPBA or hypochlorite were unsuccessful. However, the use of a cytochrome P450 chemical model, *meso*-tetraphenylporphyrinatomanganese

chloride, as a catalyst with sodium hypochlorite produced the 6,7-epoxide (**13**) (Equation (1)). The 4,5;6,7-diepoxide was prepared similarly ⟨89CPB1410⟩.



(12) (13) (1)

8.10.2.4.3 Nucleophilic attack at carbon

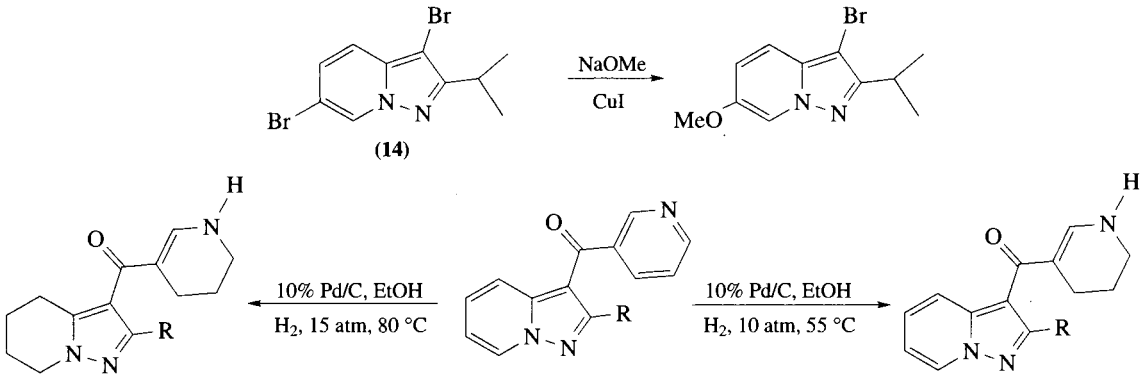
Nucleophilic substitution of hydrogen has not been reported, but the displacement of halogens suitably positioned in the six-membered ring as in (**14**) was readily achieved ⟨92CPB639⟩.

8.10.2.4.4 Nucleophilic attack at hydrogen

Reaction of pyrazolo[1,5-*a*]pyridine with *n*-butyllithium at −78 °C selectively deprotonated C-7. This was suggested to be due to chelation with the *peri* nitrogen. Reaction with various electrophiles then completed a valuable method for regioselective substitution at C-7 ⟨92JOC5538⟩.

8.10.2.4.5 Reactions at surfaces

The ring system is fairly resistant to reduction, and halogen atoms were removed by reaction with hydrogen using a palladium-on-charcoal catalyst ⟨92CPB639⟩. When more forcing conditions were used, the six-membered ring was reduced (Scheme 2) ⟨86CPB2828, 88AP(321)517⟩.



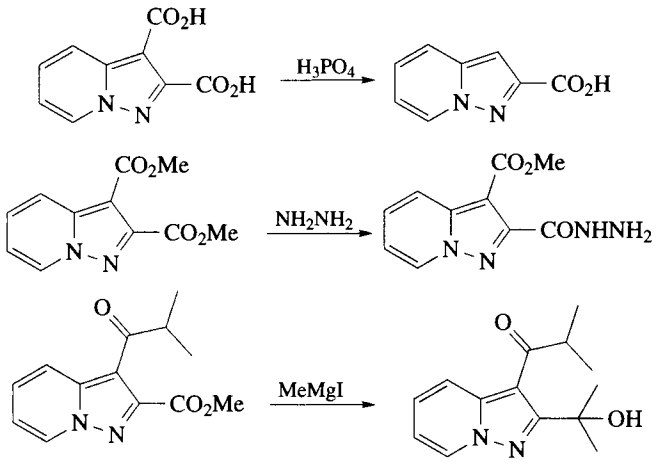
Scheme 2

8.10.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

8.10.2.5.1 Carboxylic acids and esters

Useful differences in reactivity were found between substituents at C-2 and C-3. This was rationalized by recognizing that those at C-3 can be expected to display some of the characteristics of

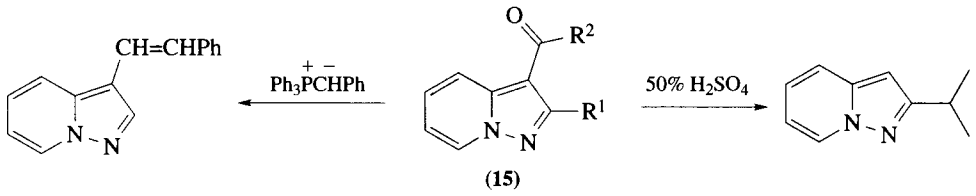
vinylogous carbamic acids and urethanes. Hence the carboxylic acid group at C-3 was subject to facile decarboxylation and was selectively removed by heating with acid, while the C-2 esters reacted preferentially with nucleophiles (Scheme 3) ⟨81JHC1149, 92CPB631⟩.



Scheme 3

8.10.2.5.2 Aldehydes

The formyl group at C-3 does show the normal reactions of an aldehyde, as evidenced by the successful Wittig reaction on (**15**; $R^1 = R^2 = H$) ⟨93H(35)915⟩. However, as was found for the carboxylic acid group, the C-3 acyl group of (**15**; $R^1 = Pr^i$, $R^2 = Me$) was readily removed by treatment with acid (Scheme 4) ⟨92CPB631⟩.



Scheme 4

8.10.2.6 Synthesis

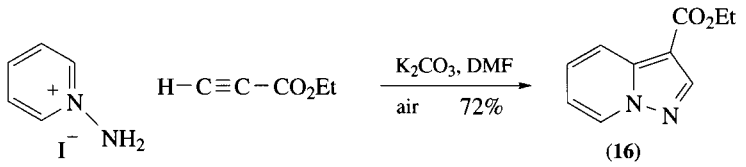
8.10.2.6.1 Fully conjugated rings

The earlier reviews described a number of synthetic approaches to this system. The most generally useful, however, were observed to be those starting with *N*-aminopyridinium derivatives and constructing the five-membered ring. The chemistry of *N*-aminoazonium salts, and heteroaromatic *N*-imines in general, has been reviewed ⟨81AHC(29)73⟩. Syntheses reported since the publication of the first edition continue to reflect the above-mentioned observation.

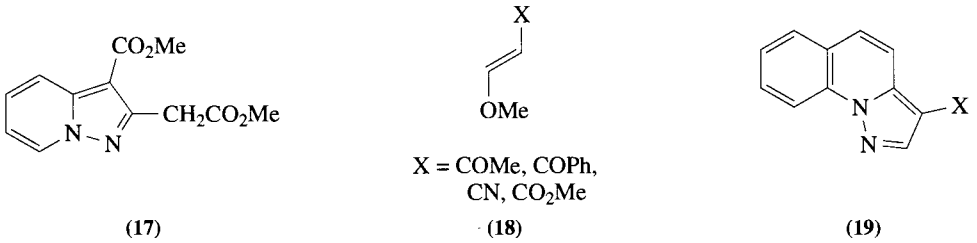
(i) Construction of the five-membered ring

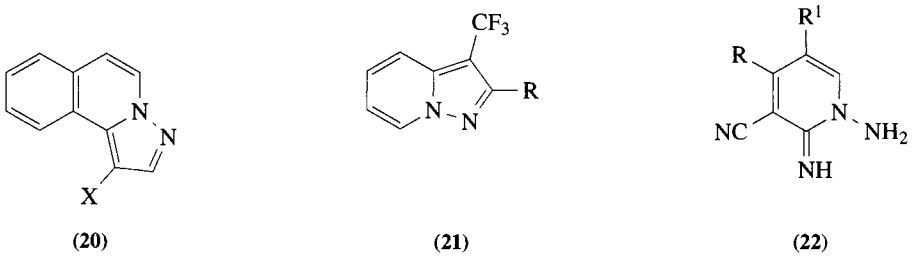
In the reaction of *N*-aminopyridinium salts with substituted alkynes, improved yields of the final product were claimed to result from the passage of air into the reaction mixture. Compound (**16**), for example, was obtained in 72% yield (Equation (2)) ⟨88AP(321)505⟩. A number of two-carbon units other than alkynes have been used. Amongst these were active methylene derivatives, for

example dimethyl 3-oxoglutarate, which gave compound (**17**) ⟨92CPB631⟩, and substituted vinyl compounds such as (**18**). The use of (**18**) led to 3-substituted pyrazolo[1,5-*a*]pyridines or, on reaction with *N*-aminoquinolinium and isoquinolinium salts, to the benzo derivatives (**19**) and (**20**) ⟨90JHC263⟩. The facile hydrolysis and decarboxylation of (**19**) or (**20**) where (X = CO_2Me) completed an attractive pathway to the parent compounds. The use of perfluoropropene or butene led to (**21**; R = F, CF_3) ⟨82JCS(P1)1593⟩. Formation of the same two bonds occurred in the condensation of 1-amino-2(1*H*)-pyridin-2-imines (**22**) with 1,3-dicarbonyl compounds. In this case, however, isolation of an intermediate showed that the C—C bond formed first ⟨94JHC1157⟩.



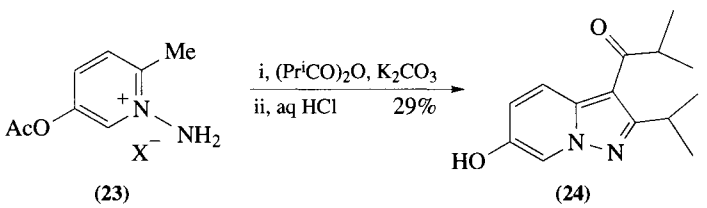
(2)



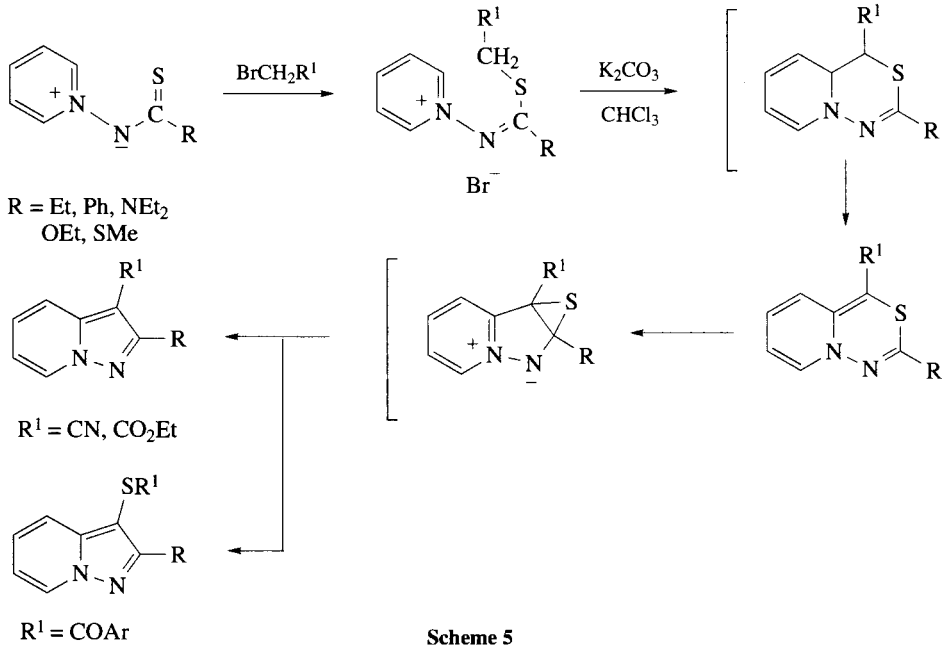


A recently developed related sequence is shown in Scheme 5 ⟨87CPB156⟩. The structure of the final product was found to be independent of the nature of R (R = Et, Ph, NEt_2, OEt, SMe) but to be strongly influenced by the nature of R^1. The involvement of 1,3,4-thiadiazine intermediates was demonstrated by NMR spectroscopy and, in a few cases, by isolation. Synthesis of the previously inaccessible pyrazolo[1,5-*a*]pyridine-2-thiols was achieved following this route, by initially protecting the thiol as, for example, the 2-cyanoethylthio group ⟨90CPB2662⟩.

All of the above syntheses are compatible with substituents on the six-membered ring. However, the use of 3-substituted *N*-aminopyridinium salts unsubstituted at C-2 and C-6 produced mixtures. In the reactions with alkynes, mixtures of 4- and 6-substituted pyrazolo[1,5-*a*]pyridines in varying ratios were obtained ⟨75JCS(P1)406⟩. More recent syntheses gave similar ratios of isomers to those found previously ⟨93BMC1477, 85BCJ1432⟩. Selective syntheses of these compounds have been achieved using the alternative approach as shown for the synthesis of (**24**) (Equation (3)) ⟨92CPB639⟩. The moderate yield (29%) obtained, however, is in line with previous experience using this approach ⟨84AHC(36)343⟩.



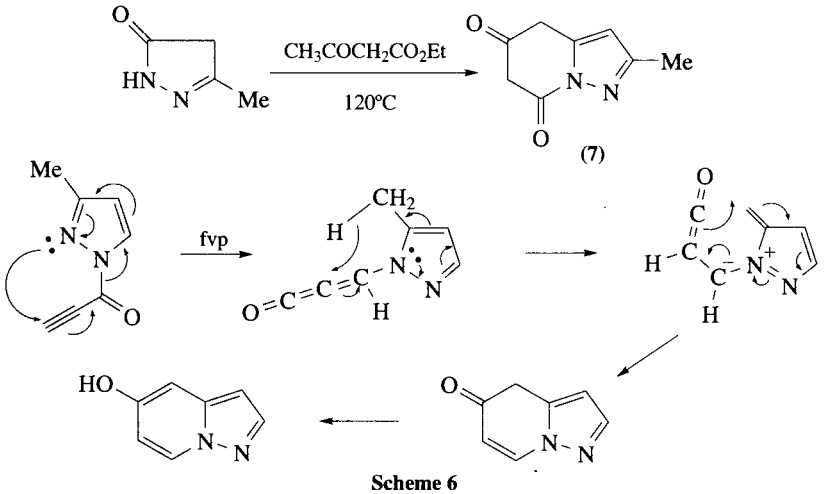
(3)



Scheme 5

(ii) Construction of the six-membered ring

A few examples of individual syntheses of this type were noted in the first edition, and the production of (7) should be added to these ⟨85H(23)2251⟩. A more general approach involving flash vacuum pyrolysis of 1-(alkyn-2-oyl)-3-methylpyrazoles has now been developed ⟨94AJC991⟩. The proposed mechanism is shown in Scheme 6.

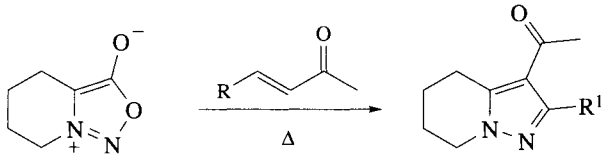


Scheme 6

8.10.2.6.2 Saturated and partially reduced rings

The first edition contained little information on the synthesis of these systems. This is also true of other relevant reviews ⟨84AHC(36)343, 90AHC(49)193⟩ and, indeed, the ring systems do appear to have been largely neglected. The favored route to the 4,5,6,7-tetrahydro system is probably reduction of the fully conjugated system (Section 8.10.2.4.5), but the direct synthesis of a series of 3-acyl

derivatives by 1,3-dipolar cycloaddition to the sydnone (**25**) followed by loss of carbon dioxide has been reported (Equation (4)) ⟨89TL4625⟩. When R = alkyl, loss of RH competes with loss of H_2.



(25) R^1 = R or H (4)

8.10.2.7 Important Compounds and Applications

Much of the work on pyrazolo[1,5-*a*]pyridines has been stimulated by the variety of physiological activities that have been claimed for these compounds. Amongst these claims are those for anti-asthmatic, antiallergic, and cerebral activity ⟨B-89MI 810-01⟩, inhibition of platelet aggregation ⟨86CPB2833, 84EUP121197⟩, inhibition of cardiac infarction ⟨93JAP(K)0501063⟩, calcium antagonistic activity ⟨93JMC1425⟩, analgesic activity ⟨88AP(321)517⟩, dopamine autoreceptor agonistic activity ⟨93BMC1477⟩ and serotonin antagonistic activity ⟨92JAP(K)04257591⟩. Of the many compounds involved in these claims, only compound (**12**), known as ibudilast or KC404, appears to be listed in the current Merck Index where it is reported as an antiasthmatic, antiallergenic, cerebral vasodilator.

8.10.3 ISOXAZOLO[2,3-*a*]PYRIDINE AND ISOTHIAZOLO[2,3-*a*]PYRIDINE

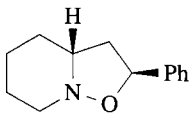
In the first edition these systems were treated in Volume 6, Chapter 4.29. They were discussed, along with many other systems, in the sections on "Isoxazole fused with Azines" and "Isothiazole fused with Azines." Very little information was available on isothiazolo[2,3-*a*]pyridines, while most of that on the isoxazolo[2,3-*a*]pyridines concerned the saturated system. Further discussion of this latter system was included in a wide-ranging review of saturated 6/5 bicyclic ring fused systems with bridgehead nitrogen ⟨90AHC(49)193⟩. The intervening years have done little to change the situation referred to above, and the limited number of subsections that follow is a reflection of this.

8.10.3.1 Experimental Structural Methods

8.10.3.1.1 NMR spectroscopy

A limited amount of ^{1}H NMR data was found for the fully conjugated rings in the few papers dealing with their syntheses (Section 8.10.3.5.1). In the perhydroisoxazolo[2,3-*a*]pyridines the ^{1}H spectra were complex and were seldom assigned. On the other hand the assignment of the absorptions for the ^{13}C spectra of a number of substituted compounds has been performed ⟨93MRC12⟩. When, as was often the case, the compound existed in solution as a mixture of *trans*-fused and *cis*-fused conformers, the absorptions for the *cis* conformers, apart from that for C-2, were upfield of those for the corresponding carbon in the *trans* conformer (Table 1).

Table 1 Carbon-13 NMR spectral data ($CDCl_3$ at −20°C) for

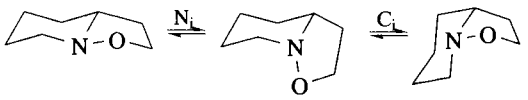


	C (2)	*C (3)*	*C (3a)*	*C (4)*	*C (5)*	*C (6)*	*C (7)*
trans conformer	77.32	43.02	66.62	29.23	24.72	23.71	55.01
cis conformers	78.35	38.94	59.81	25.12	23.87	18.45	49.90

8.10.3.2 Thermodynamic Aspects

8.10.3.2.1 Conformations

The perhydroisoxazolo[2,3-*a*]pyridine ring system can exist as a mixture of the three conformers (**26**), (**27**), and (**28**) (Scheme 7). The two *cis*-fused conformers are interconverted by chair inversion (C_i) while one *cis* conformer (**27**) is converted to the *trans* conformer by nitrogen inversion (N_i). The barrier to nitrogen inversion is known to be raised by the presence of an α oxygen atom ⟨81AG(E)521⟩, and complete band shape analyses of the 50.3 MHz ^{13}C NMR spectra of a number of substituted perhydroisoxazolo[2,3-*a*]pyridines provided values for $\Delta G^{\ddagger}$ for the nitrogen inversion process in the range 65.2–69.0 kJ mol^{-1} ⟨93MRC12⟩. In a number of cases only the *trans* conformer was detected, but in those cases where equilibrium mixtures of conformers were present, ΔG° values ranged from about 1–5.5 kJ mol^{-1}. Further analysis of the spectra suggested that the minor component consisted of a mixture of the *cis* conformers with type (**27**) favored.



(**26**) (**27**) (**28**)

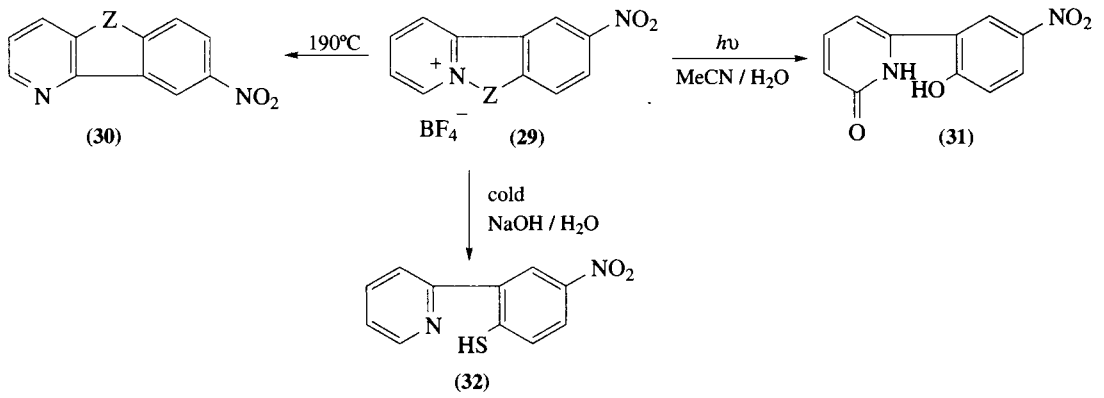
Scheme 7

8.10.3.3 Reactivity of Fully Conjugated Rings

Little information is available concerning either system. The isothiazolium ring is known to be unstable in the presence of nucleophiles, and products of attack at sulfur have been reported.

8.10.3.3.1 Thermal and photochemical reactions

Significant differences have been reported between the behavior of the benzisoxazolo-[2,3-*a*]pyridinium and benzthiazolo[2,3-*a*]pyridinium cations. On heating (**29**; Z = O) rearranged to (**30**; Z = O) via an aryl oxenium ion intermediate. Similar treatment of (**29**; Z = S) resulted in no reaction or gave intractable residues in which no (**30**; Z = S) could be detected ⟨82JHC509⟩. In a similar vein, photolysis of (**29**; Z = O) yielded (**31**) while (**29**; Z = S) was recovered unchanged (Scheme 8) ⟨82JHC509⟩.



(**30**) (**29**) (**31**) (**32**)

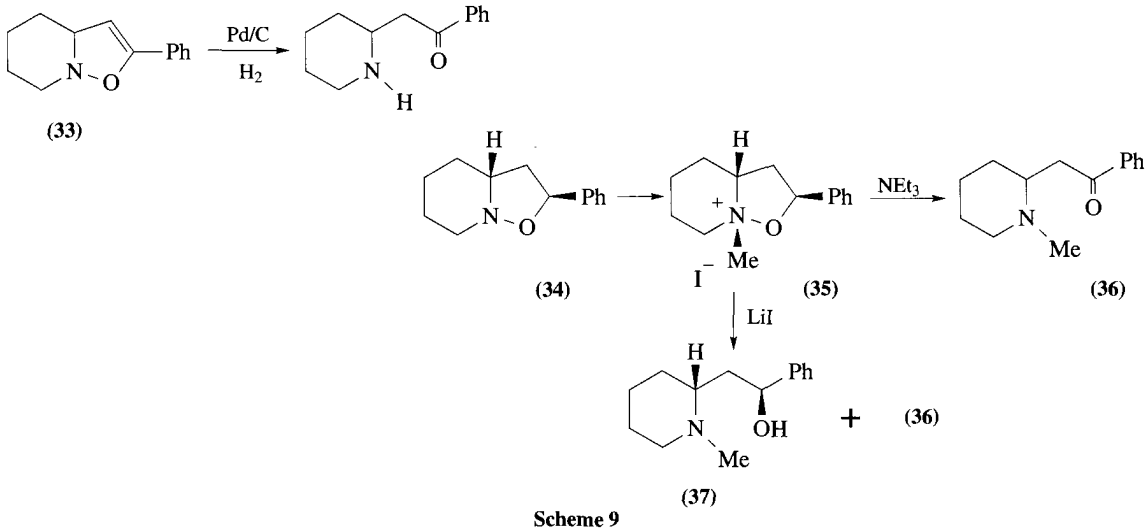
Scheme 8

8.10.3.3.2 Nucleophilic attack

On treatment with cold aqueous sodium hydroxide, salt (**29**; Z = S) was converted to the thiophenol (**32**). The reaction was envisaged to proceed via attack by hydroxide on sulfur to yield the sulfenic acid, followed by a dismutation reaction (Scheme 8) ⟨82JHC509⟩.

8.10.3.4 Reactivity of Saturated and Partially Reduced Rings

Essentially all of the reactions of interest involve the opening of the five-membered ring. Reductive cleavages of the N—O bond in isoxazolines and isoxazolidines have been known for many years, and were reported on in the first edition. One recent application was the conversion of a fused isoxazoline (**33**) to a β-amino ketone ⟨88TL5917⟩. An alternative sequence leading to these synthetically useful compounds first quaternized the N of a perhydro compound (**34**) and then reacted the product with a tertiary amine ⟨88TL5949⟩. If the quaternary salt (**35**) was reacted with lithium iodide, a readily separable mixture of the ketone (**36**) and (±)-allosedamine (**37**) resulted (Scheme 9) ⟨89CB2019⟩.

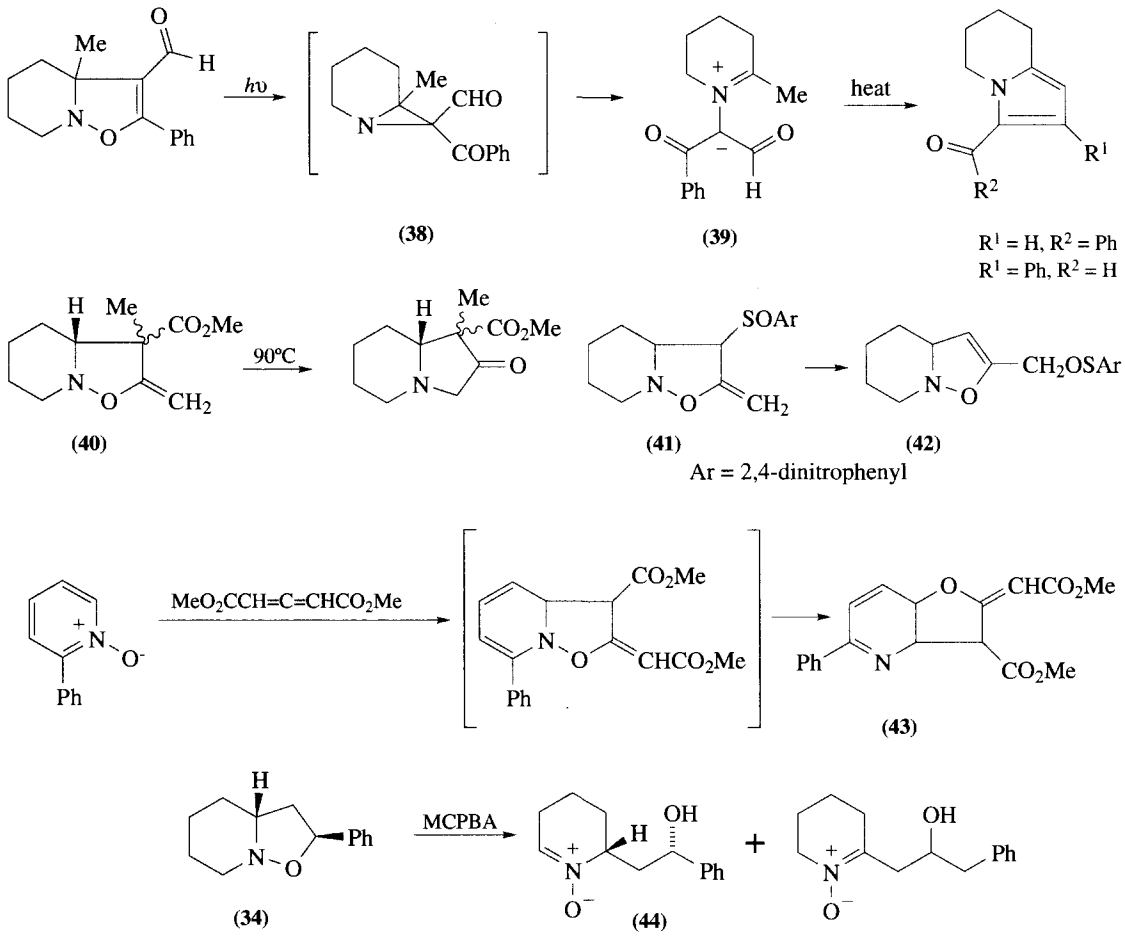


Scheme 9

Unusually stable azomethine ylides (**39**) have been produced by the UV-induced cleavage of suitably substituted fused isoxazolines. It was proposed that the reaction proceeded via an initial symmetry-allowed conversion to an acyl aziridine (**38**) followed by ring opening. On heating, the azomethine ylides were converted to tetrahydroindolizines (Scheme 10) ⟨94MI 810-01⟩.

An interesting thermally induced rearrangement of certain 2-*exo*methylene substituted perhydroisoxazolo[2,3-*a*]pyridines, for example (**40**), converted them to indolizidinones ⟨88JOC955⟩. The reaction was thought to proceed via homolytic cleavage of the N—O bond. The related 3-sulfoxide (**41**) could not be isolated as it underwent a very facile 2,3 sigmatropic rearrangement to the allylic sulfenate (**42**) ⟨91JOC4252⟩. Yet a further type of rearrangement of this class of compounds, also thought to proceed via a biradical pathway, was involved in the formation of (**43**) (Scheme 10) ⟨94H(37)257⟩.

The oxidative ring opening of a perhydroisoxazolo[2,3-*a*]pyridine is an important reaction since it produces a substituted nitrone suitable for further synthetic use. An early report that oxidation of (**34**) with MCPBA yielded only the less substituted nitrone (**44**) ⟨86TL1489⟩ has been shown to be incorrect. Mixtures with (**44**) as the minor component were obtained (Scheme 10) ⟨90JCS(P1)2323, 91SL47, 93T7373⟩. The product mixture obtained, in this and several similar cases, has been correlated with the conformational mix adopted by the starting material. It was suggested that the *trans* isomer led to the more substituted nitrone and the *cis* isomers to the less substituted nitrone ⟨93T7373⟩. This is possible because, as previously indicated in Section 8.10.3.2.1, there is a high energy barrier to interconversion of the *cis* and *trans* isomers by nitrogen inversion.



Scheme 10

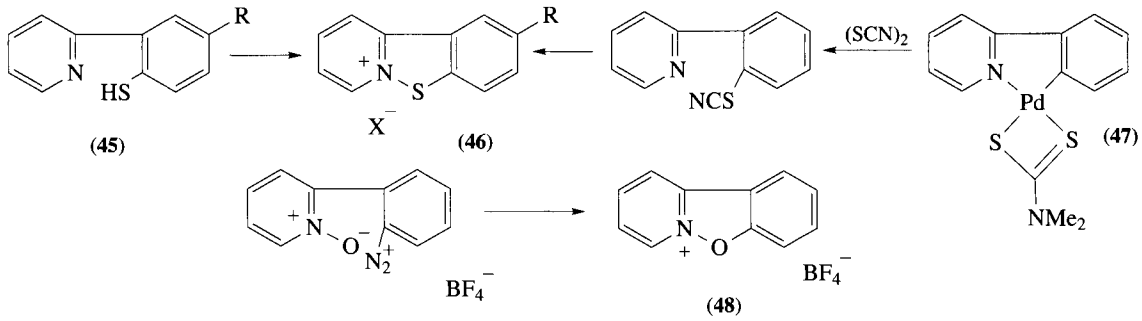
8.10.3.5 Synthesis

8.10.3.5.1 Fully conjugated systems

No further syntheses of either the isothiazolo- or isoxazolo[2,3-*a*]pyridinium cations have appeared in the literature, but syntheses of the benzo derivatives have been recorded. In all cases, not surprisingly, the syntheses involved construction of the five-membered ring. Conversion of the thiol (**45**; R = H) to the desired product (**46**; R = H, X = I_3) was carried out by oxidation with iodine ⟨85CJC882⟩ while conversion of (**45**; R = NO_2, CN) to (**46**; R = NO_2, CN, X = BF_4) was done by treatment with NCS followed by silver tetrafluoroborate ⟨82JHC509⟩. The perchlorate salt of (**46**; R = H) has also been prepared from the cyclopalladated complex (**47**). Although only the unsubstituted compound was prepared by this sequence, it was claimed to be compatible with a wide range of substituents (Scheme 11) ⟨90JCS(P1)2881⟩. The unsubstituted benzisoxazolo[2,3-*a*]pyridinium cation (**48**) was made via an intramolecular phenylation reaction ⟨78MI 810-01⟩.

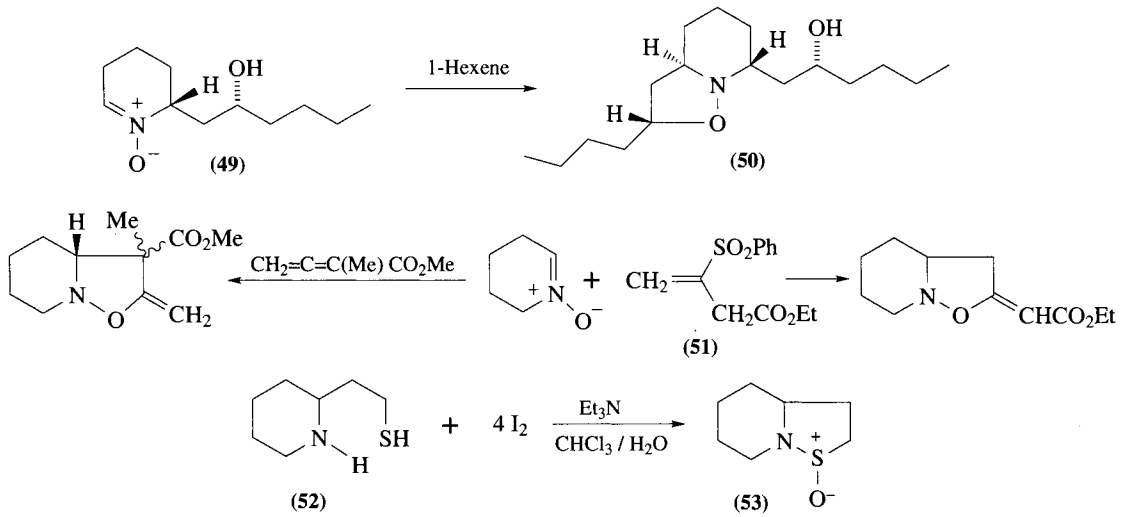
8.10.3.5.2 Saturated and partially reduced rings

The importance of fully or partially hydrogenated isoxazolo[2,3-*a*]pyridines as intermediates in the synthesis of stereochemically complex molecules, particularly alkaloids, has led to a continued high level of interest in their preparation. The route of choice remains the 1,3-dipolar cycloaddition reaction between a tetrahydropyridine *N*-oxide, that is a nitrone, and a dipolarophile. A number of methods for the production of the nitrone for *in situ* reaction have been developed. They include the oxidation of the secondary amine, piperidine, with hydrogen peroxide in the presence of



Scheme 11

catalytic amounts of tungstate or selenium dioxide ⟨90JOC1736, 87TL2383⟩ and the oxidation of the hydroxylamine by palladium black, tetra-*n*-propylammonium perruthenate, photochemically, or electrochemically ⟨83TL1049, 94TL6571, 87TL2649, 86JOC549⟩. In reactions with alkenes the basic questions of regioselectivity, where production of the 2-substituted compound is favored, and stereoselectivity, where the *exo* mode is favored, were reported on in the first edition and have been discussed further by Tufariello ⟨B-84MI 810-01⟩. Later results with alkenes and alkynes remain in line with these earlier findings ⟨90JCS(P1)2323, 88TL5949, 90JCS(P2)1035, 88T5911, 88TL5917⟩. With substituted nitrones such as (**49**) the attack of the dipolarophile was on the less hindered face and in the *exo* mode. This produced compounds such as (**50**), key intermediates in the syntheses of *trans*-2,6-disubstituted piperidines (Scheme 12) ⟨90JCS(P1)2323, 89JCS(P1)2415⟩. Efforts at asymmetric syntheses have largely used alkenes carrying chiral auxilliaries. The most useful, chiral allyl and vinyl ethers and chiral crotonates, produced perhydroisoxazolo[2,3-*a*]pyridines in high yields, with values for the diastereomeric excess >90% ⟨92TL3765, 91MI 810-01, 93SL395⟩.



Scheme 12

The reactions of allenes with nitrones were promoted by the presence of an electron-withdrawing group on the allene. Addition took place across the activated double bond ⟨88JOC955⟩. The alternative mode of addition was achieved by using the allene equivalent (**51**) (Scheme 12) ⟨89JOC810⟩.

In the sulfur series oxidation of the thiol (**52**) with aqueous iodine produced the sulfur lactam analogue (**53**) (Scheme 12) ⟨90JOC4156⟩.

8.10.4 IMIDAZO[1,2-*a*]PYRIDINE AND IMIDAZO[1,5-*a*]PYRIDINE

Earlier reviews of these systems may be found in Volume 5, Chapter 4.10 of the first edition of *Comprehensive Heterocyclic Chemistry*, and in the Weissberger series on heterocyclic chemistry ⟨61HC(15-1)460, 61HC(15-1)643, 77HC(30-2)117⟩. The broad range of useful pharmacological activities

shown by substituted imidazo[1,2-*a*]pyridines has resulted in a large volume of published work since the appearance of the first edition. On the other hand relatively little new chemistry has been found for the imidazo[1,5-*a*]pyridines, and the earlier treatment does not require substantial expansion.

8.10.4.1 Theoretical Methods

The results of quantum chemical calculations were rather fully described in an earlier review ⟨77HC(30-2)117⟩. More recently CNDO/2 and MNDO calculations for imidazo[1,2-*a*]pyridines and some simple derivatives were carried out using parameters obtained from an x ray study ⟨82AJC1761, 88JCR(S)324⟩. The results were not dramatically different from those of the earlier studies. *Ab initio* calculations using the minimal basis set (STO-3G) and, much more satisfactorily, a split-valence basis set (4-31G) were used to obtain Mulliken net charges for both parent systems ⟨88JA2699⟩. Proton affinities were also calculated. The values obtained compared well with those measured using ICR techniques and showed imidazo[1,2-*a*]pyridine to be more basic than the [1,5-*a*] fused isomer.

An alternative approach to the rationalization of reactivity patterns, involving the three-dimensional visualization of molecular electrostatic potential surfaces, has had some success in explaining the results of the nitration of substituted imidazo[1,2-*a*]pyridines ⟨85EJM501⟩.

8.10.4.2 Experimental Structural Methods

Considerable spectroscopic data has been recorded for the many compounds synthesized in recent years, but, as far as the IR, UV, and mass spectra are concerned, the earlier compilations are entirely adequate ⟨77HC(30-2)117⟩.

8.10.4.2.1 X-ray studies

The structures of a number of imidazo[1,2-*a*]pyridines have been determined, and a few references are cited below. In most cases the objective was structural confirmation. As expected the ring system was planar, and in all cases the results were unexceptional ⟨82AJC1761, 84HCA1897, 85JMC876, 86JCR(S)202, 89JMC1686, 90CB327, 94JOC5084⟩.

8.10.4.2.2 Ultraviolet and fluorescence spectroscopy

Rotational band contour analysis ⟨89JSP(138)398⟩ and CNDO/S calculations ⟨92MI 810-01⟩ showed that the low energy absorption in the UV spectra of imidazo[1,2-*a*]pyridines was of the π–π^* type. Both ring systems showed fluorescence with very high quantum yields, and gave spectra with maxima around 370 nm for the [1,2-*a*] and 440 nm for the [1,5-*a*] fused parent compounds ⟨77JPC12⟩. In the [1,2-*a*] series, fluorescence was lost on introduction of a nitro group or on reduction of the pyridine ring, but for a number of simple derivatives, a linear relationship with concentration was shown to hold down into the nanogram range ⟨79MI 810-01⟩. Fluorescence maxima at much longer wavelengths have been reported for some highly substituted 7-arylimidazo[1,2-*a*]pyridines (469–525 nm) ⟨90CB327⟩ and for 2-(2-hydroxyphenyl)imidazo[1,2-*a*]pyridine (599 nm) ⟨95JPC76⟩. The nature of the excited-state processes for this latter compound and the corresponding 3-substituted [1,5-*a*] system were shown to be quite different ⟨95JPC76⟩. Attempts were made to utilize the fluorescent properties of the [1,5-*a*] system for the analysis of low concentrations of chloroform ⟨91JOC2400⟩ and of the [1,2-*a*] system for the marking of hypoxic cells ⟨92JMC1920⟩.

8.10.4.2.3 NMR spectroscopy

(i) Proton NMR

The spectra of the parent compound and of some simple derivatives were collected in an earlier review ⟨77HC(30-2)117⟩. A few citations of papers containing data for substituted [1,2-*a*] ⟨80OMR(14)52, 81JOC1026, 91CPB1556⟩ and [1,5-*a*] fused systems ⟨80JHC555, 86AP(319)43⟩ are given.

The presence of H-3, useful for distinguishing between 2- and 3-substituted imidazo[1,2-*a*]pyridines, has been demonstrated by means of the characteristic long-range coupling between H-3 and H-8 ($J_{3,8} \approx 0.75$ Hz) ⟨90CB327⟩ or by the NOE shown on irradiation of H-5 ⟨91CPB1556⟩. No analogous NOE was, however, observed for 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine ⟨94JOC5084⟩. Alternatively, the presence of a substituent at C-3 may often be detected by the dramatic effect on the *peri* H at C-5 ⟨80OMR(14)52, 85CB4099⟩.

(ii) Carbon-13 NMR

No data were included in the earlier reviews so the assignments for the parent systems are shown in Table 2 ⟨87JHC805⟩. A sampling of sources of data for some substituted imidazo[1,2-*a*]pyridines ⟨79BSF(2)529, 81T83⟩ and imidazo[1,5-*a*]pyridines ⟨86AP(319)43⟩ is included.

Table 2 Carbon-13 spectral data (DMSO).

	1	*2*	*3*	*5*	*6*	*7*	*8*	*8a*
Imidazo[1,2-*a*]pyridine		133.2	112.9	126.5	111.7	124.1	116.9	145.0
Imidazo[1,5-*a*]pyridine	120.0		129.1	123.8	112.8	119.8	118.5	130.8

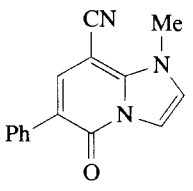
(iii) Nitrogen-14 and Nitrogen-15 NMR

The general points discussed in Section 8.10.2.2.2(ii) are relevant here as well. As mentioned there, both ^{14}N and ^{15}N NMR spectra have been recorded ⟨82OMR(18)87, 84OMR(22)209, 90MRC988⟩. The absorption positions, quoted as ppm shielded relative to neat nitromethane for solutions in DMSO, are imidazo[1,2-*a*]pyridine N-1 at 139.19 and N-4 at 178.04; imidazo[1,5-*a*]pyridine N-2 at 107.32 and N-4 at 185.27 ⟨90MRC988⟩.

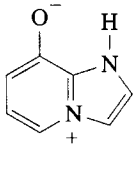
8.10.4.3 Thermodynamic Aspects

8.10.4.3.1 Tautomerism

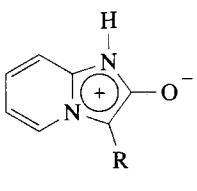
Considerable variation has been found in the preferred tautomeric structure of hydroxy substituted imidazo[1,2-*a*]pyridines. As expected, compounds substituted at the five position existed in the oxo form (**54**) ⟨79JOC3803, 89H(29)1551⟩. 8-Hydroxyimidazo[1,2-*a*]pyridine existed as such in the solid state (x-ray analysis), while in solution the hydroxy tautomer was the minor component in equilibrium with the betaine (**55**) (UV, ^{13}C NMR) ⟨88AX(C)1215, 86JCR(S)50⟩. An x-ray study provided firm evidence for the meso-ionic structure of (**56**; R = CH_2CO_2Me) in the solid state, while in solution in DMSO, ^{13}C NMR demonstrated that it was the major component in an equilibrium with the keto tautomer (**57**) ⟨84HCA1897⟩. A meso-ionic structure has also been established for (**56**; R = NO_2) ⟨84JCS(P1)69⟩ but the 3-phenyl and various other 3-aryl compounds, on the basis of IR spectra in nujol, have been claimed to exist as the 2-hydroxy tautomers ⟨86T1169⟩. On the other hand, the isomeric 2-phenyl compound, which was earlier reported as the 3-hydroxy tautomer, has been shown to exist as the meso-ionic structure (**58**) ⟨89JOC5763⟩.



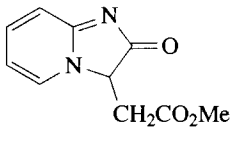
(54)



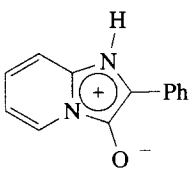
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(56)



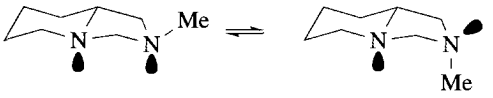
(57)



(58)

8.10.4.3.2 Conformations

A number of NMR studies on the conformations of perhydroimidazo[1,5-*a*]pyridine and some simple alkyl derivatives have been reviewed in detail ⟨90AHC(49)193⟩. The *trans*-fused conformers are strongly favored, for example for 2-methylperhydroimidazo[1,5-*a*]pyridine to the extent of >98%. The unfavorable parallel orientation of the lone pairs on the nitrogens, which in the corresponding O-2 or S-2 systems leads to an increase in the proportion of the *cis*-fused conformer by inversion of N-4, is here avoided by the inversion of N-2, thus producing an equilibrium of the *trans* conformers with ≈ 83% (**59**) (Equation (5)).



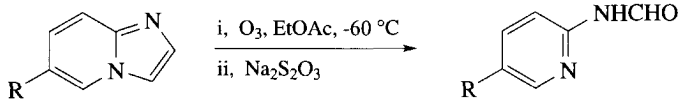
(59) (5)

8.10.4.4 Reactivity of Fully Conjugated Rings

The basic chemistry of these ring systems, in each case best thought of as a π-excessive (five-membered) ring fused to a π-deficient (six-membered) ring, was very clearly and thoroughly covered in the first edition. Familiarity with this treatment is assumed, and no attempt has been made to repeat or review material found there. More recent contributions, for the most part, reflect work on more varied and extensively substituted compounds.

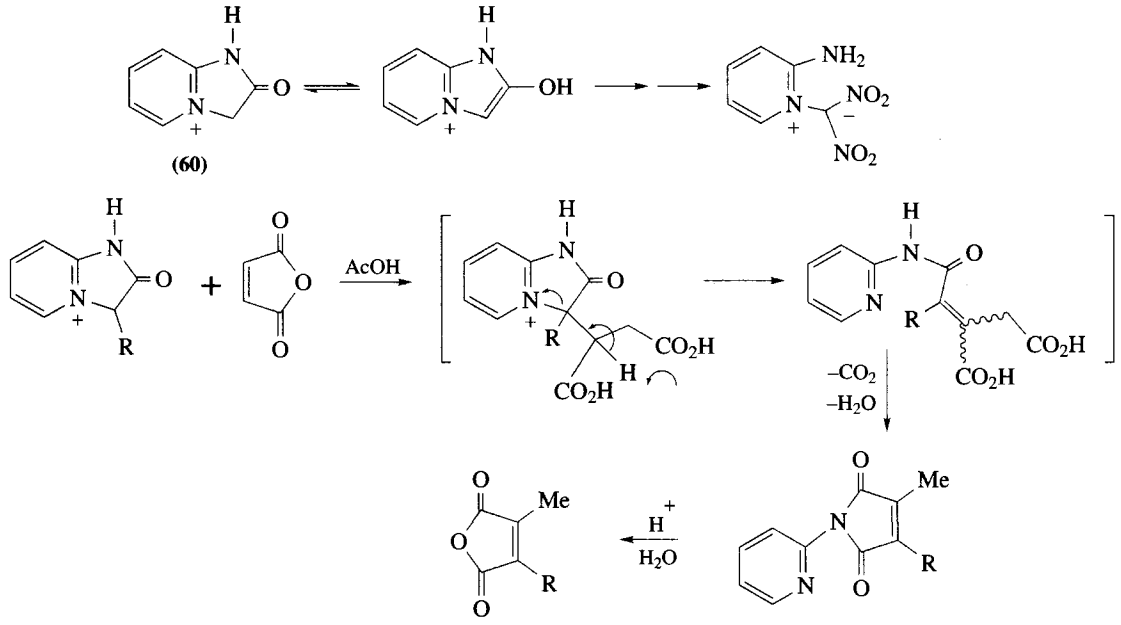
8.10.4.4.1 Electrophilic attack at carbon

Imidazo[1,2-*a*]pyridines unsubstituted at C-3 almost always react with electrophiles at that position. Iododiphenylphosphine and phosphorus trichloride should be added to the list of electrophiles mentioned in the first edition ⟨92JGU1369⟩. Nitration of the 2-phenyl compound using a mixture of nitric and trifluoracetic acids produced substitution at C-3 ⟨83JOU1403⟩ in contrast to an earlier report of nitration in the phenyl ring on reaction with nitric/sulfuric acid mixtures. The presence of a strong deactivating group, such as ethoxycarbonyl at C-2, or an activating alkoxy group at C-8, did not alter the preference for reaction at C-3 ⟨82AJC1761, 86JCR(S)404, 90CPB2352⟩. However, in 8-hydoxyimidazo[1,2-*a*]pyridine, which in neutral solution existed at least in part as the betaine (**55**), the six-membered ring was sufficiently activated that reaction occurred at C-5 or C-7 ⟨86JCR(S)404⟩. Nitration of imidazo[1,2-*a*]pyridines activated by substitution at C-2 may result in ring cleavage as was found for (**60**) ⟨84JCS(P1)69⟩. Compounds like (**60**) are very reactive Michael donors and this reaction, followed by opening of the five-membered ring, formed the basis of a synthesis of unsymmetrically substituted maleic anhydrides (Scheme 13) ⟨86HCA396, 84HCA1897⟩. A basically similar sequence with α-halohydrazides replacing maleic anhydride led to the formation of substituted *N*-aminomaleimides, and hence to maleic anhydrides ⟨90T445⟩. Under neutral conditions the 2–3 bond of imidazo[1,2-*a*]pyridines was cleaved by ozone at −60°C and led, after a reductive work-up, to protected 2-aminopyridines (**61**) in moderate yields (Equation (6)) ⟨92CPB666⟩. When the substituent R contained a vinyl group, products which were isolated contained this group unchanged. Under acidic conditions, however, a selective ozonolysis of alkenyl substituents was achieved ⟨91CPB1556, 92MI 810-02⟩.



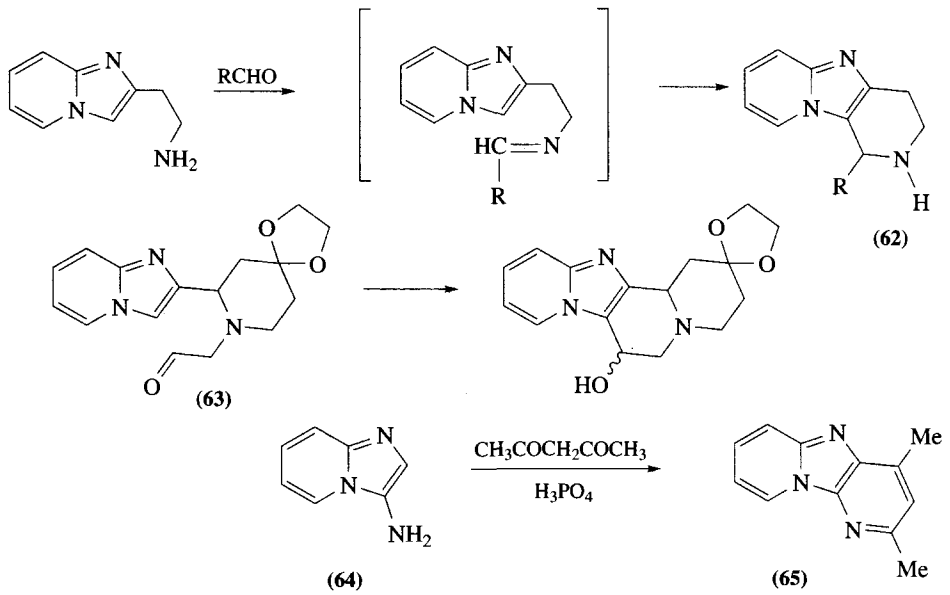
(61) (6)

The nucleophilic character of the ring carbon atoms of imidazo[1,2-*a*]pyridine has been utilized for the formation of more complex ring systems. Examples of closures through C-3 are shown in Scheme 14 ⟨93H(36)2451, 95H(41)21⟩. Attempts to bring about reaction through C-2 of the isomer of (**63**) substituted at C-3 failed, but ring closure through C-2 was achieved in the formation of (**65**) ⟨94H(38)1527⟩. A similar reaction on the 5-amino isomer of (**64**) produced ring closure to C-6. The



Scheme 13

azacarboline skeleton of (**62**) has also been synthesized by a sequence involving attack by C-3 on isocyanate or carbodiimide groups. Competitive attack by N-1 was observed ⟨94JOC6413⟩.

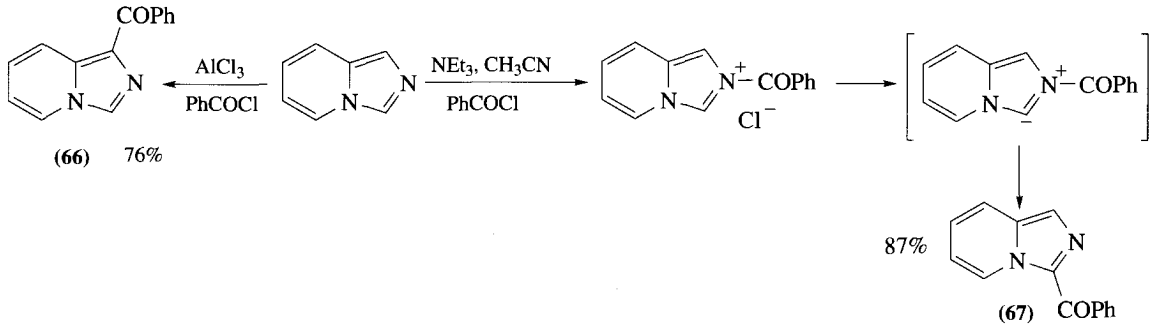


Scheme 14

As reported in the first edition, the [1,5-*a*] fused system reacts mainly at C-1, although reaction at C-3 is sometimes competitive and is favored when C-1 is blocked. It has been shown that acylation may be directed to C-1 (**66**) or C-3 (**67**) by choice of conditions (Scheme 15) ⟨90TL5833⟩.

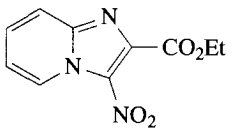
8.10.4.4.2 Nucleophilic attack at carbon

In the imidazo[1,2-*a*]pyridine series, nucleophilic displacement of halides from C-5 or from C-2 when assisted by an adjacent EWG, was documented in the first edition. In similar fashion the nitro group of (**68**) has been shown to be displaced by RS^- ⟨81JOC1026⟩. *Peri*-disubstituted imidazo[1,2-

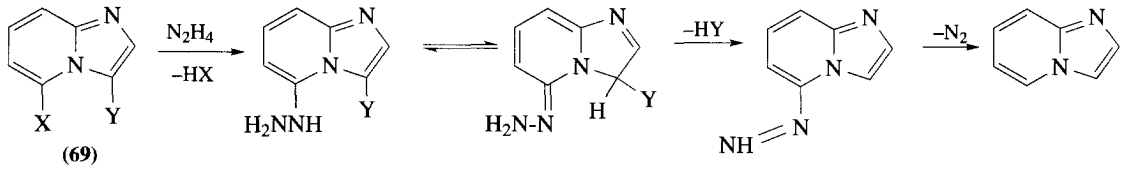


Scheme 15

a]pyridines (**69**; X, Y = Br or NO_2) on reaction with hydrazine underwent displacement of both substituents giving overall reduction. The proposed pathway is shown in Scheme 16 ⟨87JCS(P1)1159⟩.



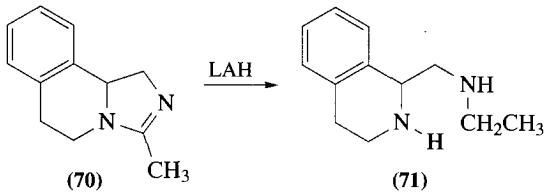
(68)



(69)

Scheme 16

Similar nucleophilic displacements do not appear to have been documented for compounds of the [1,5-*a*] series. However, compounds containing a 4,5-dihydroimidazole ring were subject to ring cleavage, for example (**70**) to (**71**) on reaction with hydrogen nucleophiles (Equation (7)) ⟨90JCS(P1)385⟩.



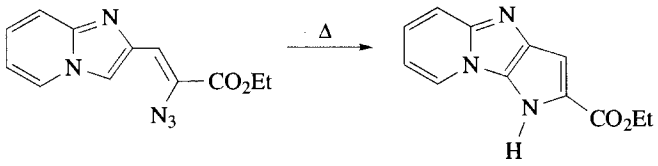
(70) **(71)** (7)

8.10.4.4.3 Nucleophilic attack at hydrogen

In agreement with the earlier reported results, the anion formed by reaction of imidazo[1,2-*a*]pyridine with phenyl lithium reacted with carbonyl compounds to yield products substituted at C-3. However, it failed to react with a number of other electrophiles ⟨94H(38)551⟩. No useful results were obtained after the reaction of the parent heterocycle with *n*-butyl lithium ⟨86JCR(M)1842⟩, but reaction of 3-methylimidazo[1,2-*a*]pyridine gave predominantly substitution at C-8 on quenching with methyl iodide ⟨83S987⟩. The presence of a methoxy group at C-3, however, promoted rapid equilibration to the thermodynamically favored 5-lithiated derivative, which was successfully reacted with a range of electrophiles ⟨83S987⟩. In the [1,5-*a*] fused series the presence of an ethylthio group at C-3 also directed formation of the anion to the *peri* position (C-5) ⟨80TL2195⟩. 5-Methylimidazo-[1,5-*a*]pyridine was preferentially deprotonated at the methyl group to yield an ambident nucleophile which alkylated at the methyl group, but reacted with other electrophiles at C-3 ⟨85JMC164⟩.

8.10.4.4.4 Reactions with nitrenes

Intramolecular reactions with nitrenes generated by thermolysis or photolysis of an azido group ⟨89JCS(P1)1895, 92JHC691⟩, or by reaction of triethyl phosphite with a nitro group ⟨89JCS(P1)1895⟩, gave moderate yields of the product (**72**) due to reaction at C-3 in preference to N-1 (Equation (8)).



(8)

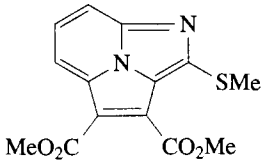
(72)

8.10.4.4.5 Reactions at surfaces

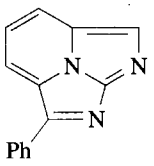
In imidazo[1,2-*a*]pyridines, reduction of the six-membered ring occurred fairly readily and has been reported, when using palladium on charcoal as the catalyst, to be competitive with reduction of a nitro group or with debenzylation ⟨89CPB2293, 86JCR(S)404⟩. A similar facile reduction has been reported for imidazo[1,5-*a*]pyridines ⟨91JMC725⟩.

8.10.4.4.6 Cycloadditions

The [π8 + π2] cycloaddition of DMAD and indolizines is well known ⟨84CHEC-I(4)459⟩. The reaction is usually carried out in the presence of a dehydrogenating agent to yield a cycl[3.2.2]azine. Imidazo[1,2-*a*]pyridines reacted similarly to yield 1-azacycl[3.2.2]azines ⟨61JOC431, 88JHC185⟩. The use of 2-methylthioimidazo[1,2-*a*]pyridine and DMAD yielded (**73**) which was converted to the parent ring system ⟨88JHC185⟩. Benzonitrile reacted with 3-ethylthioimidazo[1,5-*a*]pyridine to yield the cyclazine (**74**). The mechanism of the reaction was not established but may also involve a [π8 + π2] cycloaddition ⟨80TL4193⟩.



(73)



(74)

8.10.4.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Nothing remarkable has been reported, but a few useful results should be noted. Carboxylic esters at C-6 of the [1,2-*a*] fused system may be viewed as part of a vinylogous urethane, and are significantly less reactive than are those at C-5 ⟨94TL2157⟩. 8-Hydroxyimidazo[1,2-*a*]pyridine showed useful "oxine-like" metal-chelating properties ⟨91MI 810-02⟩.

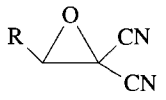
8.10.4.6 Synthesis

8.10.4.6.1 Imidazo[1,2-a]pyridine

Since the publication of the first edition of this work numerous reactions resulting in the formation of the imidazo[1,2-*a*]pyridine ring system have been reported. Nevertheless the method of choice for the synthesis of most imidazo[1,2-*a*]pyridines remains the condensation of a 2-aminopyridine and an α-halocarbonyl compound, usually a ketone or aldehyde.

(i) Construction of the five-membered ring

As indicated above the most important synthetic procedure is of this type, and a small sample of the many papers reporting on its use is given ⟨85JMC876, 88JHC129, 89JMC1686, 89JMC2204, 92CPB371, 93JHC563⟩. The reaction pathway, proposed many years ago, of initial attack by the ring nitrogen, has been placed on a solid foundation by a number of studies ⟨82T49, 82JHC1437, 86JHC1031⟩. Reduced basicity of the pyridine ring nitrogen or steric hindrance may result in attack by the exocyclic nitrogen becoming competitive, but under the normal reaction conditions the product of this reaction does not cyclize. This may, however, cause lowered yields ⟨82JHC1437⟩. The sequence usually uses α-bromo or α-chlorocarbonyl compounds, but was also successful with α-fluoroketones if tin(II) chloride was used to bring about ring closure ⟨88S199⟩. The use of α-ketohydroximoyl chlorides or α-ketohydrazidoyl chlorides produced 3-nitroso or 3-arylazo derivatives respectively ⟨84JHC1029, 88PS(40)41, 83JHC639⟩. α-Haloacyl cyanides were the proposed reactive species in condensations between 2-aminopyridines and dicyano epoxides (**75**) under acid conditions ⟨86T1169⟩. Alternative condensation partners for 2-aminopyridines include α-epoxyaldehydes and ketones ⟨81JOC3735, 83TL5599, 85CB4099⟩, 1,2-diols (ruthenium complex-catalyzed ⟨93CL1317⟩, α-dicarbonyl compounds, particularly glyoxals ⟨89JOC5763, 92H(34)2065, 89T6841⟩ and, to form 2,3-dihydro compounds, 1,2-dihaloethanes ⟨87CI(L)243⟩.

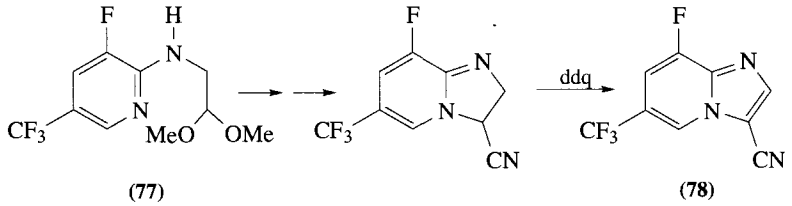


(**75**)

In a modest variation on the above theme (**76**), prepared from 2-aminopyridine, was cyclized to 3-methylimidazo[1,2-*a*]pyridine by refluxing in formic acid ⟨88JHC677⟩. A completely different sequence involved the use of aminoacetaldehyde acetals as the source of the atoms of the five-membered ring. Condensation with substituted piperidones in the presence of tin(IV) chloride led directly to 5,6,7,8 tetrahydro compounds ⟨94JOC5084⟩, while reaction with 2,3-difluoro-5-trifluoromethylpyridine produced (**77**). Cyclization of (**77**) via the cyanohydrin gave the dihydro compound which was oxidized to (**78**) (Scheme 17) ⟨91JHC971⟩. Some other fundamentally different sequences involved the intermediacy of ylides or carbenes. Thermal cyclizations of (**79**), prepared as shown (Scheme 18), or of the isolable ylide (**80**) were readily achieved. Although imidazo[1,2-*a*]pyridines were prepared by this route, better yields were obtained for the benzo derivatives ⟨87JHC1365, 91H(32)2373⟩. Flash vacuum pyrolysis of *N*-substituted isoxazol-5-ones under the correct, carefully controlled conditions led to imino carbenes (**81**) which cyclized to imidazo[1,2-*a*]pyridines or their benzo derivatives (**82**) in excellent yields (Scheme 19) ⟨93T8147⟩.



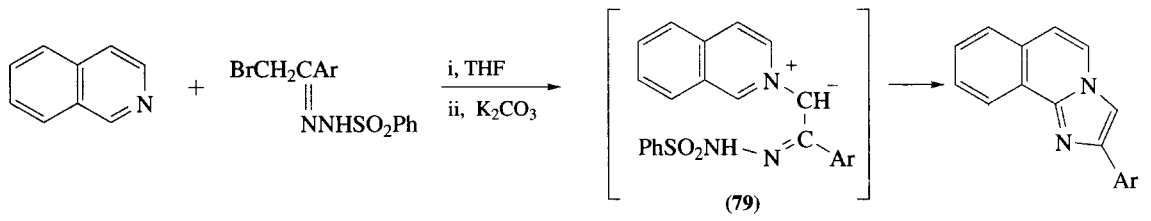
(**76**)



(**77**) (**78**)

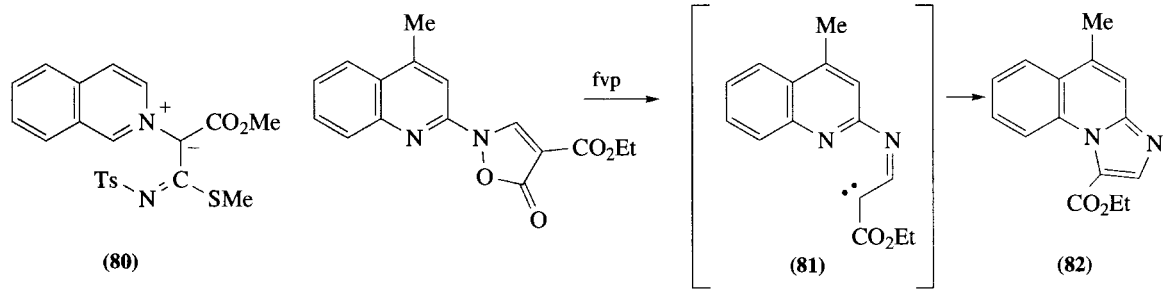
Scheme 17

A number of other sequences which either appear to lack generality for this ring system, or in which only poor yields were obtained, have been reported ⟨83JOU2153, 86H(24)1209, 86JCS(P1)1769, 88JHC1449, 91CHE636, 94JHC393⟩.



(79)

Scheme 18



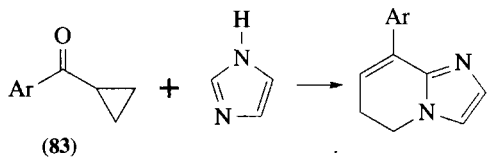
(80) (81) (82)

Scheme 19

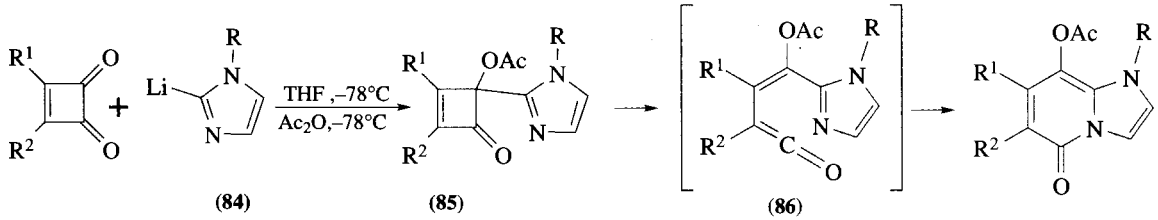
(ii) Formation of the six-membered ring

No single procedure of wide applicability has emerged. The sequences reported are largely divided into annulations of imidazoles or reactions of cyclic ketene aminals.

Imidazole itself was converted to 8-aryl-5,6-dihydroimidazo[1,2-*a*]pyridines by reaction with (**83**) or the corresponding 4-halobutyrophenone (Equation (9)). The use of 2-methylimidazole resulted in cyclization to C-4 of the imidazole ring producing the corresponding 3-methylimidazo[1,5-*a*]pyridines. Oxidation (MnO_2 or S) smoothly produced the fully conjugated ring system ⟨87JOC1863⟩. 1-Alkylimidazoles were annulated via reaction of transient vinylketenes (**86**) formed by the thermolysis of cyclobutenones (**85**) (Scheme 20) ⟨94JOC7737⟩. The lithiated imidazole (**84**; R = Bn) has also been condensed with a protected sugar to produce, after several further steps, a highly substituted 5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine ⟨94H(37)673⟩. Deprotonation of 2-methylimidazole produced (**87**) which on reaction with 3-alkoxyacroleins yielded (**88**) which was cyclized and dehydrated to imidazo[1,2-*a*]pyridinium salts (Scheme 21) ⟨89S109⟩. Heating 1-arylacetylimidazoles (**89**) with DMAD directly produced 7-arylimidazo[1,2-*a*]pyridines in good yields (Scheme 22) ⟨90CB327⟩.

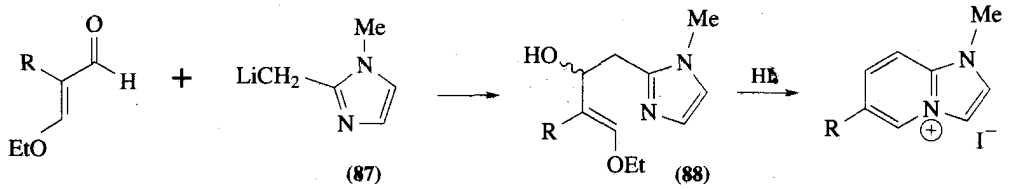


(83) (9)



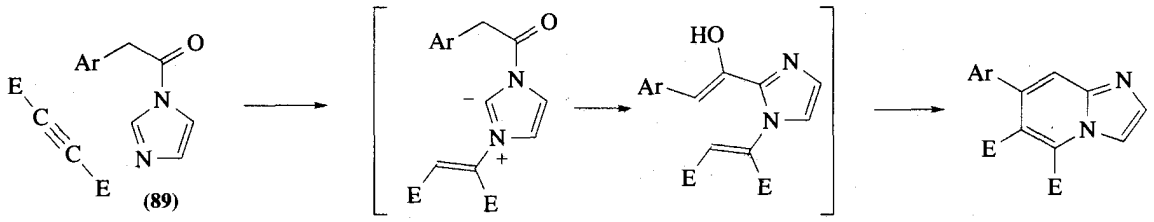
(84) (85) (86)

Scheme 20



(87) (88)

Scheme 21

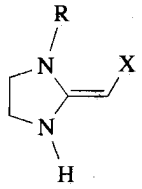


(89)

E = CO_2Me

Scheme 22

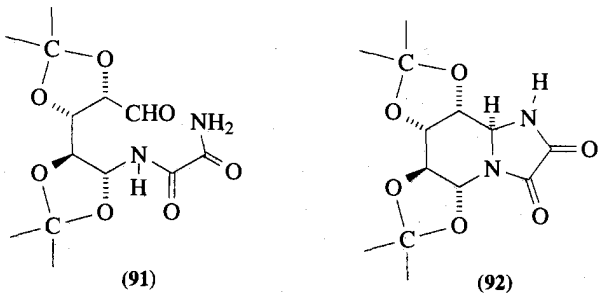
Ketene aminals such as (**90**; X = NO_2, Ac, or CO_2R) have been treated with a variety of bis electrophiles, mostly Michael acceptors, to produce imidazo[1,2-*a*]pyridines at various levels of hydrogenation. Yields in general were good ⟨86CB2208, 88TL5005, 90JCR(S)32, 90BCJ1921, 91M959, 93BCSJ2118, 93AP(326)199, 93AP(326)335⟩.



(90)

(iii) Formation of both rings

The isolation of the active immunomodulator kifunensine has provoked interest in the synthesis of the 2,3-dioxoperhydroimidazo[1,2-*a*]pyridine ring system. One approach involved the double cyclization of (**91**). Many conditions were attempted but only 6M NH_3-MeOH at room temperature, which produced (**92**) in 71% yield, was successful. It was proposed that the six-membered ring was formed first ⟨91CPB1392⟩.

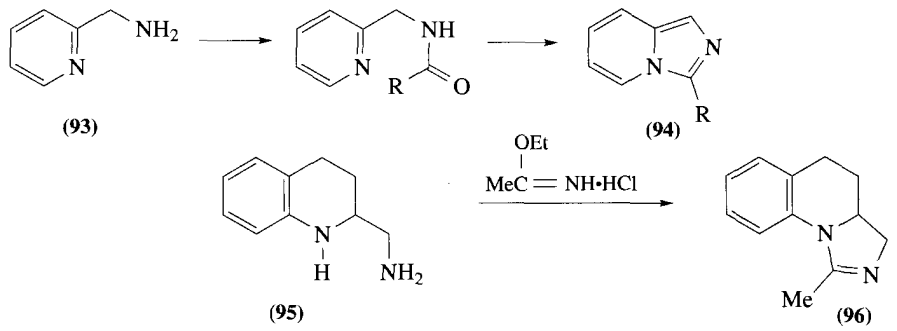


(91) (92)

8.10.4.6.2 Imidazo[1,5-a]pyridine

(i) Construction of the five-membered ring

In the first edition all the reported routes to imidazo[1,5-*a*]pyridine and its benzo derivatives were of this type. In most cases they involved reaction of a 2-aminomethyl substituted heterocycle with a "one-carbon unit" destined to become, for example, C-3 in imidazo[1,5-*a*]pyridine as in (**93**) to (**94**) (Scheme 23). In general these procedures continue to find favor. Examples include acylation followed by thermal closure ⟨93JHC1253⟩ or closure using phosphorus oxychloride at around 100°C ⟨84JCS(P1)229, 85JMC164, 90JMC1924, 91JMC725, 93JHC473⟩, phosphorus oxychloride and triethylamine at room temperature ⟨94OPP429⟩, or phosphorus trichloride and triethylamine at −15°C ⟨79JHC1349⟩, and thioacylation followed by closure using mercuric salts ⟨89H(28)239⟩. In the early 1990s good to excellent yields of the fully conjugated ring system were obtained using the "one-carbon units" *N,N*-dimethylformamide dimethyl acetal, diethoxymethyl acetate, or triethyl orthoformate ⟨91JHC1715⟩. Ethyl acetimidate hydrochloride was condensed with (**95**) to yield (**96**) (Scheme 23) ⟨90JCS(P1)385⟩.



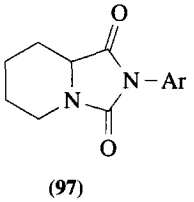
Scheme 23

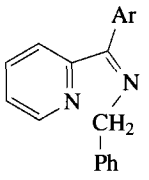
An alternative approach involved the condensation of heterocycles carrying 2-carboxy or related substituents with isocyanates and isothiocyanates. Numerous applications to the syntheses of perhydro compounds such as (**97**) have been recorded ⟨90AHC(49)193, 88GER(O)3643748, 92EUP468930, 92EUP493323⟩. Condensation of acid hydrazones with carbonyl compounds produced 3-substituted-1-ones ⟨93CHE1215⟩.

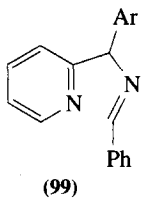
A number of basically different sequences leading to imidazo[1,5-*a*]pyridines have been reported. In most cases, however, their generality remains to be established. Treatment of imine (**98**) with acid resulted in cyclization via imine (**99**). The same product resulted from reaction of (**98**) with base in the presence of the oxidant benzophenone ⟨86TL3713⟩. The *N*-benzylamide (**100**) was cyclized to 3-phenylimidazo[1,5-*a*]pyridine by treatment with phosphorus pentachloride. The reaction was postulated to involve, amongst other intermediates, the nitrile ylide (**101**) ⟨93JCS(P1)675⟩. Nitrile ylides such as (**102**) gave [3 + 2] cycloadditions with pyridine to produce dihydroimidazo[1,5-*a*]pyridines ⟨81JHC247⟩. An analogous intramolecular cyclization was shown by (**103**), the structure of which is shown as an iminocarbene ⟨86JCS(P1)1119⟩. Azomethine ylides (**104**) also closed to 1,3-disubstituted dihydroimidazo[1,5-*a*]pyridines which were spontaneously oxidized to the fully conjugated systems ⟨92T10423⟩. Condensation of pyridine with methyl chlorothioimidates (**105**) produced quaternary salts which were trapped by nucleophilic isocyanides to form 1-amino-imidazo[1,5-*a*]pyridinium salts (**106**) ⟨93T2319⟩.

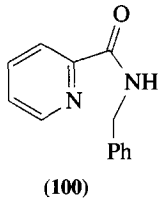
(ii) Construction of the six-membered ring

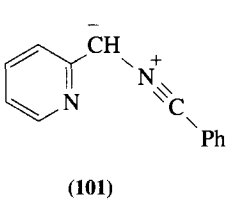
The few procedures that have been developed all lead to fully or partially hydrogenated ring systems. The most generally useful involved modifications of the established annulation by attack of π-electrons on *N*-acyliminium ions, for example (**107**) to (**108**) (Equation (10)) ⟨82JOC2787, 84JOC3812, 84JOC4745⟩. Tetrahydroimidazo[1,5-*a*]pyridines were formed by treatment of (**109**) with base ⟨91JMC725⟩ and of (**110**) with triflic anhydride ⟨91HCA934⟩.

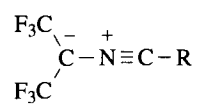

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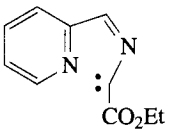

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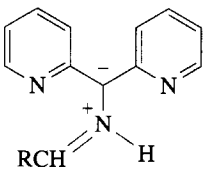

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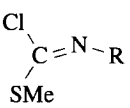

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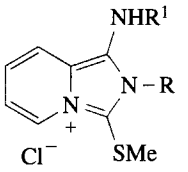

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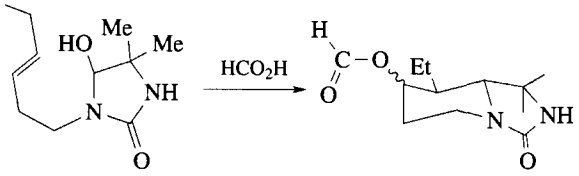

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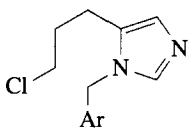

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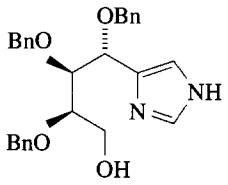

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(106)


(10)

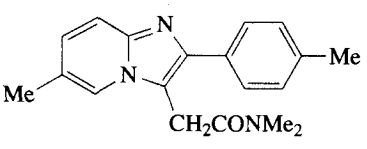
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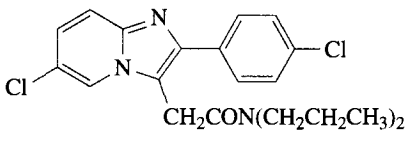

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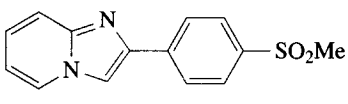

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8.10.4.7 Important Compounds and Applications

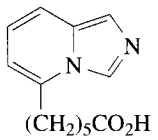
Claims have been made for a tremendously broad range of useful pharmacological activities for substituted imidazo[1,2-*a*]pyridines. The listing below is certainly not complete with respect to either the variety of the claims, or the number of claimants for a particular type of activity, but does give the reader a feel for the extent of the work in this area. Reported are claims for antibacterial ⟨82EJM109⟩, antifungal ⟨93MI 810-01⟩, anthelmintic ⟨81JMC1518⟩, antiviral ⟨94BMC1937⟩, antiprotozoal ⟨90JMC298⟩, antiinflammatory ⟨91MI 810-03, 83FES911⟩, anticonvulsant, anxiolytic, hypnotic ⟨88FRP2612927⟩, immunomodulatory ⟨91JAP(K)03014580, 86EUP194484⟩, and, perhaps most extensively, gastrointestinal and antiulcer activities where at least four pharmaceutical companies have filed patents ⟨89JMC1686, 88USP4721718, 88EUP266890, 88EUP290003, 90JAP(K)02270873⟩. Furthermore, derivatives have been claimed to be cardiotonics ⟨92CPB666, 86JAP(K)61218589⟩, blood platelet aggregation inhibitors ⟨86JAP(K)61218589⟩, acetylcholinesterase inhibitors ⟨93MI 810-02⟩, angiotensin II antagonists ⟨93GEP(O)4203872⟩, 5HT antagonists ⟨89JAP(K)01258674⟩, and β-blockers ⟨90FRP2638747⟩. The current edition of the Merck Index includes mention of Zolpidem (**111**) and Alpidem (**112**), categorized as anxiolytic and hypnotic compounds and Zolmidine (**113**), an anti-ulcerative.


(111)

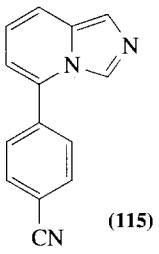

(112)


(113)

The variety of activities claimed for substituted imidazo[1,5-*a*]pyridines is much less extensive, but some very useful compounds have been described. Pirmagrel (CGS13080) (**114**) is an important thromboxane A_2 synthetase inhibitor ⟨84USP4444775, 85JMC164⟩. In the period under review more than 30 studies on applications of the compound were noted. Fadrozole (**115**) is a selective inhibitor of aromatase and suppresses estrogen production ⟨85EUP165904, 91JMC725⟩. Perhydroimidazo[1,5-*a*]pyridine-1,3-diones and 3-thioxo analogues have found extensive use as herbicides and numerous patents have been granted ⟨90AHC(49)193, 88GEP(O)3643748, 92EUP468930, 92EUP493323⟩.



(114)



(115)

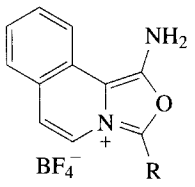
8.10.5 OXAZOLO[3,2-*a*]PYRIDINE AND OXAZOLO[3,4-*a*]PYRIDINE

In the first edition these systems formed a part of the general section on "Oxazole fused with Azines" in Chapter 4.29 of Volume 6. In the case of the [3,2-*a*] fused system, most interest centered on the meso-ionic 2-olates while almost all the information on the [3,4-*a*] fused system involved perhydro compounds. Overall, however, rather little information about the chemistry of the systems was recorded. In the years since then considerable work has been done with perhydrooxazolo[3,2-*a*]pyridines but, apart from that, the general picture has remained as described above.

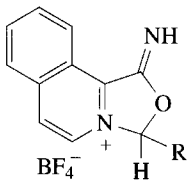
8.10.5.1 Fully Conjugated Rings

8.10.5.1.1 Structure: tautomerism

In accordance with general findings in heteroaromatic chemistry the amino [3,4-*a*] fused salts have been shown to exist almost completely as the amino tautomers (**116**) ⟨77JA165⟩ rather than as the imino tautomers (**117**) as previously claimed ⟨73JA2392⟩.



(116)

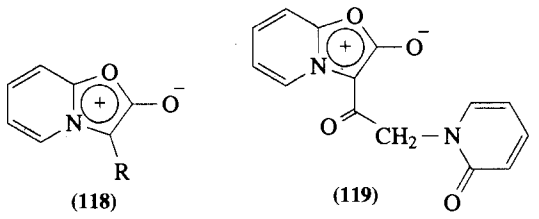


(117)

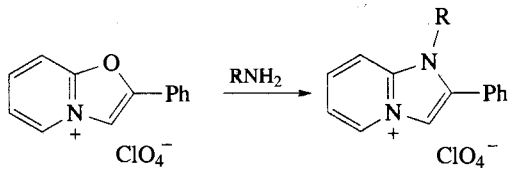
8.10.5.1.2 Reactivity

Discussion is concerned mainly with the [3,2-*a*] fused system. Additional examples of the reactions described in the first edition are cited, but no new chemistry has been reported. Electrophilic substitution at carbon requires activation of the ring by electron-donating substituents, and most examples involve meso-ionic 2-olates (**118**). The unstable parent (**118**; R = H) was very readily acylated at C-3 to (**118**; R = acyl), and in the absence of an added acylating agent, "self-acylation" occurred to yield (**119**) or the product of further reaction ⟨88RRC729⟩. The 3-acyl compounds were stabilized by delocalization of the negative charge, but the effectiveness of this was significantly decreased, and the reactivity hence increased, by substitution at C-5 which forces the acyl group out of planarity with the ring ⟨89RRC1251⟩. Reactions of these 2-olates with nucleophiles such as

amines, alcohols or water led in all cases to cleavage of the bond between C-2 and O ⟨90RRC747⟩. The mechanisms, however, differed in matters of detail depending on the presence or absence of substituents at C-3 and C-5 ⟨91RRC1113, 91RRC1299⟩. Similar nucleophile-initiated cleavage of the five-membered ring is known to occur with oxazolo[3,2-*a*]pyridinium salts in general. Reaction with amines led to subsequent reclosure of the ring and formed imidazo[1,2-*a*]pyridinium salts (**120**) (Equation (11)) ⟨82JCS(P1)131⟩.



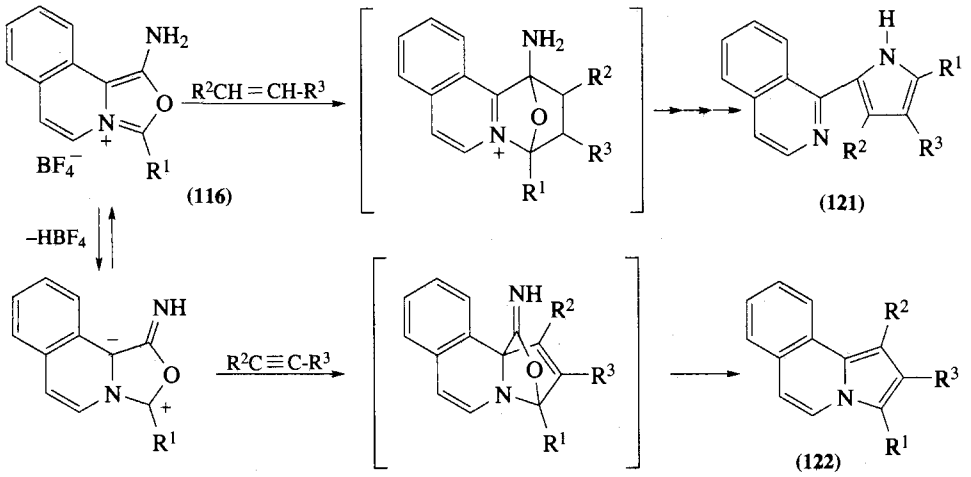
(118) (119)



(120)

(11)

Benzoxazolo[3,4-*a*]pyridinium salts (**116**) are known to give cycloadditions of the [4 + 2] and [3 + 2] type with alkenes and alkynes. The primary adducts were readily converted to alternative heterocyclic systems (**121**) and (**122**) which were usually the isolated major products (Scheme 24) ⟨79JOC111, 82JOC3098⟩. The formation of oxazoles from the reaction of alkynic aldehydes with (**116**) was claimed to result from the Diels–Alder pathway with the carbonyl group acting as the dienophile ⟨93JCS(P1)1839⟩.



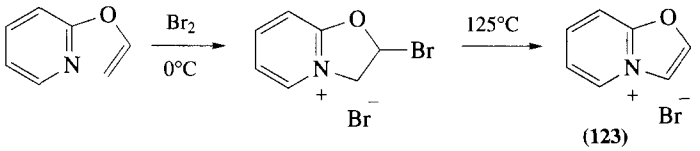
Scheme 24

8.10.5.1.3 Synthesis

(i) Oxazolo[3,2-a]pyridinium salts

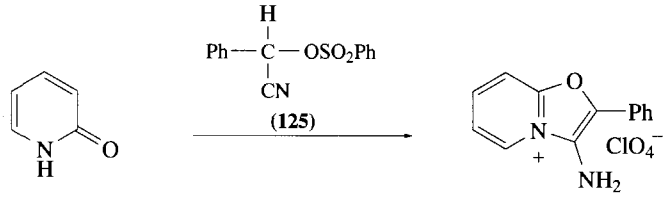
The synthesis of these cations was recently included in a broader review ⟨91CHE921⟩. In addition to the procedures covered in the first edition, the parent cation (**123**) has been reported to be formed in excellent overall yield from 2-vinyloxypyridine (Scheme 25) ⟨86CHE1132⟩. The 3-amino salt

(**124**) was formed by reaction of 2-pyridone with the cyanohydrin derivative (**125**) (Equation (12)) ⟨83S582⟩.



(**123**)

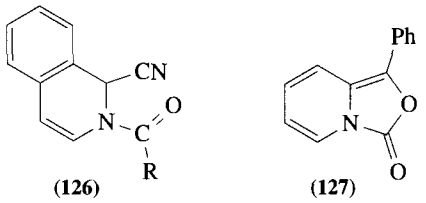
Scheme 25



(**124**) (12)

(ii) Oxazolo[3,4-a]pyridinium salts

In the benzo series salts (**116**) have long been known to result from the treatment of the corresponding Reissert compounds (**126**) with HBF_4 ⟨71JA4479, 77JA165⟩. Reissert compound chemistry has also been used to synthesize (**127**) ⟨85CI(L)125⟩.



(**126**) (**127**)

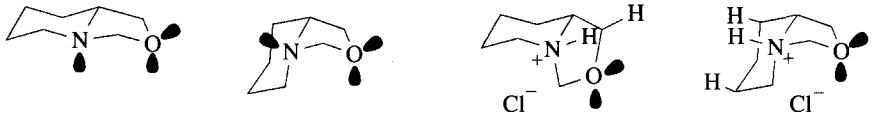
8.10.5.2 Saturated and Partially Reduced Rings

The chemistry of both of these perhydro systems was discussed as a part of a wider review ⟨90AHC(49)193⟩. Particular attention was paid to the synthesis and utilization of perhydrooxazolo[3,2-*a*]pyridines and to the conformational analysis of the [3,4-*a*] fused system.

8.10.5.2.1 Structure: conformations

The conformational preference of the parent perhydrooxazolo[3,4-*a*]pyridine for the *trans* conformer [≈70% (**128**), 30% (**129**) in the equilibrium mixture] was discussed in the first edition and, along with the preferences of several simple substituted examples, in greater detail in a later review ⟨90AHC(49)193⟩. The relief of the unfavorable parallel arrangement of the lone pairs on oxygen and N-4, and the generation of a favorable generalized anomeric effect involving the nitrogen lone pair are factors responsible for the significant amount of (**129**) present at equilibrium. Formation of the hydrochloride salts, by reaction of perhydrooxazolo [3,4-*a*]pyridine in ether with hydrogen chloride gas, yielded a mixture of 28% *trans* and 72% *cis* salts. Unlike the case of the free base, the conformational equilibrium of the *cis* salt contained about 24% of the O-outside conformer (**130**). This was ascribed to an increased anomeric stabilization and a smaller number of *syn* axial interactions between the $^+$N—H bond and CH bonds in the O-outside conformer (**130**) relative to the O-inside conformer (**131**) ⟨88MRC748⟩. Detailed NMR studies of the conformational preferences of disubstituted ⟨89MRC299, 89JCR(S)92⟩ and of benzo-fused ⟨88MRC518, 93JCR(S)170, 94H(37)431⟩ per-

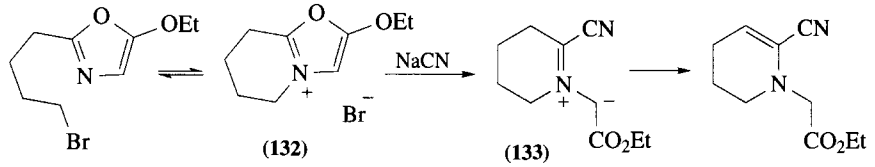
hydrooxazolo[3,4-*a*]pyridines have been reported. Conformational analyses on a number of heterocyclic systems, including perhydrooxazolo[3,4-*a*]pyridine, have been carried out using a modified MM285 program. Agreement with experimental results was inconsistent ⟨91JST(263)157⟩.



(128) (129) (130) (131)

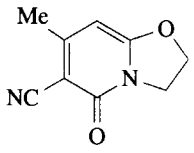
8.10.5.2.2 Reactivity

The chemistry of the cationic [3,2-*a*] fused compounds is dominated by nucleophile-induced cleavage of the five-membered ring. In the first edition this was clearly documented for the 2,3-dihydrooxazolo[3,2-*a*]pyridinium system, and has since been shown to occur with the 5,6,7,8-tetrahydro cation (**132**) on reaction with certain hard nucleophiles (Scheme 26) ⟨92JOC3070⟩. The involvement of the azomethine ylide (**133**) was demonstrated by trapping experiments. The 2,3-dihydro-5-one (**134**) was similarly cleaved on reaction with nucleophiles ⟨84IJC(B)18⟩. Use of amines resulted in reclosure to imidazo[1,2-*a*]pyrid-5-ones ⟨84IJC(B)24⟩.



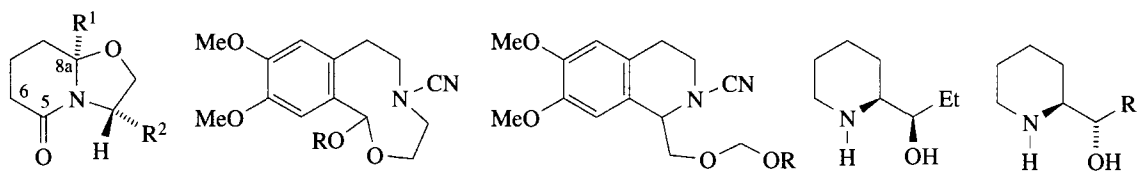
(132) (133)

Scheme 26



(134)

Perhydrooxazolo[3,2-*a*]pyridines have become increasingly important intermediates in the asymmetric syntheses of substituted piperidines ⟨86JOC4475, 89TL5137, 94TL2223⟩ and 4,4-disubstituted cyclohexenones ⟨85JA7776, 88TL5339, 91T9503⟩. Typically compounds such as (**135**; $R^1 = (CH_3)_2CH$ or Ph, $R^2 = CH_3$ or H) have been used as chiral precursors for highly diastereoselective reactions at C-5, C-6, or C-8a. This was followed by removal of the O to C-3 unit by reductive and/or hydrolytic procedures. An alternative use was for the synthesis of nine-membered ring compounds (**136**) by reaction with CNBr. In the corresponding [3,4-*a*] fused series, the bond between N and C-3 cleaved and led to tetrahydroisoquinolines (**137**) ⟨86AJC893⟩. As with the [3,2-*a*] fused compounds, perhydrooxazolo[3,4-*a*]pyridines have found use as intermediates in the syntheses of substituted piperidines of defined stereochemistry. The reactions undergone by the various compounds are unremarkable, the interest being in the stereochemical biasing obtained ⟨90H(30)263, 91H(32)2311, 94TA1463⟩. Controlled formation of either *erythro* (**138**) ⟨83TL4577⟩ or *threo* (**139**; R = Me, Et, Ar) ⟨86H(24)621, 88SC2017⟩ 2-substituted piperidines has been reported. The benzo compounds have been used in similar fashion for the synthesis of 1,2,3,4-tetrahydroisoquinolines with defined stereochemistry ⟨85H(23)395⟩.

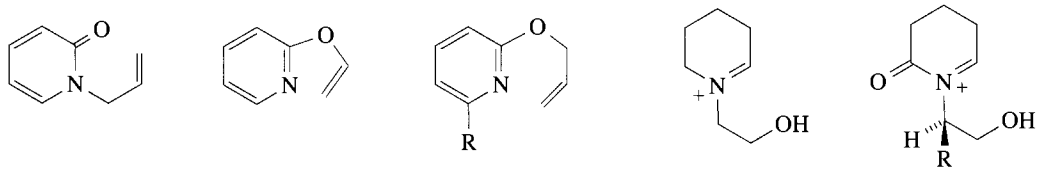


(135) (136) (137) (138) (139)

8.10.5.2.3 Synthesis

(i) Oxazolo[3,2-a]pyridines

The methods for synthesis of 2,3-dihydrooxazolo[3,2-*a*]pyridinium compounds recorded in the first edition, and in the review on the synthesis of thiazolo- and oxazolo[3,2-*a*]pyridinium systems ⟨91CHE921⟩ all involved construction of the five-membered ring. In most cases ring formation was initiated by reaction of a suitably positioned alkene with a halogen. Further examples of suitable substrates include (**140**–**142**) ⟨85JOU1852, 86CHE1132, 87CHE574⟩. Formation of the five-membered ring was also often the final step in the synthesis of perhydrooxazolo[3,2-*a*]pyridines. Closure was usually by attack of oxygen on a transient iminium ion such as (**143**), generated from the *N*-oxide ⟨91TL1443⟩ or by UV irradiation of *N*-(2-hydroxyethyl)piperidine in the presence of a ketone ⟨94TL1715⟩. Alternatively the electrophile was an acylium ion such as (**144**) ⟨89JOC4243, 93H(36)1493, 94TL2223⟩.

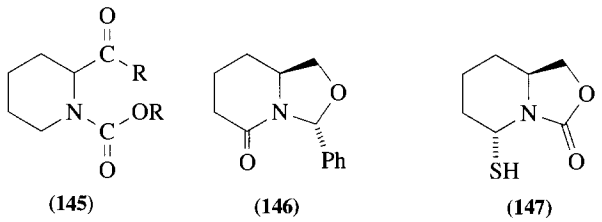


(**140**) (**141**) (**142**) (**143**) (**144**)

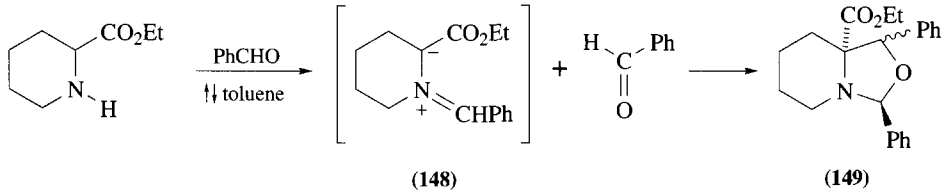
Syntheses of the bicyclic system from acyclic starting materials have also been reported. These involved the condensation of 2-amino alcohols with 1,5-dicarbonyl compounds such as glutaraldehyde ⟨93H(36)1493⟩, 5-oxohexanoic acid or its methyl ester ⟨85JA7776, 91JCS(P2)735⟩ or methyl 5-oxopentanoate ⟨94TL2223⟩. These sequences, however, proceeded via initial formation of the five-membered ring ⟨91JCS(P2)735, 94TL2223⟩. In both these types of syntheses the use of chiral 2-amino alcohols led to products of high enantiomeric purity.

(ii) Oxazolo[3,4-a]pyridines

Construction of the five-membered ring is a long established method for the preparation of this ring system, especially for the 3-one derivatives. Numerous examples of condensations of piperidyl-2-carbinols with "one-carbon units" (aldehydes, ketones, phosgene, ethyl chloroformate, diethyl carbonate, cyanogen bromide) may be found in the first edition or in a later review ⟨90AHC(49)193⟩. Slight variations, such as the reductive cyclization of carbamates (**145**) are also well known ⟨88SC2017, 91TL6723⟩. Use of appropriate starting materials has led to homochiral products (**146**) and (**147**), of value in asymmetric syntheses ⟨88SC2017, 94TA1463⟩. A very different approach involved 1,3-dipolar cycloadditions of the azomethine ylide (**148**). Reaction with benzaldehyde led to (**149**) as a 70 : 30 mixture of epimers at C-1 (Scheme 27) ⟨88BSF143⟩.



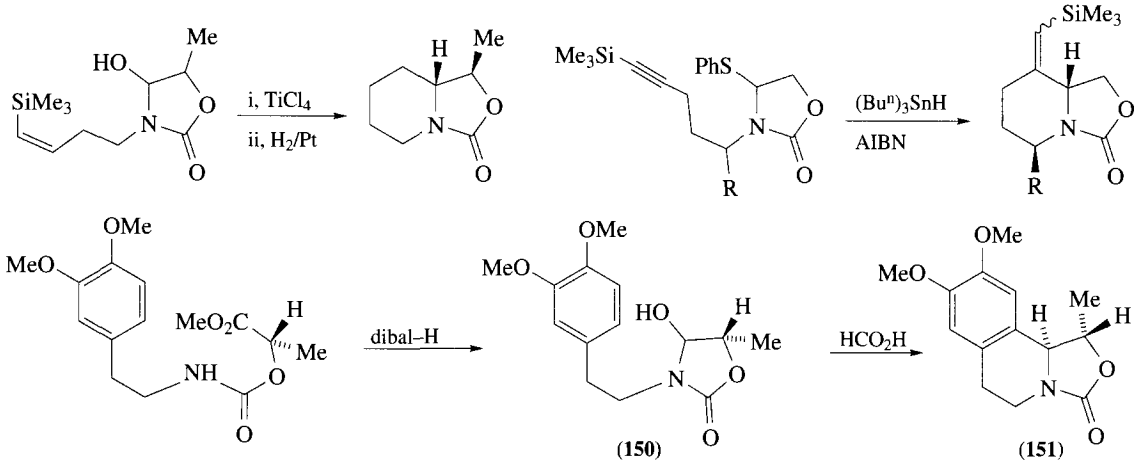
(**145**) (**146**) (**147**)



(**148**) (**149**)

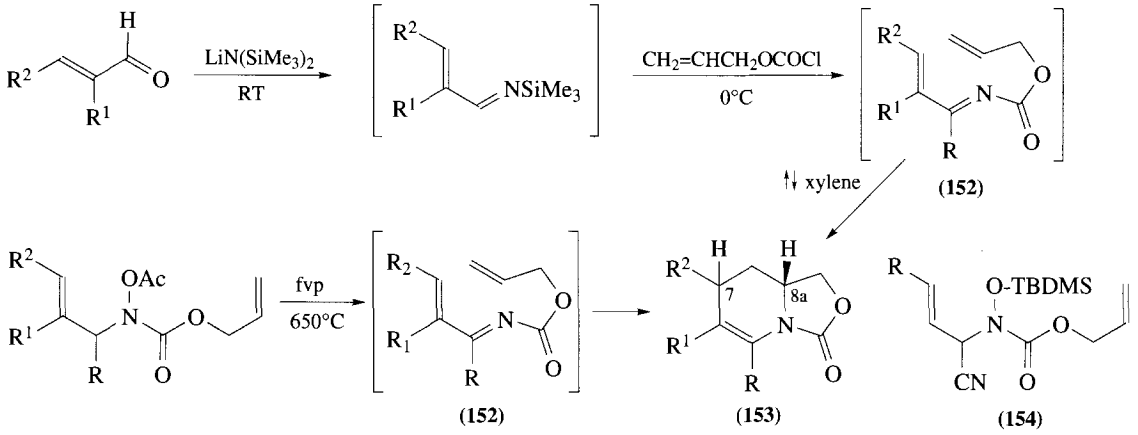
Scheme 27

Since the first edition several sequences involving construction of the six-membered ring have been published. In most cases these are variations on the well-established, highly diastereoselective cyclizations of *N*-acyliminium ions ⟨85JOC3243, 86H(24)621⟩ and α-acylamino radicals ⟨90H(30)263, 91H(32)2311⟩. Compound (**151**) was obtained enantiomerically pure as shown (Scheme 28) ⟨85H(23)395⟩. Alternative routes to racemic precursors of (**151**) have been described ⟨83JOC3835, 85SC883⟩.



Scheme 28

Synthesis of the ring system from acyclic precursors by means of the intramolecular imino Diels–Alder reaction was discussed in the first edition. The alternative Diels–Alder sequence using a 1-azadiene has since been described. The appropriately substituted 1-azadienes (**152**) were generated as transient intermediates during flash vacuum pyrolysis of hydroxamic acid derivatives at ≈ 650 °C ⟨83JA7696⟩ or, under much milder conditions, as shown in Scheme 29 from α,β-unsaturated aldehydes ⟨90TL3753⟩. In both cases the Diels–Alder reaction was found to proceed via competitive *exo* and *endo* pathways, with the *exo* pathway predominating, that is for (**153**) the major isomer has the 7-H and 8a-H *trans*. Conversion of α,β-unsaturated aldehydes to α-cyanohydroxamic acid derivatives (**154**) led to 1-azadienes (**152**) isolable when R = CN, which underwent the Diels–Alder reaction under milder conditions and with greater selectivity for the *exo* pathway (Scheme 29) ⟨90JOC5646⟩.



Scheme 29

8.10.5.3 Important Compounds and Applications

The oxazolopyridine ring system is found embedded in the structures of a number of complex biologically active molecules such as the antibiotic streptazolin or the antitumor agent quinocarcin. Derivatives of the simple systems have not shown much by way of useful activity although some

benzo[3,4-*a*] fused compounds have been claimed to be antidepressants ⟨89EUP322263⟩. The most important aspect of the chemistry of these systems is probably the use made of them, as described in Section 8.10.5.2.2, in the stereochemically controlled syntheses of more complex molecules.

8.10.6 THIAZOLO[3,2-*a*]PYRIDINE AND THIAZOLO[3,4-*a*]PYRIDINE

The review of these systems formed part of Chapter 4.29 in volume 6 of the first edition. They were treated, along with many other systems, in Section 4.29.7, "Thiazole fused with Azines." The chemistry of the [3,2-*a*] fused systems, in particular fully conjugated and 2,3-dihydro compounds, was extensively discussed; structure, reactivity, and synthesis all receiving considerable attention. In addition, reviews on the chemistry of dihydrothiazolo[3,2-*a*]pyridinium-8-olate and related systems ⟨81H(15)1349⟩, and on the syntheses of thiazolo[3,2-*a*]pyridinium systems ⟨91CHE921⟩ are available. A brief discussion of perhydrothiazolo[3,2-*a*]pyridines was included in a review of saturated bicyclic 6/5 ring systems ⟨90AHC(49)193⟩. Although a significant number of papers involving compounds of the [3,2-*a*] fused system have been published since the early 1980s, little of a fundamental nature has been added. The descriptions presented here have accordingly been kept brief, and the organization of the material differs somewhat from that used in other parts of this chapter.

The situation with respect to the thiazolo[3,4-*a*]pyridines is rather different. Very little information was contained in the first edition, and only a handful of papers, all concerned with partially or fully reduced ring systems, have appeared in the period since then. Comment on the perhydro system was included in the above-mentioned review ⟨90AHC(49)193⟩.

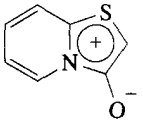
8.10.6.1 Cationic Systems: Fully Conjugated and 2,3-Dihydro Rings

8.10.6.1.1 Structure

The first edition contained full sets of tables of x-ray and spectral data along with relevant discussion. Some further data may be found in the following references: x-ray studies ⟨87AX(C)1739, 88CHE1248, 88CHE1391⟩, ^{1}H NMR ⟨83CHE498, 86JHC1889, 90CHE221⟩. SCF calculations, using the PPP approximation, were carried out to rationalize the UV/Vis spectra of the deeply-colored 3-olates ⟨80CHE1221, 83CHE622⟩. Net charges and LUMO coefficients for the fully conjugated parent cation were calculated using CNDO/2 ⟨84JHC809⟩. A good correlation with the site of attack by nucleophiles was found.

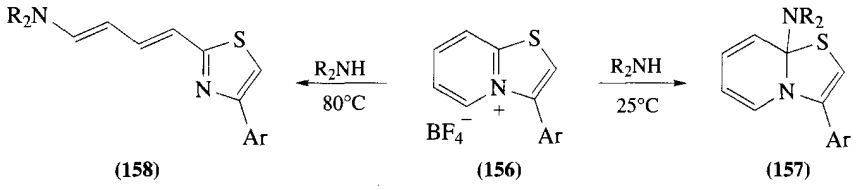
8.10.6.1.2 Reactivity

Little needs to be added to the extensive collection of information contained in the first edition, but a few further examples of the major reaction types are cited. Electrophilic attack at carbon requires the presence of activating substituents. The parent 3-olate (**155**), which is itself unstable and not isolated, reacted very readily at C-2 with acylating agents ⟨82JOC1136⟩, aldehydes and diazonium salts ⟨79CHE1081⟩. Further examples of nucleophilic displacement of halides from active azine positions have appeared ⟨84ACS(B)293⟩. Reaction of the fully conjugated cation (**156**) with amines has been shown to produce either the pseudo base (**157**) by attack at C-8a or the ring-opened product (**158**) by attack at C-5 (Scheme 30) ⟨84JHC809⟩.



(**155**)

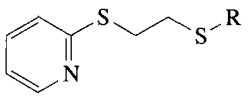
Ring-opening reactions are quite common with 2,3-dihydro cations. The production of *S*-vinyl and *N*-vinyl compounds, initiated by deprotonation at C-2 or C-3 respectively, was fully discussed in the first edition. In addition attack at C-3 by sulfur nucleophiles produced high yields of ethylene disulfide derivatives (**159**) ⟨81SC443⟩. In the more reactive benzo compounds (**160**), ring-opening



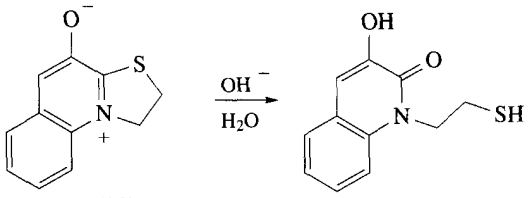
(158) (156) (157)

Scheme 30

occurred under conditions where the analogous bicyclic compounds were generally stable ⟨84ACS(B)109⟩.



(159)



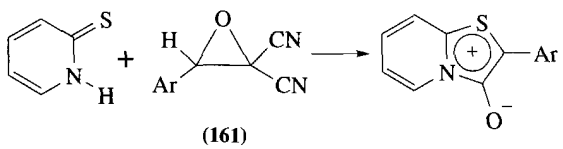
(160) (13)

8.10.6.1.3 Synthesis

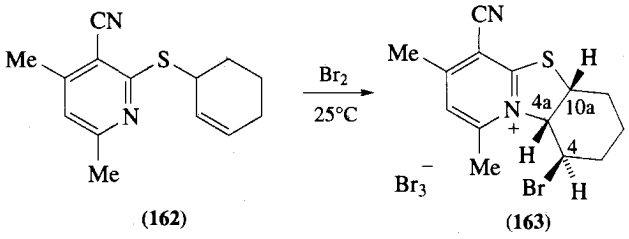
Synthesis of these ring systems was extensively discussed in the first edition and in two other reviews ⟨81H(15)1349, 91CHE921⟩. These sources should be consulted for details, but a few further examples of the most generally useful procedures are cited below.

(i) Formation of the five-membered ring

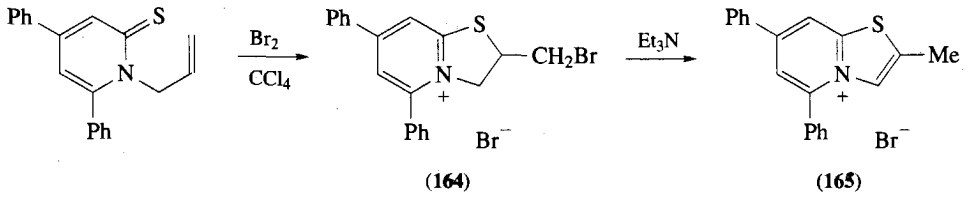
This is the most widely used approach with the final step generally forming the bond between N and C-3. For the 2,3-dihydro system the precursors are typically prepared from pyridine-2-thiones and 1,2-dihalo or otherwise suitably disubstituted ethanes. The use of α-halocarbonyl compounds produces 2-(2-oxoethylthio)pyridines, precursors for fully conjugated compounds. An interesting variation on this was the use of the dicyanoepoxide (**161**) as an α-haloacyl equivalent (Equation (14)) ⟨81S981⟩. An alternative approach involved the reaction of 2-allylthio- or 2-vinylthiopyridines with halogens. Mechanistic details of the ring closure step have been investigated using (**162**) as a probe. It was shown to be a synchronous *trans* addition leading selectively to the 4-H, 4a-H *trans*, 4a-H, 10a-H *cis* product (**163**) (Equation (15)) ⟨88CHE1248, 90CHE221⟩. A simple modification of this procedure, initial attachment of the allyl group to nitrogen followed by bromine initiated closure to sulfur, has been used to form either the 2,3-dihydro (**164**) or the fully conjugated (**165**) system (Scheme 31) ⟨83SC933⟩.



(161) (14)



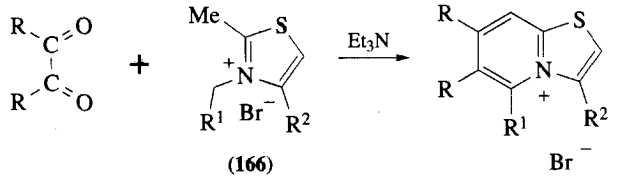
(15)



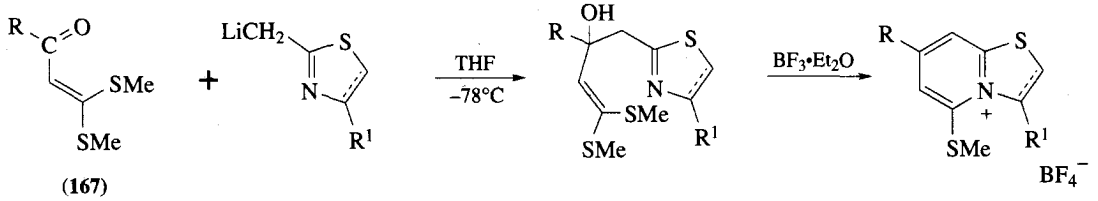
Scheme 31

(ii) Formation of the six-membered ring

This is a much less investigated approach with only a few isolated examples recorded in the first edition. In most cases the sequences involved generation of a nucleophilic substituent at C-2 of a thiazole ring. Further examples include the reaction of 2-methylthiazolium salts (**166**) with α-dicarbonyl compounds (Equation (16)) ⟨86JHC1899⟩ and the use of α-oxoketenedithioacetals (**167**) as electrophiles (Scheme 32) ⟨90T4295⟩.



(16)



Scheme 32

8.10.6.2 Saturated and Partially Reduced Rings

8.10.6.2.1 Structure: conformations

In each case the fully reduced system (**168**) may exist as a mixture of a *trans* (**169**) and two *cis* conformers (**170**) and (**171**), interconvertible by chair and nitrogen inversions. The situation for the [3,4-*d*] fused parent compound (**168**; X = S, Y = CH_2) was described in the first edition as 64% *trans* (**169**) and 36% *cis* (**170**). A further investigation involving variable temperature ^1H and ^{13}C NMR reported essentially the same result ⟨88JCS(P1)1173⟩. The slightly lower percentage of the *trans* conformer relative to that in the corresponding O-containing compound (**168**; X = O, Y = CH_2),

which has 73% *trans* conformer (**169**), was ascribed to greater anomeric stabilization of the *cis* conformer in the sulfur system. A ^{1}H and ^{13}C NMR study of the parent compound of the [3,2-*a*] fused system (**168**; X = CH_2, Y = S) found that the *trans* conformer was the minor component of the equilibrium mixture (43% (**169**); 57% (**170**)) ⟨81OMR(17)103, 90AHC(49)193⟩.

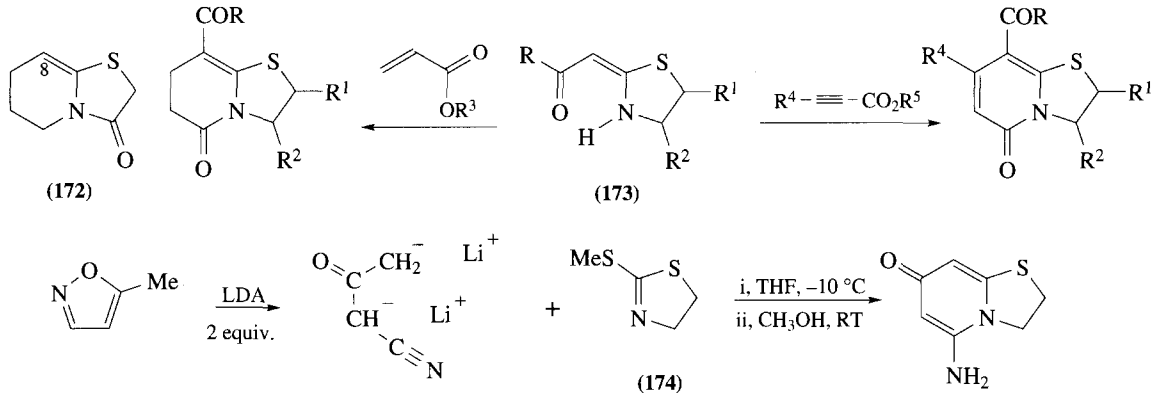


(168) (169) (170) (171)

8.10.6.2.2 Synthesis and reactions

(i) Partially reduced systems

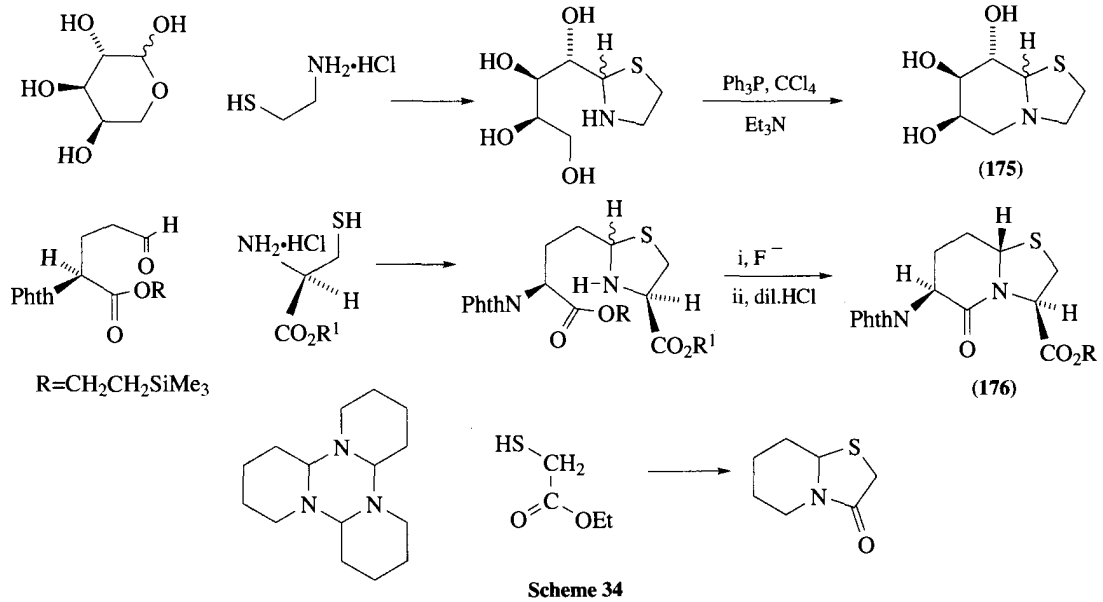
The logic underlying the synthetic sequences aimed at [3,2-*a*] fused compounds mimics that of sequences described in Section 8.10.6.1.3. Thus reaction of piperidine-2-thione with bromoacetyl chloride formed the five-membered ring producing (**172**) which reacted readily at C-8 with acid chlorides and aldehydes ⟨94H(37)441⟩. Conjugate addition of the ketene N,S acetal (**173**) to α,β-unsaturated esters led in good to excellent yields, to formation of the six-membered ring at various levels of hydrogenation ⟨90S162, 91JCS(P1)3077, 83H(20)1021⟩. A more moderate yield was obtained in a sequence featuring nucleophilic attack on the thiazoline (**174**) (Scheme 33) ⟨85TL259⟩.



Scheme 33

(ii) Saturated ring systems

The thiazolidine ring is a cyclic N,S acetal, and most syntheses of perhydrothiazolo [3,2-*a*]pyridines construct the five-membered ring by condensation of aldehydes or ketones either as such or masked. This usually, but not obligatorily, takes place prior to the formation of the six-membered ring. Examples are shown in Scheme 34 ⟨92JOC5661, 91MI 810-04, 85TL647, 86CPB105⟩. Separation of the C-8a epimers of (**175**) was complicated by the very facile epimerization of this center. Chiral instability of the corresponding center C-2 in substituted thiazolidines is well known ⟨89JHC589, 81JHC1047⟩. Compound (**176**), which may be recognized as a dipeptide based on glutamic acid and cysteine, did not show the same instability at C-8a. When deprotected and incorporated in a peptide chain it forces the chain to adopt a shape which mimics very closely that resulting from a β-turn at that point in the chain. It thus permits testing of the importance of various possible conformations to the biological activity of the peptide ⟨91MI 810-04, 91MI 810-05⟩. A similar use has been made of the enantiomer of deprotected (**176**) ⟨93JMC2356⟩. An alternative procedure for the formation of the five-membered ring involved the peroxide-initiated cyclization of (**177**) (Equation (17)) ⟨82TL5039⟩.

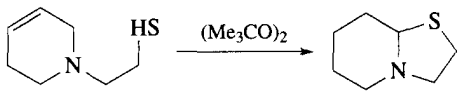


R=$CH_2CH_2SiMe_3$

(175)

(176)

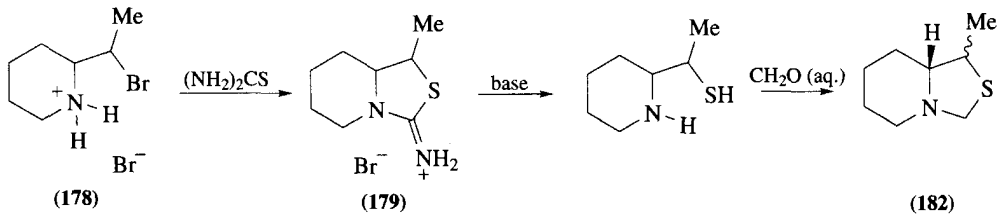
Scheme 34



(177)

(17)

In the case of perhydrothiazolo[3,4-*a*]pyridines, syntheses proceeding via construction of the five-membered ring usually involved 2-haloethyl substituted heterocycles ⟨81MI 810-01, 88JCS(P1)1173, 90AP(323)93⟩. These compounds were cyclized directly to 3-substituted perhydrothiazolo[3,4-*a*]pyridines (**179**) or (**180**) (Scheme 35 and Equation (18)). Initial intramolecular displacement of bromide may occur to produce, for example, (**181**) from (**178**) and hence mixtures of products ⟨88JCS(P1)1173⟩. Alternatively the halides were converted to thiols and then condensed with carbonyl compounds to cyclic N,S acetals (**182**) (Scheme 35) ⟨88JCS(P1)1173⟩. A different approach utilized a stepwise condensation of the masked 1,3-dipolar reagent (**183**) (Scheme 36) ⟨87JOC4423⟩. *N*-Acyliminium chemistry has permitted syntheses involving construction of the six-membered ring to be achieved with the customary excellent control of stereochemistry as in (**184**) ⟨79TL1347, 82T3255, 85T2861⟩. The products of these reactions were intermediates on the path to substituted piperidines of defined stereochemistry (**185**). Desulfurization was readily achieved by reaction of the 3-ones (**184**) with Raney nickel (Scheme 37). Prior conversion to the N, S acetal by LAH reduction or to the sulfone gave less satisfactory results on reaction with Raney nickel ⟨85T2861⟩.

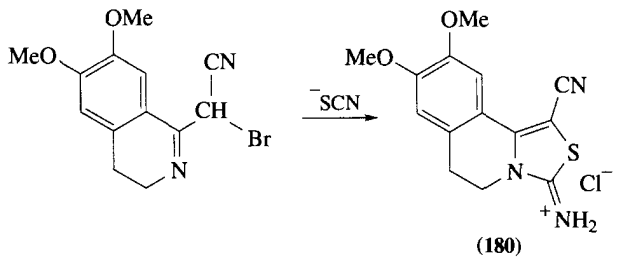


(178)

(179)

(182)

Scheme 35

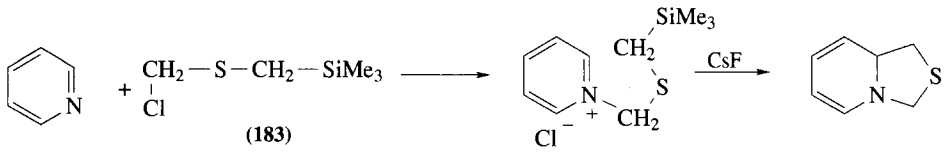


(180)

(18)

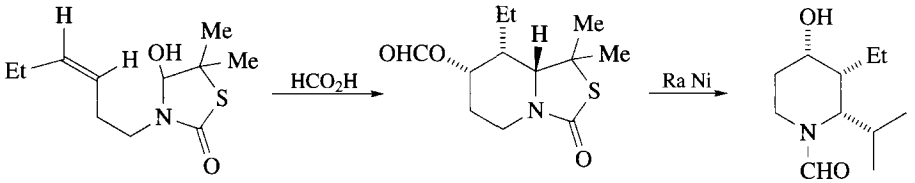


(181)



(183)

Scheme 36

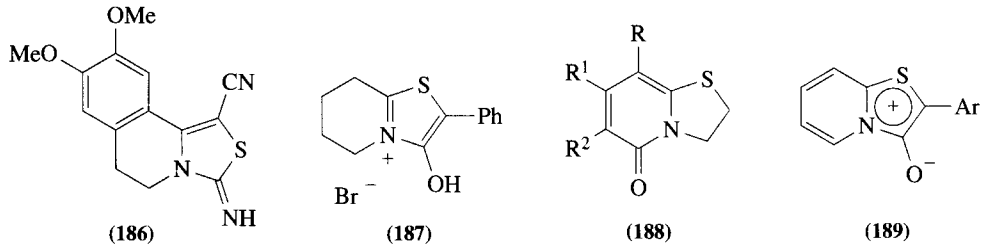


(184) (185)

Scheme 37

8.10.6.3 Important Compounds and Applications

In the first edition it was reported that compounds of these series were useful as coronary dilators and ulcer inhibitors. Similar claims have also been made for different compounds with (**186**) reported to be a potent coronary dilator ⟨81MI 810-01⟩ and (**187**) to be useful in the treatment of ulcers ⟨81USP4289697⟩. In addition, analgesic activity has been shown for (**188**) ⟨81BRP1588166⟩ and potent *in vitro* antitrichomonal activity demonstrated for (**189**). Unfortunately *in vivo* activity was not comparable and the compounds were generally too toxic to be useful ⟨85JMC1673⟩.

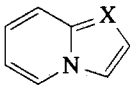


(186) (187) (188) (189)

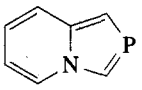
8.10.7 SYSTEMS CONTAINING A LESS COMMON HETEROATOM

A few examples of systems containing phosphorus, arsenic, or selenium in the five-membered ring were found. In view of space limitations, treatment has been restricted to the listing of a selection of relevant references. [1,3]Azaphospholo[1,2-*a*]pyridine (**190**; X = P) ⟨87TL1511, 91CB475⟩;

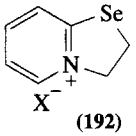
[1,3]azaphospholo[1,5-*a*]pyridine (**191**) ⟨91CB475, 92IJC(B)254, 92TL1049, 92HAC359⟩; [1,3]azaarsolo[1,2-*a*]pyridine (**190**), X = As) ⟨87TL1511⟩; selenazolo[3,2-*a*]pyridine (**192**) ⟨83IJC(B)328, 88JGU745, 90JGU2465⟩.



(**190**)



(**191**)



(**192**)

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8.11
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: One Extra Heteroatom 0 : 1

GURNOS JONES
Keele University, UK

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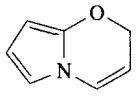
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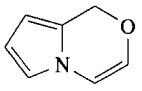
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8.11.1 INTRODUCTION

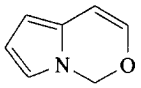
The systems covered by this chapter are shown below. They are the pyrrolooxazines (**1**)–(**4**), the pyrrolothiazines (**5**)–(**8**), pyrrolopyrimidines (**9**) and (**11**), the pyrrolopyrazine (**10**), and the pyrrolopyridazine (**12**). In the case of the pyrrolooxazines, and -thiazines, only one of the possible H isomers is shown; examples of other isomers are known, and will appear in the chapter. The correct names are given; for convenience, the term azaindolizine will be used occasionally to cover all systems (**9**)–(**12**). In principle, fully conjugated pyrrolooxazinium or pyrrolothiazinium salts can exist but there are virtually no examples except for oxo derivatives, and most of the discussion will concern fully or partially reduced molecules. Benzo derivatives will be dealt with as they arise; of the numerous possibilities, few are of importance.



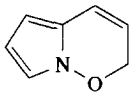
2*H*-Pyrrolo[2,1-*b*]-[1,3]oxazine (**1**)



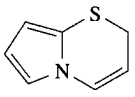
1*H*-Pyrrolo[1,2-*b*]-[1,4]oxazine (**2**)



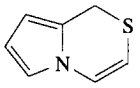
1*H*-Pyrrolo[1,2-*c*]-[1,3]oxazine (**3**)



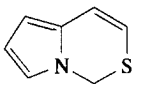
2*H*-Pyrrolo[1,2-*b*]-[1,2]oxazine (**4**)



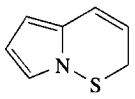
2*H*-Pyrrolo[2,1-*b*]-[1,3]thiazine (**5**)



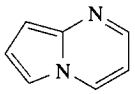
1*H*-Pyrrolo[1,2-*b*]-[1,4]thiazine (**6**)



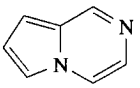
1*H*-Pyrrolo[1,2-*c*]-[1,3]thiazine (**7**)



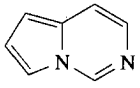
2*H*-Pyrrolo[1,2-*b*]-[1,2]thiazine (**8**)



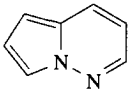
Pyrrolo[1,2-*a*]-pyrimidine (**9**)



Pyrrolo[1,2-*a*]-pyazine (**10**)



Pyrrolo[1,2-*c*]-pyrimidine (**11**)



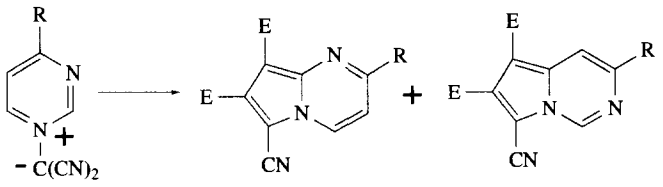
Pyrrolo[1,2-*b*]-pyridazine (**12**)

There is a comprehensive review of the "Pyrrolodiazines with a Bridgehead Nitrogen" ⟨77AHC1⟩, and coverage of the systems (**9**)–(**12**) has been limited to reports subsequent to 1977. There is a more limited review of the same systems concerned almost entirely with synthesis of fully conjugated molecules ⟨91KGS1299⟩, and there are sections in two journals by Ellis ⟨87CHE(47-1)1, 92CHE1⟩. Total entries in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) to the systems reviewed here are less than twenty, and there are no comprehensive reviews for the pyrrolooxazines and -thiazines.

8.11.2 THEORETICAL METHODS

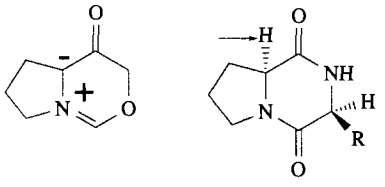
All but one of the calculations reported are on azaindolizines (**9**)–(**12**). Calculations based on the MO–LCAO–SCF method were used to obtain values for ^{1}H NMR shifts and singlet–singlet transitions, and to predict positions of attack by nucleophiles ⟨80KGS984⟩. A study using the SCF–

MO–LCAO–MNDO method allowed calculation of proton affinities and dipole moment ⟨90MI 811-02⟩. A MINDO/1 calculation on the ylide (**13**) predicted more ready addition of DMAD to position 6 than to position 2, thus rationalizing the proportion of pyrrolopyrimidines (**14**) and (**15**) formed in cycloaddition (Equation (1)) ⟨86H(24)3473⟩ (see also 8.11.9.2.2). In partly reduced systems, Molecular Orbital Package (MOPAC) heats of formation of pyrrolizine derivatives from pyrrolooxazinone (**16**) and alkynes ⟨92JA593⟩, and deprotonation preference in pyrrolopyrazinedione (**17**) were calculated ⟨79JA1885⟩.



(1)

(13) (14) E = CO_2Me (15)

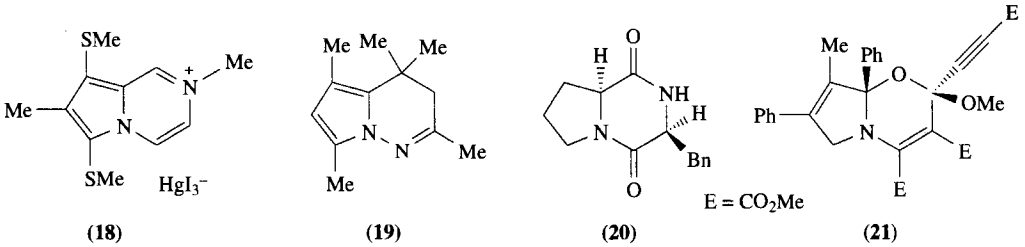


(16) (17)

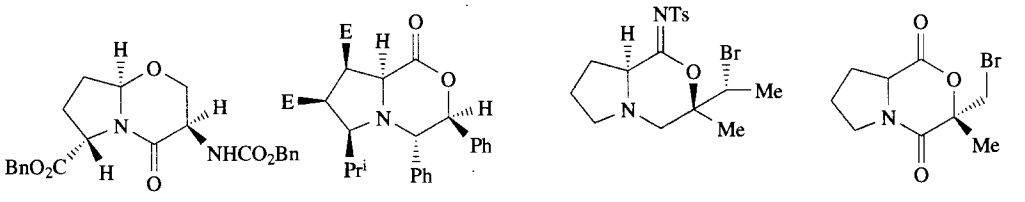
8.11.3 SPECTROSCOPIC STUDIES

8.11.3.1 X-Ray Methods

The only x-ray structure of a fully conjugated system reported is that of salt (**18**) ⟨89JCS(P2)391⟩. Most reported x-ray diffraction experiments have been used to establish structures or stereochemistry of partly or fully reduced derivatives. In the azaindolizine series, apart from the dihydropyrrolopyridazine (**19**) ⟨82CSC1111⟩, all x-ray structures are of cyclic dipeptides (pyrrolopyrazinediones). In the example (**20**) the diketopiperazine ring is a flattened chair ⟨92MI 811-05⟩. In other structures the substituent(s) at position 3 are *p*-hydroxybenzyl ⟨92MI 811-05⟩, CH_2CO_2H ⟨91MI 811-03⟩, CH_2CH_2SMe ⟨87AX(C)349⟩, dimethyl ⟨81PJC1795⟩, *t*-butyl ⟨79AX(B)513⟩, and methyl ⟨79CSC819⟩. One structure for a dihydropyrrolo[1,3]oxazine (**21**) ⟨89MI 811-01⟩, and two of perhydro derivatives ⟨91JCS(P2)735, 93CC935⟩ have been reported, of which the former (**22**) is shown. X-ray structures have established the stereochemistry of synthetic pyrrolo[1,4]oxazinones such as (**23**) ⟨92JOC6527⟩ (also ⟨93SL777⟩), the imine (**24**) ⟨91MI 811-01⟩, and the dione (**25**) ⟨91JCS(P2)53⟩.



(18) (19) (20) (21)



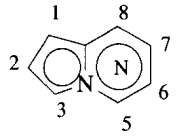
(22) (23) (24) (25)

8.11.3.2 NMR Spectroscopy

8.11.3.2.1 Proton NMR spectra

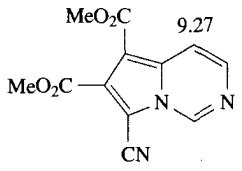
The ^{1}H NMR shifts for the azaindolizines (**10**)–(**12**) have been reported ⟨77AHC1⟩, and were subsequently tabulated (see Table 1) for comparison with calculated values ⟨80KGS984⟩. The figures for compound (**9**) have been added to the table ⟨77JOC2448⟩. The effect of protonation is also shown ⟨79KGS1109, 85JOC1324⟩. There are the usual downfield shifts for protons (H5 in the table) which are *peri* to a deshielding group on the pyrrole ring, exemplified by compound (**26**) ($\Delta\delta = 0.8$ ppm) ⟨86H(24)3473⟩. The shifts for the parent 1*H*-pyrrolo[1,4]thiazine (**6**) ⟨90MI 811-01⟩ and 1*H*-pyrrolo[1,3]thiazine (**7**) ⟨89TL4507⟩ are shown with the formulae below Table 1.

Table 1 Proton NMR shifts of azaindolizines (numbering as for indolizine).

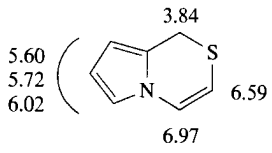


	Solvent	*H1*	*H2*	*H3*	*H5*	*H6*	*H7*	*H8*	*Ref.*
(**9**)	C	6.64	6.98	7.19	8.00–8.24	6.40–6.56	8.00–8.42		77JOC2448
(**10**)	CC	6.7–6.9		7.54	7.98	7.40		8.74	79KGS1109
	TFA	7.80	7.60	8.22	8.40	7.50		8.97	
(**11**)	C	6.50	6.94	7.37	8.84		←7.37→		80KGS984
(**12**)	C	6.31	6.67	7.52		7.79	6.32	7.51	80KGS984

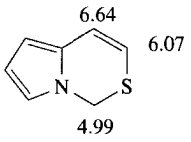
C = $CDCl_3$; CC = CD_2Cl_2; TFA = CF_3CO_2H. *J* values for (**9**); $J_{1,2} = 3.5$, $J_{1,3} = 1.5$, $J_{2,3} = 3.0$ Hz.



(**26**)



(**6**)

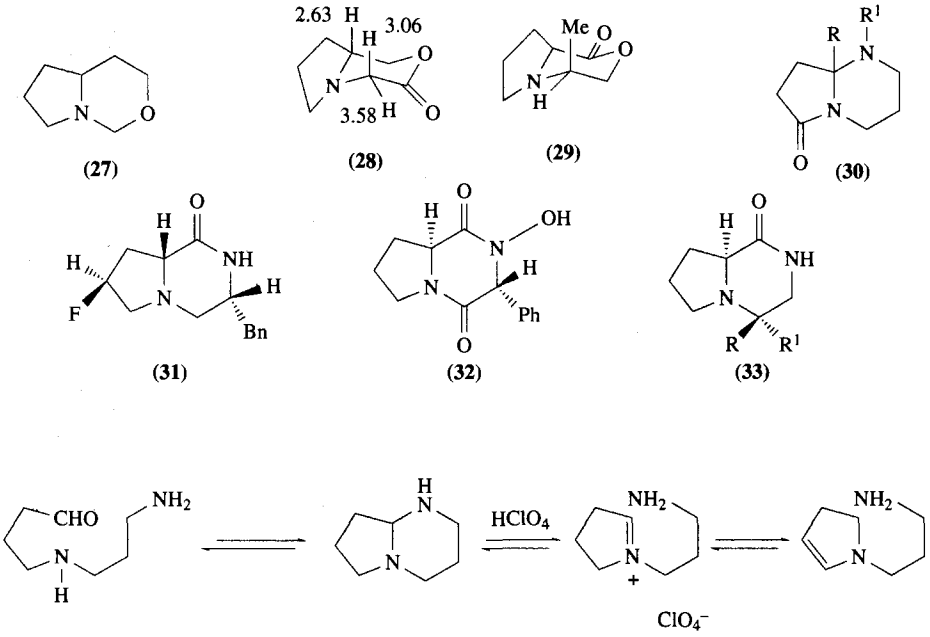


(**7**)

Many spectra have been recorded for partly or fully reduced derivatives of systems (**1**) to (**12**), mainly to confirm structure or stereochemistry. The conformation of perhydropyrrolooxazines (**27**) ⟨82OMR(20)113⟩ and of -pyrrolooxazinones (**28**) ⟨72OMR(4)509⟩ and (**29**) ⟨74CC395⟩ show the expected chair conformation in the six-membered ring; of the azaindolizines, a conformational study using *J* values has been done on the pyrrolopyrimidinones (**30**) ⟨71AP774⟩, but most interest has centered on cyclic dipeptides of proline. The phenylalanine derivative (**31**) was shown to have a diketopiperazine boat in solution, in contrast to x-ray evidence for a flattened chair in the solid state ⟨90MI 811-05⟩. Other examples of diketopiperazines ⟨88JCS(P1)2647⟩, compound (**32**) ⟨86MI 811-03⟩, and one of pyrrolopyrazinones (**33**) ⟨92T4985⟩ can be mentioned. NMR has been used to study the equilibrium between bicyclic and monocyclic systems in a suggested metabolic pathway of spermine in aqueous solution (Scheme 1) ⟨84ACS(B)526⟩.

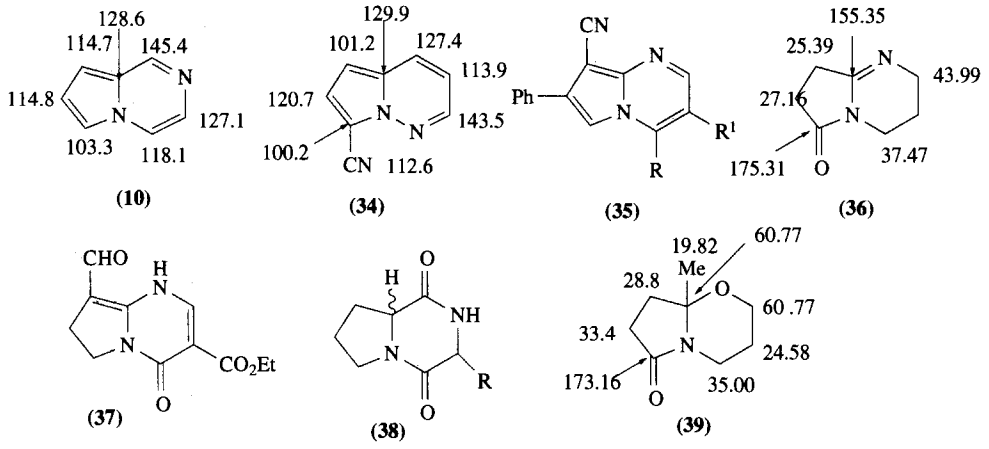
8.11.3.2.2 Carbon-13 NMR spectra

Assignments of ^{13}C shifts for fully conjugated systems are rare. The full spectrum for pyrrolopyrazine (**10**) ⟨86MRC231⟩ and for pyrrolopyridazine (**34**) ⟨87BCJ3645⟩, (see also ⟨83H(20)1009⟩) are shown; see also those for pyrrolopyrimidines (**35**) ⟨87FES717⟩; other examples in ⟨89ZC100⟩. Most



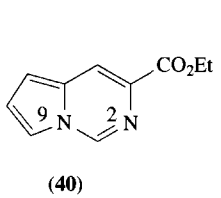
Scheme 1

carbon signals have been assigned for pyrrolopyrimidinone (**36**) ⟨84BSB191⟩, and dbn derivatives have been identified by ^{13}C signals ⟨96TA515⟩. Protonation of dihydropyrrolopyrimidinone (**37**) has been shown to give only the (*E*) form of the exocyclic enol ⟨86JCS(P2)1911⟩. A substantial amount of information is available for cyclic dipeptides of general type (**38**), where R = H ⟨86MRC41⟩, benzyl ⟨92MI 811-05⟩, *iso*propyl ⟨85S181⟩, and CH_2CO_2H ⟨79T441⟩. A fully assigned spectrum of the perhydropyrrolo[1,3]oxazinone (**39**) has been published ⟨91JCS(P2)735⟩.

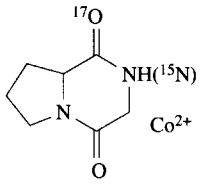


8.11.3.2.3 Other nucleii

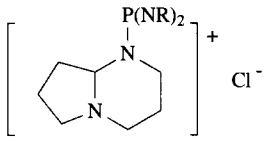
Nitrogen-15 shifts for pyrrolopyrimidine (**40**) showed the N2 signal at −129.8 ppm ($J_{N2,H}$ = 13.7 Hz) and that for N9 at 187.4 ppm relative to nitromethane ⟨87LA491⟩. For cyclic dipeptide Co^{2+} complexes of labeled compounds such as (**41**), ^{14}N and ^{15}N NMR shifts were used to determine the binding site; ^{17}O resonances were also recorded (⟨89MI 811-03⟩ for other ^{17}O shifts see ⟨85MI 811-01⟩). The N1 substituted pyrrolopyrimidines (**42**) have been examined by ^{31}P and by ^{13}C NMR ⟨93AG(E)399⟩.



(40)



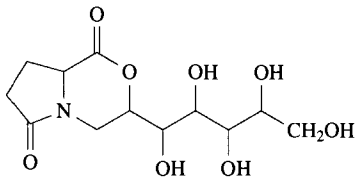
(41)



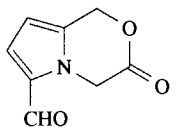
(42)

8.11.3.3 Mass Spectroscopy

The major use of mass spectroscopy has been in the identification of small quantities of natural products, such as Agropine (**43**) ⟨80TL495⟩, or in complex mixtures from Maillard reactions, as for example compound (**6**) ⟨90MI 811-01⟩ or the pyrrolo[1,4]oxazinone (**44**) ⟨93MI 811-01⟩. Resonant two-photon ionization has been used to identify thermal decomposition fragments from small peptides, including cyclo Pro/X dipeptides ⟨89RCM12⟩. The pyrrolothiazine (**7**) shows a strong M^+-1 peak which may correspond to the fully delocalized ion ⟨89TL4507⟩.



(43) Agropine



(44)

8.11.3.4 Electronic Spectra, Infrared Spectra

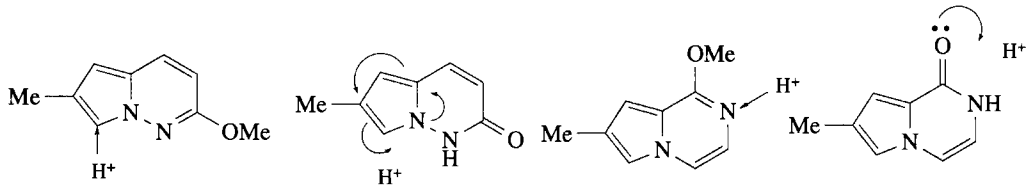
These spectra are reported predominantly as aids to structure determination. There is a calculation for the lower singlet–singlet transitions for compounds (**10**) and (**11**) compared with experimental values ⟨80KGS984⟩. The electronic spectra of compounds (**9**) ⟨77JOC2448⟩ and (**12**) ⟨77AHC1⟩ are reported elsewhere. Among more specialized techniques, UV resonance Raman spectra have been used to study the effect of *cis*, *trans* isomerism and hydrogen bonding on the amide II (C(O)—N stretch) vibration of the X—Pro bond, the model being *cyclo*(Pro–Gly) ⟨90MI 811-06⟩. Other workers have used Raman, UV fluorescence, and CD techniques to study metal complexes with cyclic dipeptides *cyclo*(Pro–Lys), (Pro–Glu), and (Pro–Cys–Cys) ⟨82HCA775⟩. A Meisenheimer complex between 1,3,5-trinitrobenzene and dbn has maxima at 438 and 517 nm in DMSO ⟨86JCR(S)344⟩.

8.11.4 THERMODYNAMIC ASPECTS

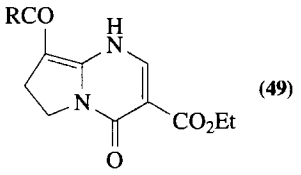
8.11.4.1 General and Aromaticity

The entries in this section are mostly concerned with protonation or with deprotonation/epimerization. There is a striking divergence between the pyrrolopyridazines (**45**) and (**46**) on one hand and the pyrrolopyrazines (**47**) and (**48**) on the other; in the former, protonation at carbon predominates ⟨92H(34)1759⟩. Protonation of the pyrrolopyrimidinone aldehydes and ketones (**49**) was studied by ^1H and ^{13}C NMR and by UV spectroscopy, showing that the preferred protonation site was at carbon 8a, giving exocyclic enols ⟨86JCS(P2)1911, 89JCS(P2)1613⟩. Proton transfer on the peptide bond in *cyclo*(Pro–Gly) was studied by ^2H NMR spectroscopy ⟨88T2483⟩, and deprotonation/equilibration on all four enantiomers of *cyclo*(Pro–His) ⟨85JMC1745⟩. A collection of thermodynamic data for small cyclic dipeptides dissolved in water provided a rationale for enthalpy

and entropy convergence temperatures for small globular protein denaturization ⟨91MI 811-03⟩. A scale of aromaticity based on calculations of diamagnetic susceptibilities places the azaindolizines in the order (**12**) < (**10**) < (**11**) ≤ indolizine < (**9**) ⟨80KGS984⟩.



(45) (46) (47) (48)



(49)

8.11.4.2 Conformation

A number of conformations have been suggested on the basis of NMR studies (see section 8.11.3.2 for compounds (**27**)–(**30**)). Cyclic dipeptides *cyclo*(Pro–X) have been most thoroughly studied, by x-ray in the solid state, and by NMR in solution. In the majority of cases the diketopiperazine ring is a boat in solution, and sometimes also in the solid, but there are a number of cases in which the diketopiperazine is a flattened chair in the solid ⟨90MI 811-04, 92MI 811-02, 92MI 811-05⟩. The x-ray structure of the N-substituted compound (**32**) has a diketopiperazine ring described as "slightly boat-shaped" ⟨86MI 811-03⟩.

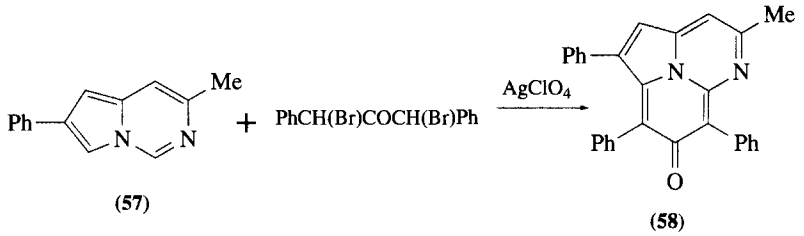
8.11.5 REACTIVITY (FULLY CONJUGATED)

Fully conjugated systems are reported only for systems (**9**)–(**12**). Reactions are subdivided into those which involve addition (mainly cycloaddition), and those which involve substitution (including *N*-alkylation), sometimes with ring opening.

8.11.5.1 Addition

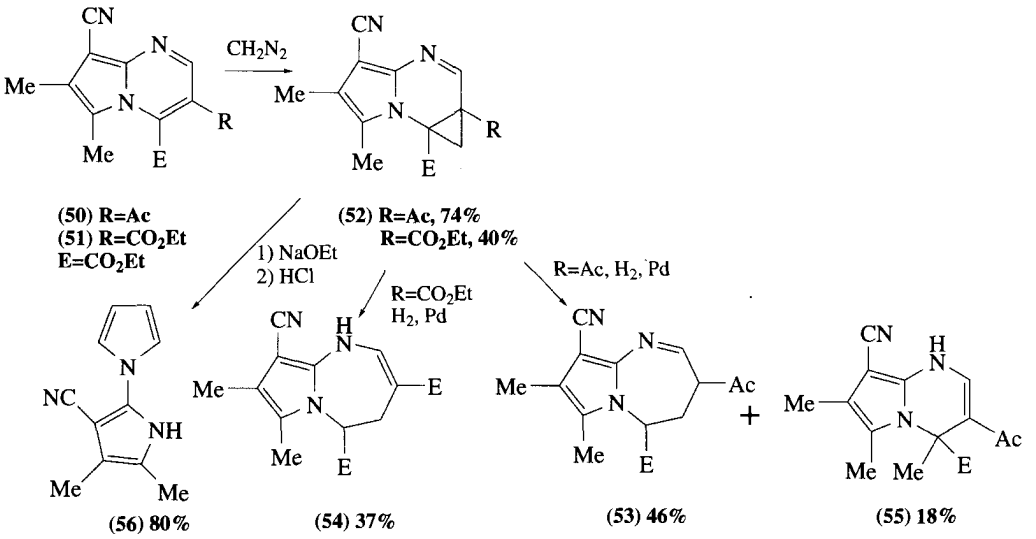
Pyrrolopyrimidines (**50**) and (**51**) react with diazomethane to give cyclopropane derivatives (**52**), in the latter case mixed with pyrazolines ⟨83JHC81⟩. The cyclopropanes are catalytically reduced to give pyrrolodiazepine derivatives (**53**) and (**54**) and pyrrolopyrimidines (**55**), and on treatment with sodium ethoxide give 2-(1-pyrryl)-pyrroles (**56**) (Scheme 2).

A reaction which may involve an [8 + 3] cycloaddition with diphenylcyclopropenone converts compound (**57**) into the azacyclazine (**58**) (Equation (2)) ⟨86YZ1098⟩.



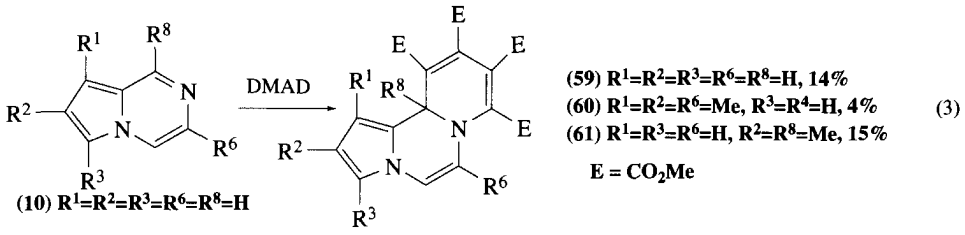
(57) (58) (2)

Reactions with DMAD have been reported for compounds (**11**) and (**12**) in which the alkyne adds across positions 1 and 7 ⟨77AHC1⟩. The reactions of DMAD with compound (**10**) and its derivatives are more variable. When no 1-methyl substituent is present, reaction at room temperature

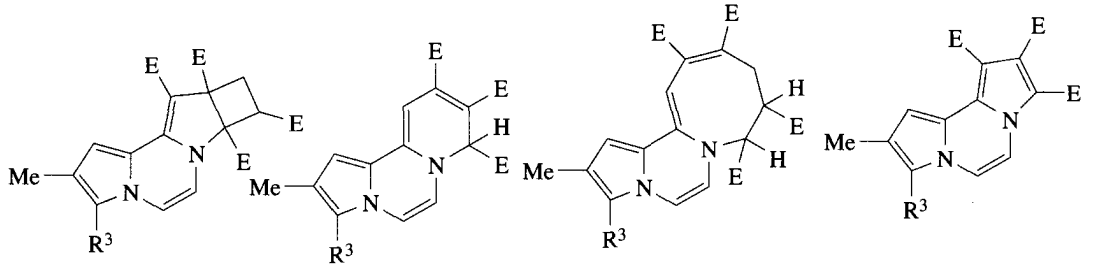


Scheme 2

gives the tricycles (**59**) and (**60**) (Equation (3)) ⟨89JOC1074⟩. A similar product (**61**) is formed when an 8-methyl pyrrolopyrazine is used, but is accompanied by four other products (**62**)–(**65**) ⟨90H(31)1459⟩.

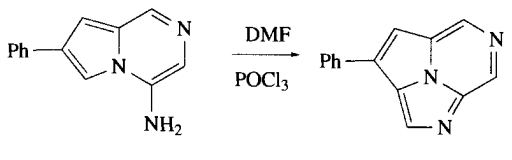


(3)



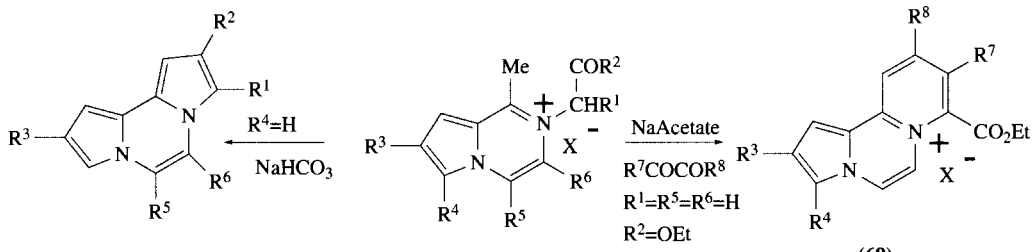
(62)	(63)	(64)	(65)
R^3=H 6%	3.3%	6%	3.3%
R^3=Me 2%	2%	7%	6%

Reactions in which the effect is to add rings, but which do not involve conventional cycloaddition, are that involving the amine (**66**) and the Vilsmeier reagent, to give diazacyclazine (**67**) (Equation (4)) ⟨78JOC3544⟩ and those involving cyclization between an activated methyl or methylene group and an adjacent carbonyl group. Examples are the synthesis of dipyrrolopyrazines (**68**) ⟨89H(28)857, 91H(32)85⟩ and the use of added α-diketone to give pyrroloquinolizinium salts (**69**) (Scheme 3) ⟨91T7329⟩.



(66) (67)

(4)



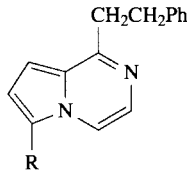
(68) 13-66%

(69)

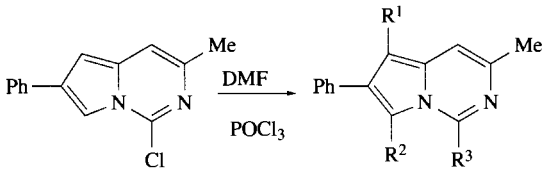
Scheme 3

8.11.5.2 Substitution

Substitution by electrophiles would be expected in the pyrrole ring of compounds (**9**)–(**12**). Such reactions on a derivative of (**10**) occur at C-6 and C-8, on compound (**11**) at C-7, and on derivatives of compound (**12**) at C-7, then C-6, and with bromine also at C-3 ⟨77AHC1⟩. Compound (**70**) reacts with butyl nitrite to give the nitroso derivative (**71**) ⟨90USP5041442⟩. A Vilsmeier reaction on pyrrolopyrimidine (**72**) gave three products, two of which also showed nucleophilic substitution of the chlorine substitutent ⟨78JOC3544⟩. TMS substituents on pyrrolopyridazine (**73**), its 3,4-benzo derivative, and the isomeric pyrrolopyrazine could be removed by TBAF ⟨83H(20)1009⟩. For protonation see Section 8.11.4.1.1. Quaternization by alkyl halides occurs at the nonbridgehead nitrogen, as in the formation of compound (**74**) (Equation (5)) ⟨91T7329⟩.



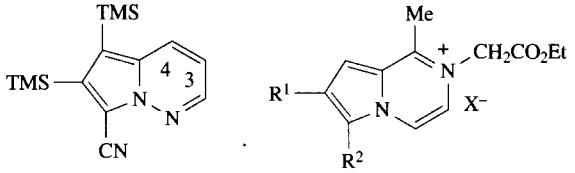
(**70**) R=H
(**71**) R=NO



(5)

(**72**)

R1=CHO, R2=H, R3=Cl, 3%
R1=CHO, R2=H, R3=NMe2, 6%
R1=H, R2=CHO, R3=NMe2, 25%

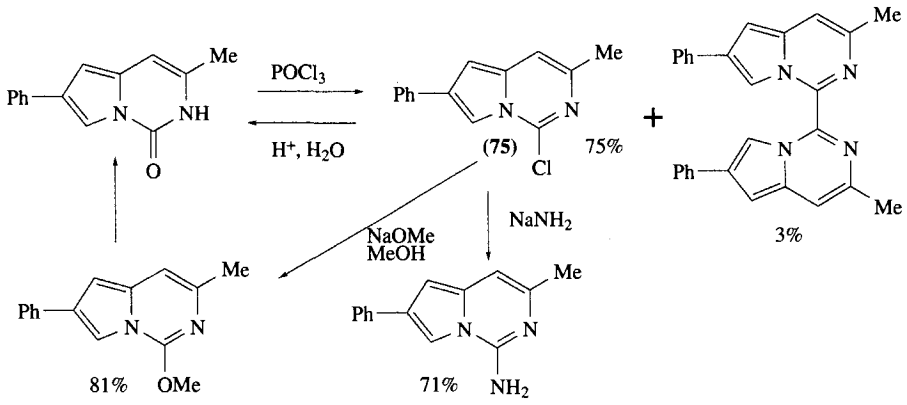


(**73**)

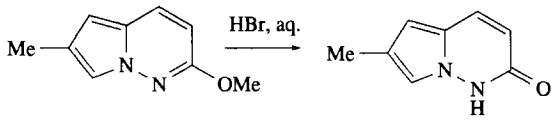
(**74**)

Nucleophilic substitution takes place on the six-membered ring. Typical reactions are shown in Scheme 4 for a 1-chloropyrrolo[1,2-*c*]pyrimidine (**75**) ⟨78JOC3544⟩. Similar sequences are reported for 2-chloropyrrolo[1,2-a]pyrimidines ⟨78JOC3544⟩ and for 1-chloropyrrolo[1,2-*a*]pyrazines ⟨89JOC1074⟩. In both cases the chloro compound is formed from the corresponding oxo derivative. The

2-methoxypyrrolopyridazine (**76**) is converted into pyridazinone (**77**) by aqueous HBr (Equation (6)) ⟨92H(34)1759⟩.

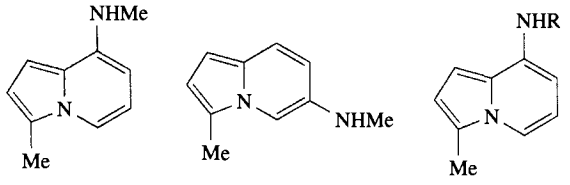


Scheme 4

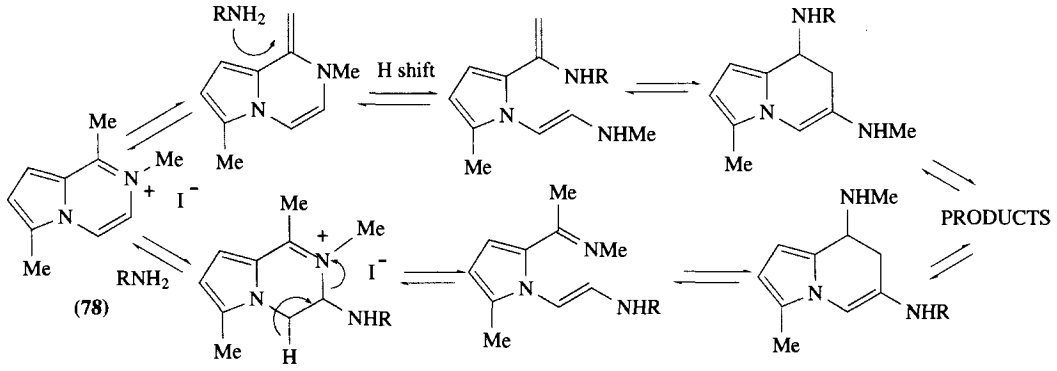


(76) (77) (6)

The *N*-methylpyrrolopyrazinium iodides (**78**) react with primary amines at 150°C in a Kost–Sagitullin rearrangement via monocyclic intermediates to give aminoindolizines. Attack is at C-1 or C-3 and recyclization can give either 8-amino- (**79**) or 6-aminoindolizines (**80**) with the former predominating ⟨92KGS921⟩. The two monocyclic intermediates allow cyclization to give two different amines, normally (**81**) which results from loss of methylamine, but as the attacking amine becomes larger, the proportion of the methylaminoindolizine increases ⟨92KGS1485⟩. Scheme 5 summarizes results from a number of papers (see also ⟨89KGS424, 91KGS763⟩).

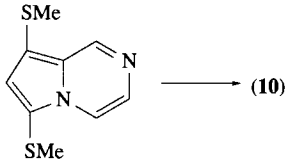


(**79**) (**80**) (**81**) **81% when R=Et**
41% when R=Bu^t



Scheme 5

Reductive substitution of methylthio groups using Raney nickel, as in compound (**82**) has been reported (Equation (7)) ⟨82TL3565⟩.



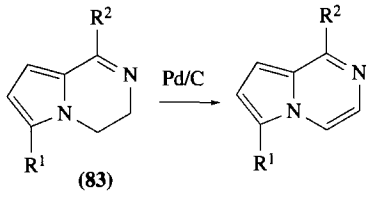
(82) (7)

8.11.6 REACTIVITY (NONCONJUGATED)

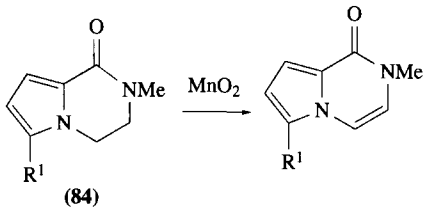
This section deals with reactivity of the ring system itself, reactions on substituents being dealt with in Section 8.11.7. The reactions are sub-divided into oxidation and reduction, substitution, addition of extra rings, and ring opening.

8.11.6.1 Oxidation and Reduction

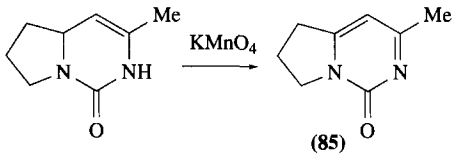
Oxidation is of importance in introducing extra unsaturation into a partly hydrogenated ring. A synthesis which produces the dihydropyrrolopyrazines (**83**) and (**84**) was completed by Pd/C dehydrogenation ⟨81S481, 91KGS763⟩ or by manganese dioxide oxidation (Equations (8) and (9)) ⟨88AJC1583⟩. At a higher level of saturation, permanganate oxidation produced pyrimidinone (**85**) (Equation (10)) ⟨77TL627⟩ and Pd/C or Raney nickel the tetrahydropyrrolopyrazines (**86**) (Equation (11)) ⟨87KFZ1054⟩. The introduction of unsaturation in compounds (**87**) is dealt with here for convenience (Equation (12)) ⟨83JHC393⟩. Aerial oxidation of the pyrrolopyridazinone (**88**) gives a radical, most probably (**89**) (Equation (13)) ⟨87JCS(P1)2511⟩. Swern oxidation of lactol (**90**) gives a lactone (Equation (14)) ⟨92SL847⟩ and Gif^{IV} oxidation of dbn introduces a carbonyl group at C-2 ⟨92MI 811-01⟩.



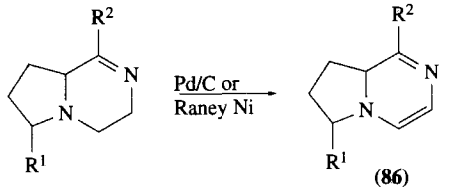
(83) (8)



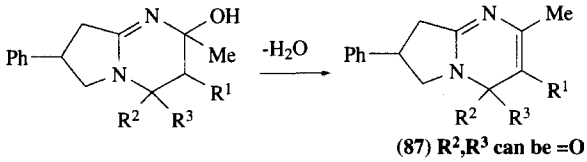
(84) (9)



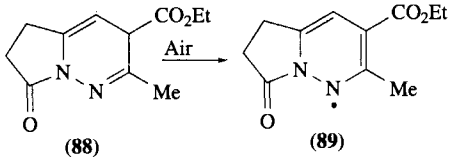
(85) (10)



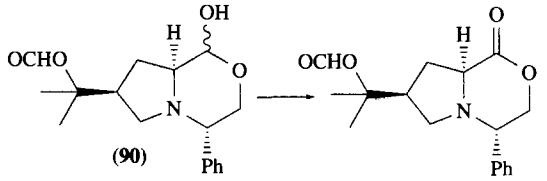
(11)



(12)

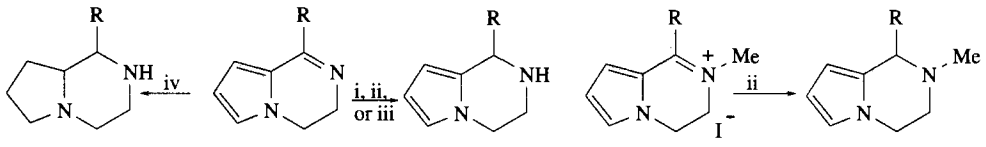


(13)



(14)

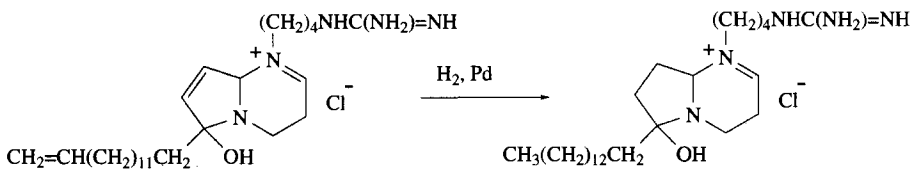
Reduction of the most unsaturated rings is dealt with first. Dihydropyridopyrazines (**91**) are reduced by sodium or potassium borohydride ⟨81S481, 81URP798104, 86ZOR2610⟩ or by hydrogen with palladium catalysts or LAH ⟨80GEP(O)2832488⟩ to the tetrahydro derivatives (**92**); quaternary salts (**93**) are also reduced by borohydride ⟨81S481⟩. Platinum, palladium or nickel catalysts with hydrogen at higher temperatures and pressures reduce compounds (**91**) or (**92**) to the perhydro derivatives (**94**) (Scheme 6) ⟨79GEP(O)2844549, 93KFZ46⟩. The tetrahydropyrrolopyrimidine (**95**) is reduced by sodium borohydride at room temperature to the perhydro derivative (**96**); at 60 °C both (**95**) and (**96**) are converted into the pyrrylpropylamine (**97**) (Scheme 7) ⟨91SL821⟩. Phloeodictine A is reduced by palladium and hydrogen to the tetrahydro derivative (**98**) (Equation (15)) ⟨92JOC3832⟩ and the various cyclic imines (**99**)–(**101**), respectively, by LAH, sodium borohydride, or hydrogen and palladium or platinum ⟨87KFZ1054⟩, and by platinum oxide and hydrogen ⟨87TL1573⟩. After acylation, pyridazine (**102**) can be further reduced to (**103**) by sodium in ammonia (Scheme 8)



(**94**) (**91**) (**92**) (**93**)

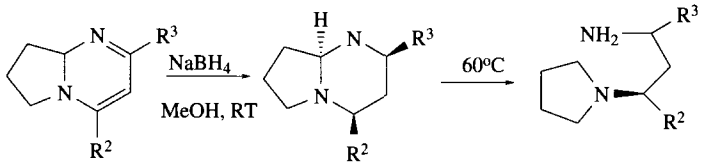
i, $NaBH_4$; ii, LAH; iii, H_2, Pd; iv, Ni, Pd, or Pt, 100-180°C, 100-80 atm. H_2

Scheme 6



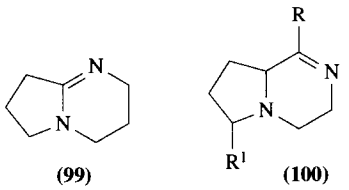
Phloeodictine A (**98**)

(15)

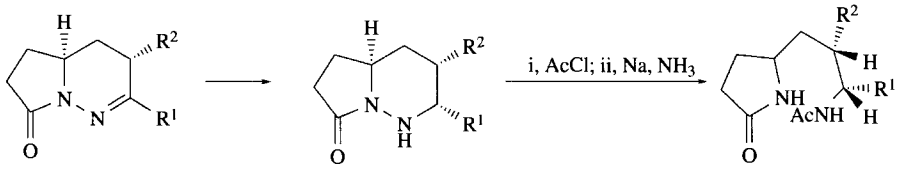


(95) (96) (97)

Scheme 7



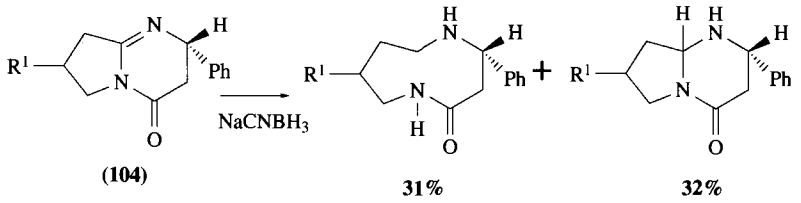
(99) (100)



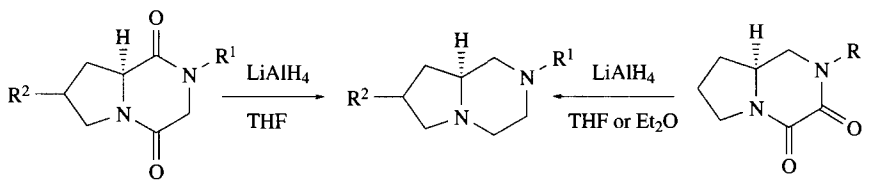
(101) (102) (103)

Scheme 8

The compound (**104**) undergoes partial cleavage of the bridging bond when treated with sodium cyanoborohydride; the mechanism has been studied by using sodium cyanoborodeuteride (Equation (16)) ⟨87H(26)85⟩. The other major interest in reduction is in the conversion of carbonyl to methylene groups. Examples of procedures are given by the reduction of compounds (**105**) ⟨93JMC2311⟩, (**106**) ⟨90JHC2181⟩, (**107**) ⟨83IJC(B)664⟩, and (**108**) (Scheme 9) ⟨89TL3551⟩.



(104) 31% 32% (16)



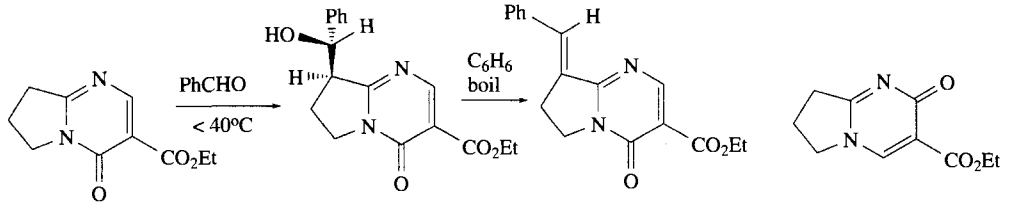
(105) R^1=R^2=H
(106) R^1=various, R^2=OH, 53-73%
(107) R=H, 40%
(108) R=Ph, 78-87%

Scheme 9

8.11.6.2 Substitution

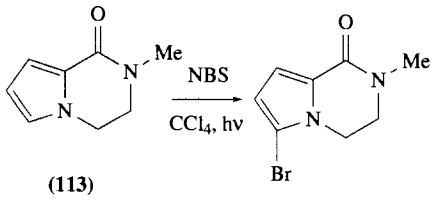
Substitution of these disparate systems is organized by increasing degree of saturation; most of the reactions are on perhydro compounds. The pyrrolopyrimidinone (**109**) reacts with benzaldehyde

at temperatures below 40 °C to give the aldol product (**110**); at higher temperatures dehydration occurs, giving (**111**) (Scheme 10); the isomer (**112**) behaves similarly to give a benzylidene derivative ⟨89JHC1061⟩. The pyrrolopyrazine (**113**) is brominated by NBS (Equation (17)) ⟨88AJC1583⟩. The pyrrolopyrimidinedione (**114**) is substituted on N-3 under Mitsunobu conditions to give (**115**) (Equation (18)) ⟨90CPB2726⟩.

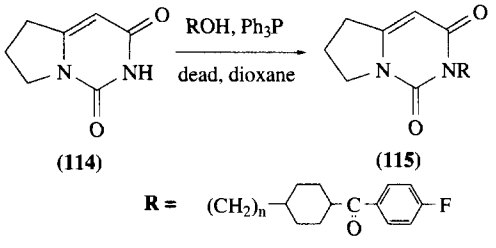


(109) (110) 38% (111) (112)

Scheme 10

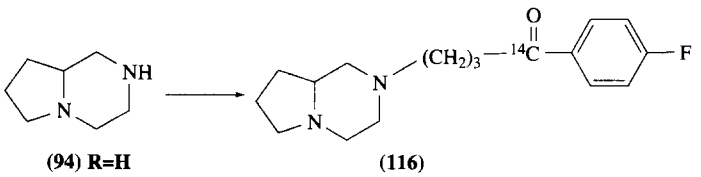


(113) (17)

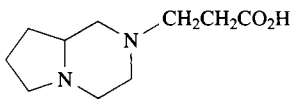


(114) (115) (18)

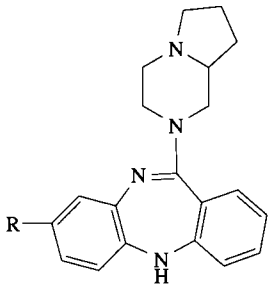
Substitution on saturated systems requires activation by adjacent groups (except at nitrogen) or the presence of a good leaving group. All substitutions quoted here involve derivatives of pyrrolopyrazine (**10**). The perhydro derivative (**94**; R = H) reacts conventionally with acid chlorides ⟨81KFZ55⟩ or alkyl halides as exemplified by the synthesis of labeled Azabutyrone (**116**) (Equation (19)) ⟨82KFZ833⟩, or in a Michael reaction with acrylic acid to produce (**117**) ⟨80KFZ87⟩, or with a dibenzodiazepinone to give (**118**) ⟨84PHA812⟩. More commonly reaction is with the amide NH of pyrrolopyrazinediones (*cyclo* (Pro–X)) to produce intermediates for the synthesis of natural products. Some conventional protecting groups will be found in other sections, but a number of authors have reported acylations with α-hydroxyacetic acid derivatives with subsequent hemiketalization to the adjacent carbonyl group, as in the preparation of compound (**119**) (Equation (20)) ⟨63HCA2306, 79EUP3286, 89CZP258579⟩). The 3-indolylmethyl derivatives (**120**) and (**121**) have been cyclized to form CN bonds by acid (Scheme 11 and Equation (21)) ⟨78JA5564, 85CPB4783⟩, and by a photochemical route ⟨77H(6)1675, 81JCS(P1)959, 82JAP(K)8211984⟩, respectively. A Michael addition with 1-methoxy-3-formylindole gives (**122**) (Equation (22)) ⟨94H(38)273⟩.



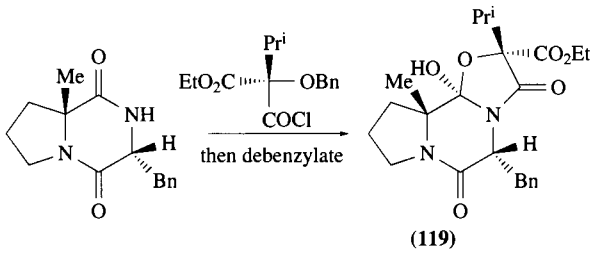
(94) R=H (116) (19)



(117)

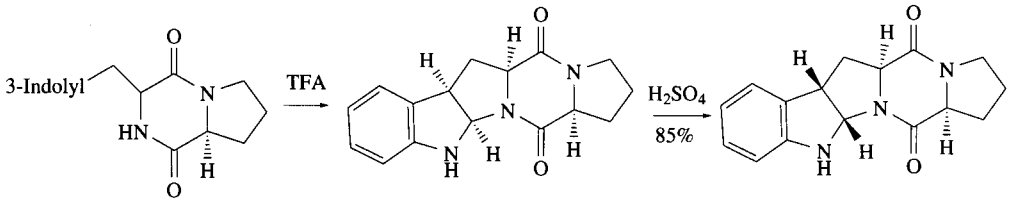


(118) R=H, Cl



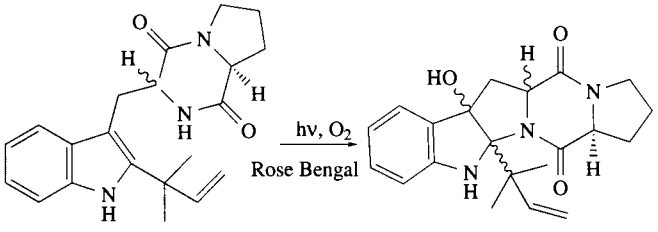
(119)

(20)



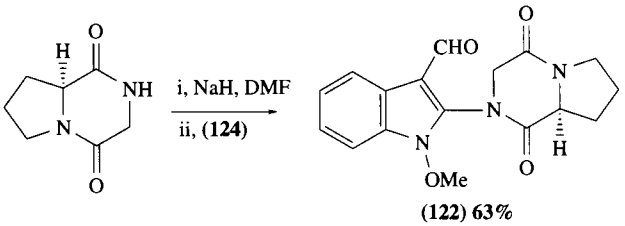
(120) **(A) + (B) (1.75:1)** **(B)**

Scheme 11



(121)

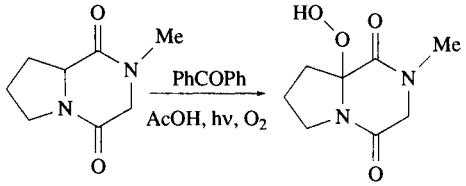
(21)



(122) 63%

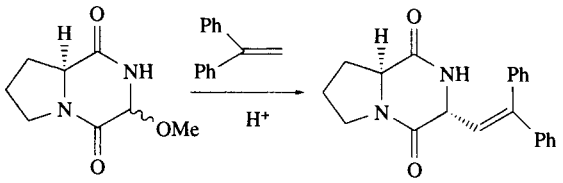
(22)

Substitution at carbon usually involves enolates, but there is one radical functionalization at C-8a to give peroxide (**123**) (Equation (23)) ⟨78CB361⟩. Functionalization at C-3 has been achieved using acid-catalyzed replacement of a methoxyl group by a styrene, giving (**124**) with 98 ± 1% d.e. (Equation (24)) ⟨91T563⟩. Most commonly used are strong bases to give an anionic center at C-3, which can react with aldehydes as in the synthesis of indole (**125**) (Equation (25)) ⟨86TL2391⟩; for an indoline aldehyde see ⟨88TL2539⟩; and the labeled tryptamine (**126**) (Equation (26)) ⟨80JA3974, 88JA5927, 93T8471⟩. In the last case the activating methoxycarbonyl group at C-3 is similarly inserted, using methyl chloroformate. In the isomeric diketopiperazine (**127**) alkylation gives substitution at C-7 (Equation (27)) ⟨92TL2187⟩. A bridged diketopiperazine (**128**) has been prepared by intramolecular S_N2'-substitution (Equation (28)) ⟨86TL3581, 88JA5927⟩. A Wittig reaction has been used to prepare the alkylidene derivatives (**129**) (Equation (29)) ⟨87TL4275⟩, and an aldol reaction to give pyrrolooxazine (**130**) ⟨91EUP438311⟩.



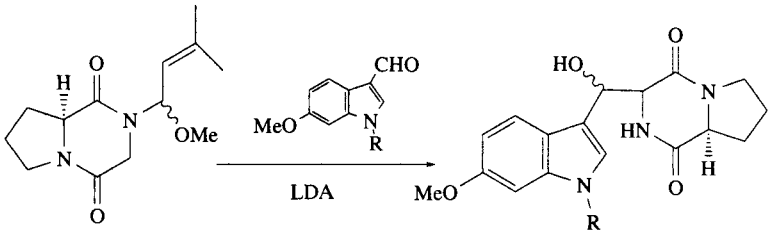
(123) 35%

(23)



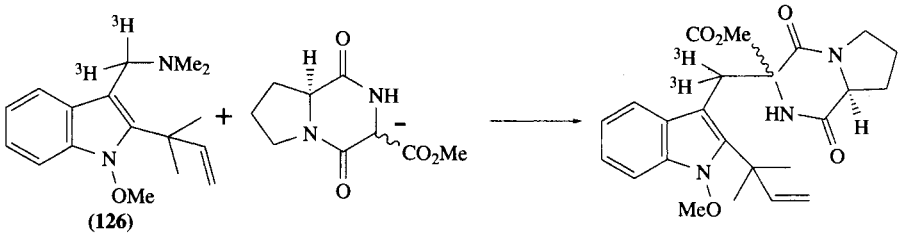
(124) 40%

(24)



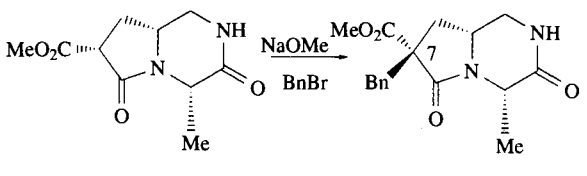
(125)

(25)



(126)

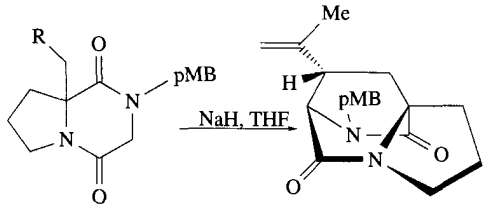
(26)



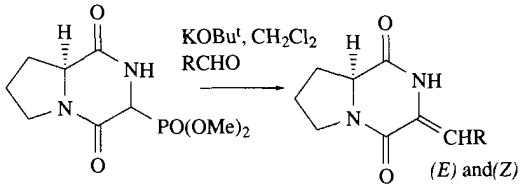
(127)

+ epimer at C7

(27)



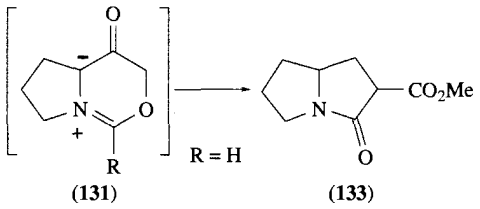
R = CH=C(Me)CH_2Cl **(128)** (28)



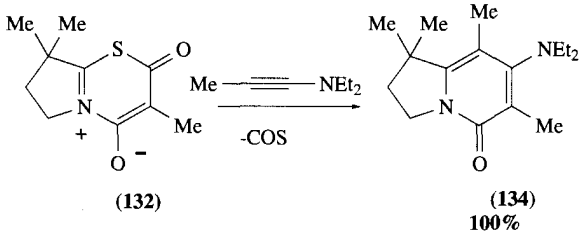
(129) various R (29)

8.11.6.3 Addition of Extra Rings

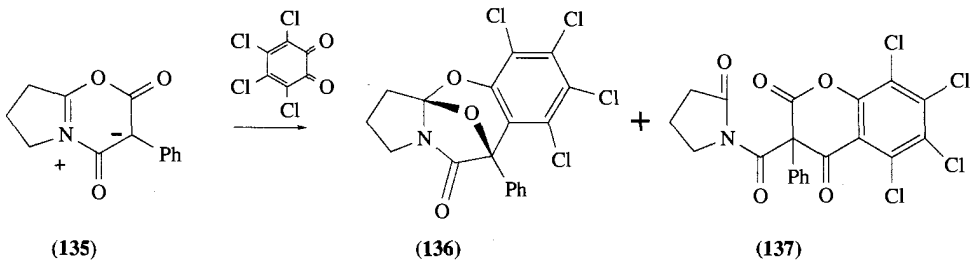
These reactions are sub-divided into those which involve cycloaddition, and those involving reaction between substituents already present. The mesoionic compounds (**131**) ⟨92JA593⟩ and (**132**) ⟨93TL5405⟩ which are reactive intermediates undergo cycloaddition reactions with loss of COS from the first addition product to give products of type (**133**) and (**134**), respectively (Equations (30) and (31)). The formation of the cycloadduct (**136**) from the mesoionic compound (**135**) is suggested to involve an eight-membered ring intermediate ⟨82ZN(B)222⟩; the pyrrolidone (**137**) is also formed (Equation (32)). Dihydropyrrolopyrazine (**91**; R = Me) reacts quite differently with diphenylcyclopropenone (**138**) and its dicyanomethylene derivative (**139**). In the former case a five-membered ring is formed to give (**140**) ⟨86S899⟩, in the latter a six-membered ring, giving (**141**) ⟨86S908⟩. The imine (**91**, R = H) reacts with a β-diketone to form a diazasteroid (**142**) (Scheme 12) ⟨93ZOB701⟩.



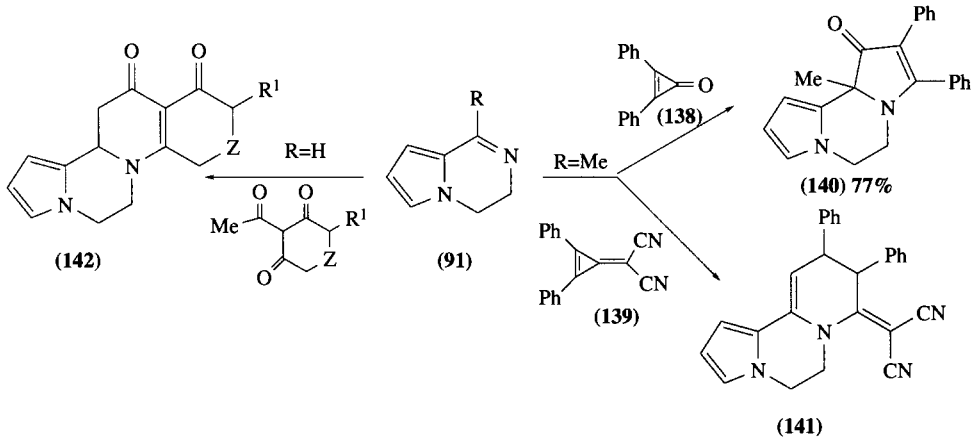
(131) **(133)** (30)



(132) **(134)** **100%** (31)

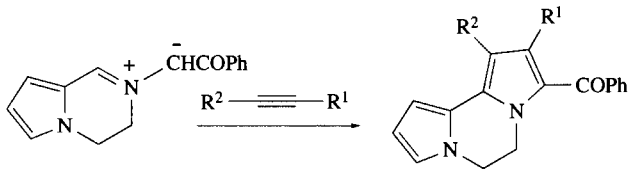


(135) **(136)** **(137)** (32)



Scheme 12

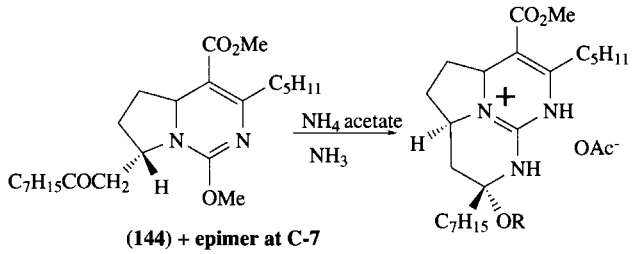
A 1,3-dipolar cycloaddition on the ylide (**143**) gives a dipyrrolopyrazine (Equation (33)) ⟨92T8793⟩. By treatment with ammonium acetate an additional pyridine ring is fused to the pyrrolopyrimidine (**144**) (Equation (34)) ⟨93TL2099⟩; a spiropyran is formed when the protected alcohol in the side chain of pyrrolopyrimidinone (**145**) is deprotected (Equation (35)) ⟨93JOC3235⟩. Tetracycles (**146**) and (**147**) are formed by cyclization between suitable substituents and an adjacent phenyl group; the reagents are acids, giving electrophilic substitution, for (**146**) (Equation (36)) ⟨90TL2189⟩, and light for (**147**) (Equation (37)) ⟨86EUP180544⟩.



(143)

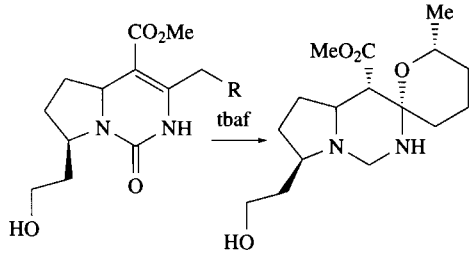
R^1=R^2=CO_2Me
R^1=H, R^2=CO_2Me

(33)



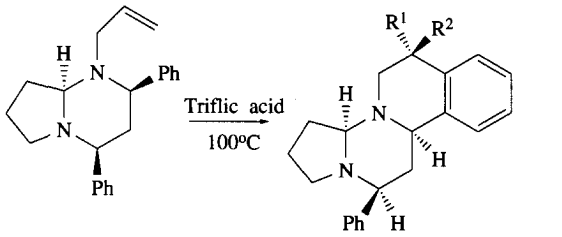
(144) + epimer at C-7

(34)

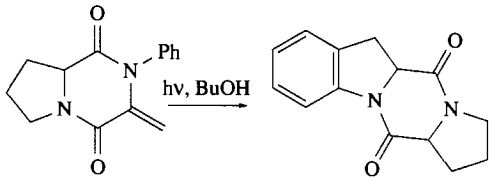


(145) R=(*S*)-3-(Bu^tMe_2SiO)$CH_2CH_2CH_2$

(35)



(36)



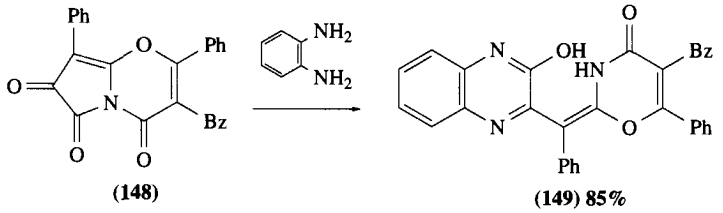
(147)

(37)

8.11.6.4 Ring Opening Reactions

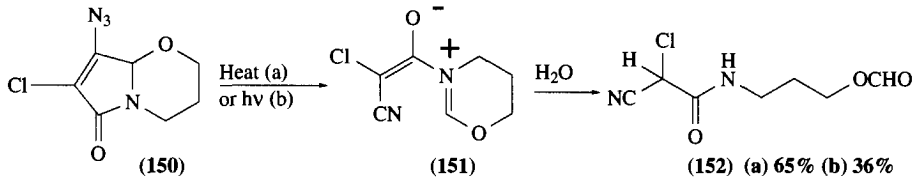
Most of the ring opening reactions have been performed on pyrrolooxazines, and many have been used as routes to enantiomerically pure acyclic or monocyclic compounds. Reactions are described for derivatives of each of the systems (**1**)–(**4**), in turn, and finally of system (**10**).

The highly substituted pyrrolo[2,1-*b*][1,3]oxazine (**148**) reacts as an α-diketone with *o*-phenylenediamine to give a quinoxaline with subsequent ring opening to compound (**149**) (Equation (38)) ⟨77LA1964⟩. The azide (**150**) on thermolysis or photolysis gives the mesoionic nitrile (**151**) which is hydrolyzed to the amidoester (**152**) (Scheme 13) ⟨81JA1769⟩. More common is opening of the acetal group to give a pyrrolidine. In the case of salt (**153**) at pH 8.3–8.81, the formation of the intermediate hemiacetal is first order in OH^- (Equation (39)) ⟨70JCS(D)900⟩. Titanium tetrachloride causes ring opening and recyclization of compound (**154**) (Equation (40)) ⟨89H(29)2089⟩, while compound (**155**) gives an *N*-pyrrylpropanol (**156**) when treated with LAH, but ketone exchange and recyclization to give the isoindolone (**157**) when heated with *o*-benzoylbenzoic acid and a proton source (Scheme 14) ⟨69JOC165⟩.



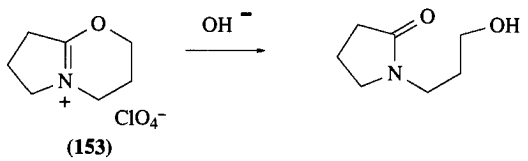
(148) (149) 85%

(38)



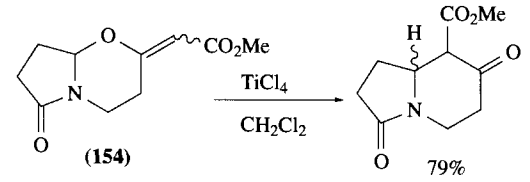
(150) (151) (152) (a) 65% (b) 36%

Scheme 13

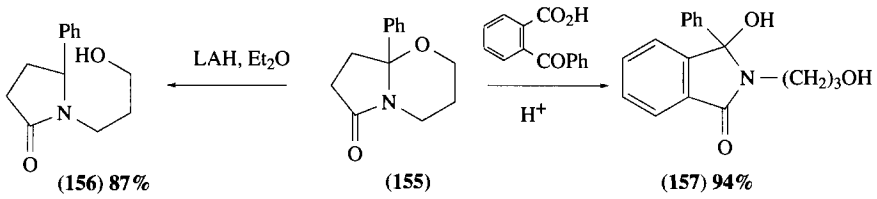


(153)

(39)

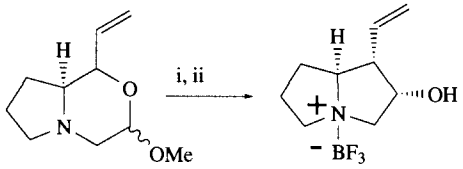


(40)



Scheme 14

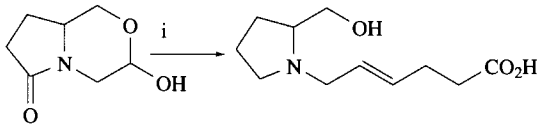
Almost all the many ring opening reactions in the pyrrolo[1,2-*b*][1,4]oxazine series are performed on cyclic acetals, lactones, or lactams and involve simple hydrolysis. The cyclic acetal (**158**) opens and recyclizes on treatment with a zirconium reagent and subsequently with BF_3 etherate to give pyrrolizine (**159**) (Equation (41)) ⟨94JA5469⟩, while the hemiacetal (**160**) reacts with the Wittig reagent (**161**) to give a prostaglandin analogue (Equation (42)) ⟨77GEP(O)2528664⟩.



(41)

(**158**) (**159**)

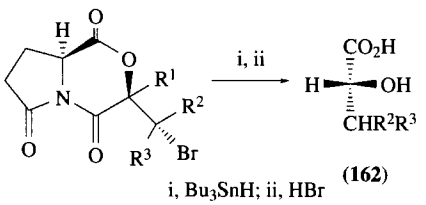
i, "Cp_2Zr"; ii, $BF_3{\cdot}Et_2O$



(42)

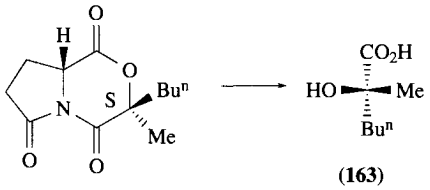
(**160**) i, $Ph_3P{=}CHCH_2CO_2H$ (**161**)

Since 1-oxo derivatives are lactones, hydrolysis can be used to produce an acyclic product from the six-membered ring, or a pyrrole or pyrrolidine derivative. The most important example of the former is the use of the asymmetric induction of proline to produce a pyrrolooxazinone usually by bromolactonization (Section 8.11.9.1.3.iii), hydrolysis then producing enantiomerically pure α-hydroxyacids. Examples are compounds (**162**) (Equation (43)) ⟨77CL1109, 78JAP(K)78108997⟩, and (**163**) (Equation (44)) (⟨86EUP198348⟩; see also ⟨78JAP(K)78108922, 81T2797, 88JMC885, 89CL465, 91JCS(P2)53⟩). An extension of this approach allows the bromoalkyl derivatives to be converted into the *N*-substituted proline (**164**) and subsequently by reduction with Vitride into epoxides (**165**) with high *ee* values (Scheme 15) ⟨80TL2733, 81JAP(K)81123976, 81T2797⟩).



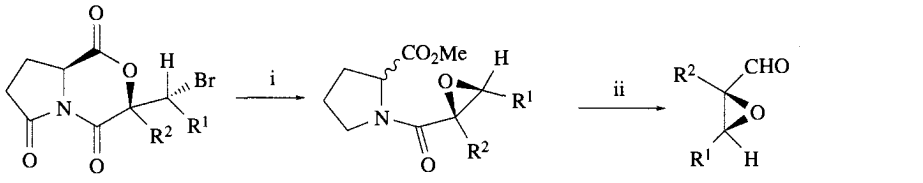
(43)

i, Bu_3SnH; ii, HBr (**162**)



(44)

(163)



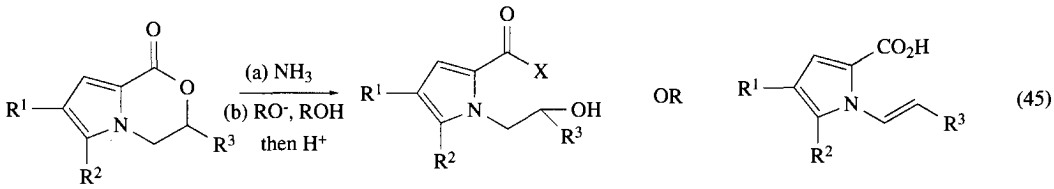
(164)

(165) R^1=Ph, R^2=Me, 72%, 98% ee

i, NaOMe, MeOH; ii, Vitride

Scheme 15

In the case of the dihydro derivatives (**166**) ⟨68MI 811-01, 70FRP1592066⟩, (**167**) ⟨72T1113⟩, and (**168**) ⟨83JOC3234⟩, the lactone is opened by ammonia, by methoxide, and by *t*-butoxide (or $POCl_3/PCl_5$); in the last case, dehydration occurs when acidification is performed (Equation (45)).



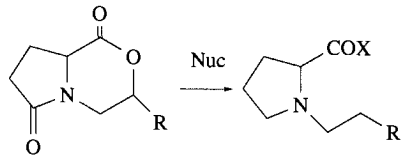
(45)

(166) R^1=R^3=H, R^2=NO_2
(167) R^1=R^2=H, R^3= Ph
(168) R^1=R^2=H, R^3=Aryl

From (**167**) when R = Me
Reagent (b) gives X=OR
Reagent (a) gives X=NH_2

From (**168**) when R = Bu^t

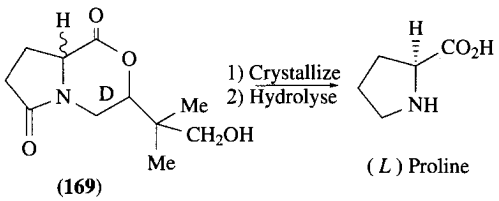
Opening of lactones to give simple proline derivatives has been used in the elucidation of the structure of Agropine (**43**) ⟨80TL495⟩, and sodium prolinate has been resolved by forming the lactone (**169**), fractionally crystallizing the diastereomers, and hydrolyzing to give pure L-proline (Equations (46) and (47)) ⟨79KPS106⟩. In the ketoanhydride (**170**) attack by nucleophiles occurs at C-3 (see below also) to give N-substituted prolines (**171**) (Equation (48)) ⟨67JOC4072⟩



(46)

(43)

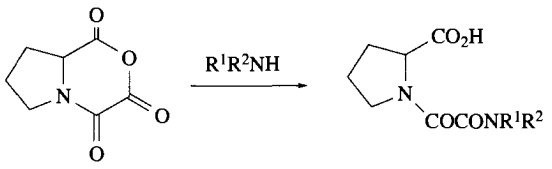
Nuc = ROH, $BnNH_2$, OH^-
R = $-(CH(OH))_3CH_2OH$



(47)

(169)

(*L*) Proline

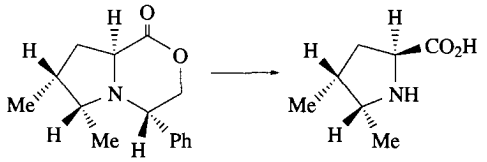


(48)

(170)

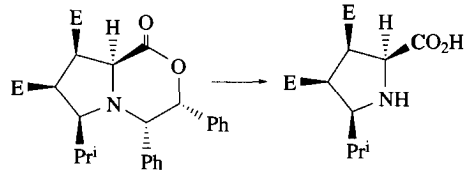
(171) $R^1R^2 = (CH_2)_4$, 53%; R^1=Ph, R^2=H, 87%

Synthesis of pyrrolo oxazines with high stereochemical purity in the pyrrolidine ring, such as (**172**) (Equation (49)) ⟨93TL537⟩ and (**173**) (Equation (50)) ⟨92JOC6527⟩ can lead, via catalytic hydrogenation, to highly substituted pyrrolidines. In another example, ring opening of the lactone (**174**) is by acryloyl chloride (Equation (51)) ⟨93T7239⟩.



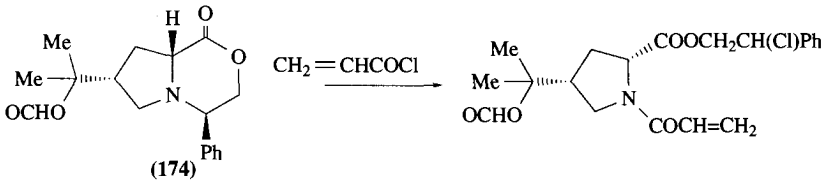
(49)

(172) 62%



(50)

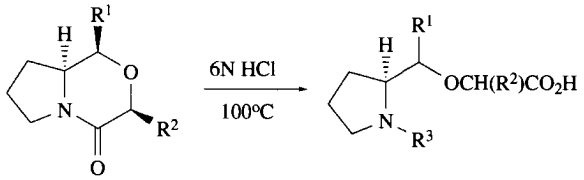
(173) E = CO_2Me 93-99%; >99%ee



(51)

(174)

A cleavage of the lactams (**175**) ⟨91JOC2624⟩ and (**176**) ⟨87JOC418⟩ with formation of 2-substituted pyrrolidines (**177**) and (**178**) has been reported (Equation (52)).



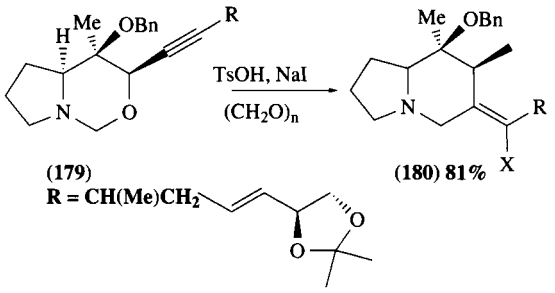
(52)

(175) and (177) R^1= ≡ TMS , R^2= Pr^i, R^3=H

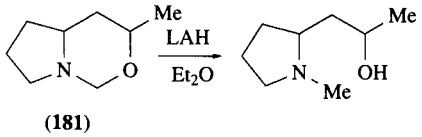
(176) and (178) R^1=H, R^2=Bn, R^3=Boc (after protection) 87%

Perhydropyrrolo[1,2-*c*][1,3]oxazines are derivatives of formaldehyde, and are cleaved by acid, the formaldehyde being trapped by dimedone ⟨60JOC2028⟩. With a suitable adjacent side chain, as in (**179**), acid cleavage, iodine promoted, in the presence of formaldehyde, gives, after recyclization, an indolizidine (**180**) (Equation (53)) ⟨92JA368⟩. Lithal has been used to prepare (±) *pseudo*hygroline from oxazine (**181**) (Equation (54)) ⟨60CCC483⟩. An indolizine is also produced from lactone (**182**) by treatment with base (Equation (55)) ⟨90H(302)885⟩, a pyrrolizidine from lactone (**183**) via an

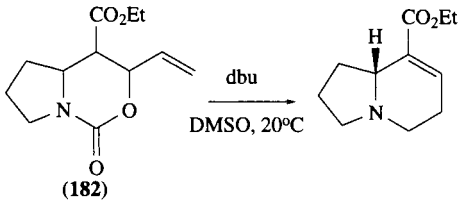
iron tricarbonyl intermediate (Equation (56)) ⟨91TL7119⟩, and a 2,5-disubstituted pyrrolidine from lactone (**184**) by a succession of reductive processes (Equation (57)) ⟨81TL4197⟩.



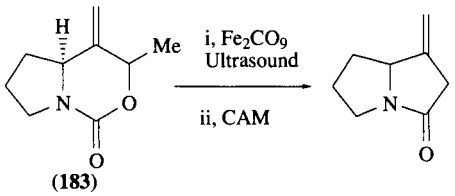
(53)



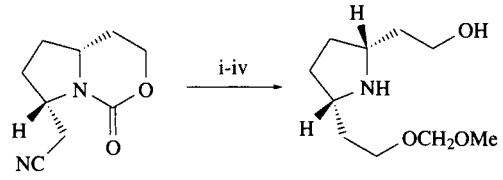
(54)



(55)



(56)

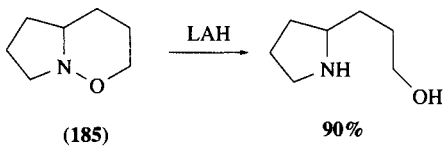


(184)

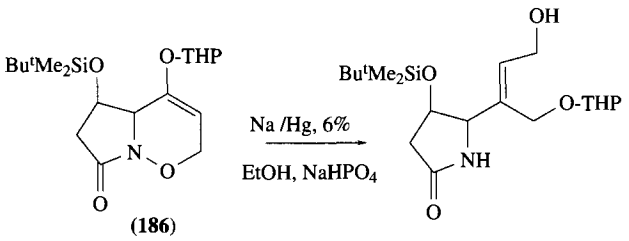
(57)

i, DIBAL; ii, $NaBH_4$, DME; iii, $MeOCH_2Br$, $Et(Pr^i)_2N$; v, $Ba(OH)_2$, boil

Pyrrolo[1,2-*b*][1,2]oxazines are cleaved by reducing agents, lithal being used for compound (**185**) (Equation (58)) ⟨60JA5148⟩ and sodium amalgam for the more complex case (**186**) (Equation (59)) ⟨80JA3632⟩.



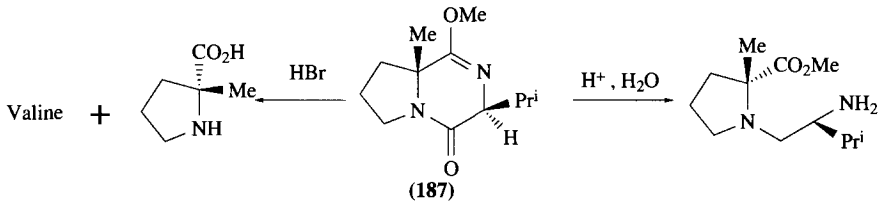
(58)



(186) (59)

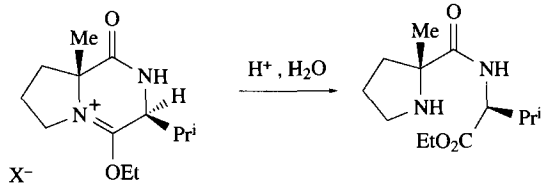
Ring opening of perhydropyrrolo[1,2-*a*]pyrimidines is described in Section 8.11.3.2.1.

Ring opening of cyclic dipeptides occurs under hydrolytic conditions (e.g. ⟨51JA2947⟩). The masked pyrrolopyrazinedione (**187**) is attacked at C-1. Under milder conditions all ring atoms are retained ⟨88LA1025⟩; more vigorous conditions give a proline derivative and L-valine (Scheme 16) ⟨87AG(E)137⟩. In the related compound (**188**) attack is at C-4 (Equation (60)) ⟨88LA1025⟩. With the pyrrolopyrimidinone (**189**) the rate determining step is attack by OH^- at C-2 (Equation (61)) ⟨82KGS518⟩.

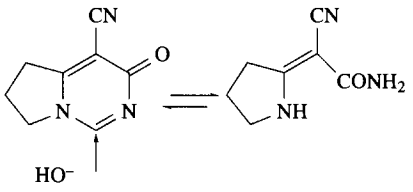


(187)

Scheme 16



(188) (60)

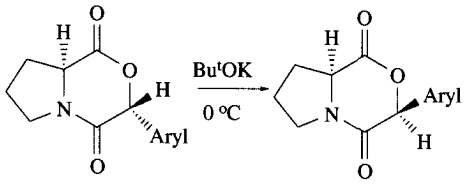


(189) (61)

8.11.7 SUBSTITUENTS ATTACHED TO CARBON

8.11.7.1 Pyrrolooxazines and Pyrrolothiazines

Most reactions of substituents attached to carbon are trivial transformations, such as hydrolysis of a nitrile to an amide on a 3,4-dihydropyrrolo[1,2-*c*][1,3]thiazine ⟨85EUP147317⟩, oxidation of a lactol (**90**) to a lactone by a Swern procedure ⟨92SL847⟩, or equilibration via enolization as in pyrrolooxazinedione (**190**) (Equation (62)) ⟨91NJC379⟩. Of more importance is the reductive debromination by tributyltin hydride of the bromomethyl derivatives formed by bromolactonization (see Section 8.11.6.4).

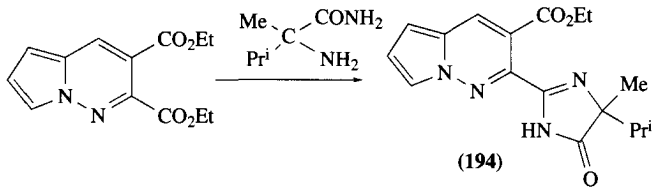


(62)

(190)

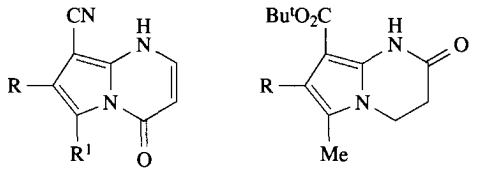
8.11.8.2 Pyrrolopyrimidines, Pyrrolopyrazines, and Pyrrolopyridazines

Many of the simple reactions (NHC=O → N=C—Cl, etc.) have been covered in Section 8.11.5.2 and more complex examples, involving cyclization between substituents, in Sections 8.11.5.1 and in 8.11.6.3. Hydrolysis of cyanides or *t*-butyl esters to carboxylic acids, with subsequent decarboxylation has been used to remove blocking groups after synthesis, as in the case of compounds (**191**) ⟨88IJC(B)1046⟩ and (**192**) ⟨87JHC661⟩. Raney nickel reduction has similarly been used to remove unwanted methylthio substituents in compound (**193**) ⟨82TL3565⟩; the methylthio groups are oxidized to sulphoxides or sulphones during metabolism in rats ⟨83AF(B)1289⟩. An ester group was converted into an imidazolone (**194**) in the synthesis of a herbicide (Equation (63)) ⟨94EUP580042⟩, and the formylpyrrolopyrimidine (**195**) was converted into the bis(pyrrolopyrimidinyl)methane (**196**) by borohydride or by sodium hydroxide in isopropanol (Equation (64)) ⟨93KGS137⟩.

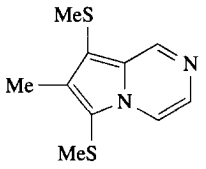


(63)

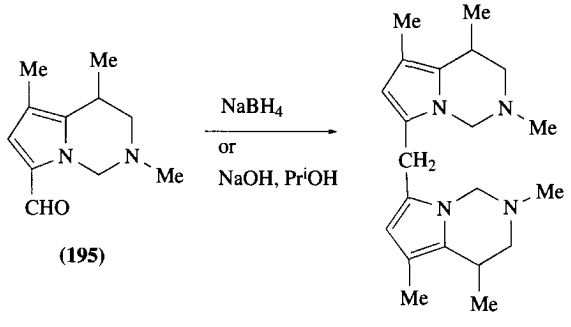
(194)



(191) (192)



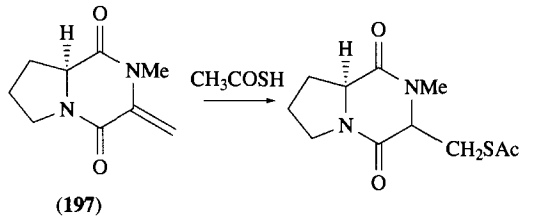
(193)



(64)

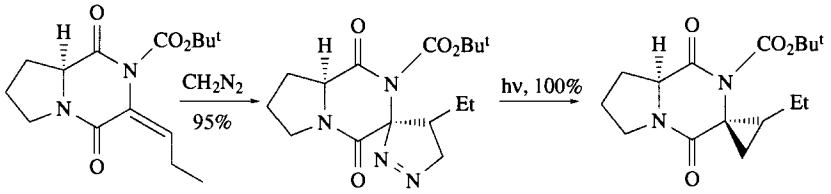
(195) (196)

There are a few reactions of double bonds, such as the addition of CH_3COSH to compound (**197**) (Equation (65)) ⟨84MI 811-01⟩ and the formation of *spiro*-cyclopropanes such as (**198**) by diazomethane addition (Scheme 17) ⟨89TL3101, 92TL5605⟩. An additional fused pyrimidine ring has been added to compounds (**199**) by a conventional route (Equation (66)) ⟨89MI 811-04⟩.



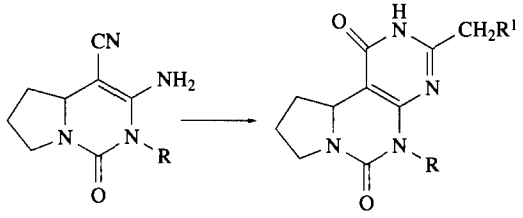
(65)

(**197**)



(**198**)

Scheme 17

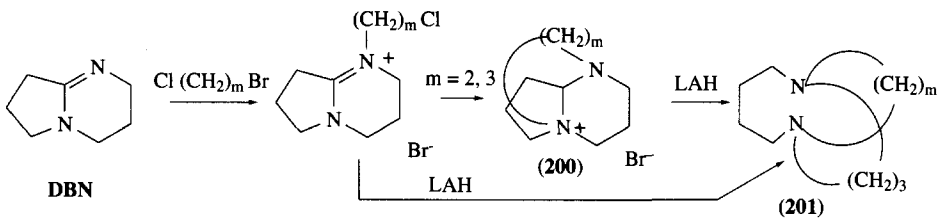


(66)

(**199**) R^1=H, Cl

8.11.8 SUBSTITUENTS AT HETEROATOMS

There are no pyrrolooxazines with substituents at heteroatoms, and the only reaction for a pyrrolothiazine is reduction of the sulfoxide group to give compound (**7**) ⟨89TL4507⟩. Most of the substituents on the nonbridgehead nitrogen in the azaindolizines are simple alkyl groups; in the *cyclo* (Pro–X) dipeptides the substituents are often protecting groups and are removed by conventional methods. Reactions involving substituents have been mentioned in Section 8.11.6.3 where formation of an extra ring is involved. Notable is the use of ylides in indolizine synthesis ⟨89H(28)857⟩ and in quinolizinium salt synthesis ⟨91T7329⟩ as mentioned in Section 8.11.5.2. A selective alkylation of dbn with ω-chloroalkyl bromides can be followed by cyclization to give bridged amines (**200**) which with LAH give diazabicycloalkanes (**201**) ⟨82TL1121⟩, which can also be obtained by a direct LAH reduction (Scheme 18).



DBN (**200**) (**201**)

Scheme 18

8.11.9 RING SYNTHESIS

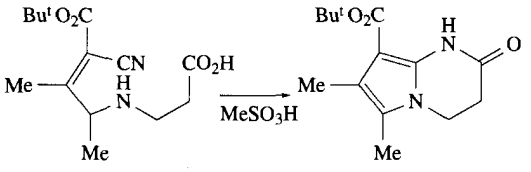
Syntheses are classified according to the number of fragments used, starting with a single precursor. Within each section, the fully conjugated systems are dealt with first. The final section deals with syntheses by ring transformation.

8.11.9.1 Syntheses from a Single Precursor

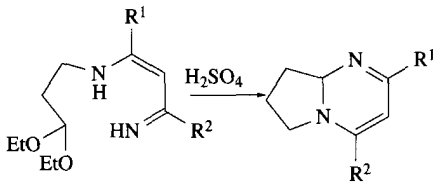
The sequence in this section is: (i) a single acyclic precursor; (ii) syntheses in which the five-membered ring is completed from a preformed derivative of the six-membered ring; and (iii) syntheses in which the six-membered ring is completed from a preformed pyrrole or pyrrolidine derivative.

8.11.9.1.1 A single acyclic precursor

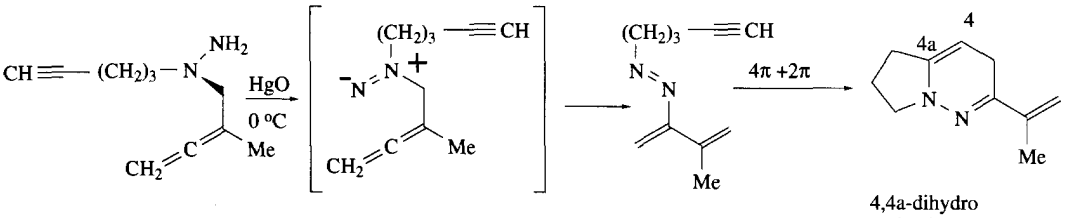
There are no syntheses of fully conjugated systems. The highest degree of unsaturation in a product is produced in the cyclization of the nitrile (**202**) by acid (Equation (67)) ⟨86MI 811-01⟩, and in the production of tetrahydropyrrolopyrimidines (**95**) by similar cyclization of the imines (**203**) (Equation (68)) ⟨91SL821⟩. In the latter case, alkylation of the imine anions introduces a substituent into position 3 of the product ⟨89S230⟩. Tetrahydro- and hexahydropyrrolopyridazines are obtained from azocompounds (**205**), in turn obtained by a [2,3]-sigmatropic shift after oxidation of hydrazines (**204**) (Scheme 19) ⟨92TL7331⟩. Compounds formed by elimination of HX undergo intramolecular cycloaddition to give dihydro- (**88**) ⟨87JCS(P1)2511⟩ and tetrahydropyrrolopyridazinones (**101**) (Equation (69)) ⟨87TL1573⟩, respectively.



(202) 48% (67)

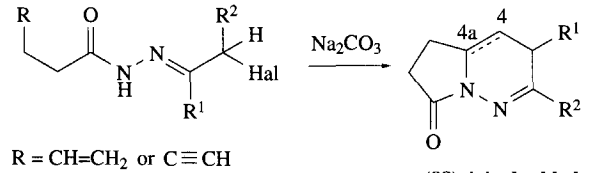


(203) (95) 40-95% (68)



(204) (205) 4,4a-dihydro derivative from *N*-pentenyl derivative

Scheme 19

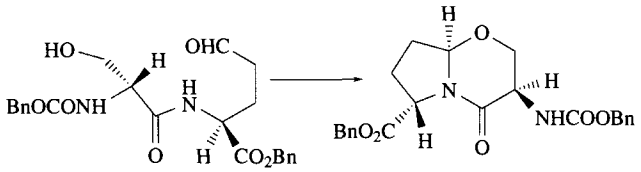


R = $CH{=}CH_2$ or $C{\equiv}CH$

(88) 4,4a double bond
(101) 4,4a- dihydro

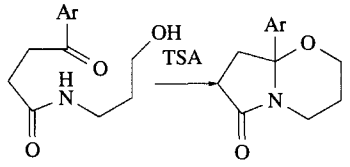
(69)

A number of syntheses of pyrrolo[1,3]oxazines start from compounds with suitably placed carbonyl, amino, alcohol, and thiol groups. Compound (**206**) provides an example with good stereochemical control (Equation (70)) ⟨93CC935⟩; in example (**207**) an aryl ketone is used (Equation (71)) ⟨76JMC436, 79AF983, 67USP3334095⟩. Similar principles have been used to synthesize pyrrolopyrazinones (**208**) (Equation (72)) ⟨92JCS(P1)1035⟩ and (**209**) (Equation (73)) ⟨92TL2187⟩, while a radical process cyclizes diallylamine (**210**) (Equation (74)) ⟨87BSF885⟩. There is a single example of a cyclization in this category which provides pyrrolopyrimidines such as (**211**) (Equation (75)) ⟨96T2629⟩.



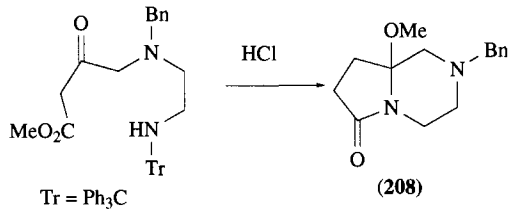
(206) 76%
Ratio of epimers at 8a = 10:1

(70)



(207)

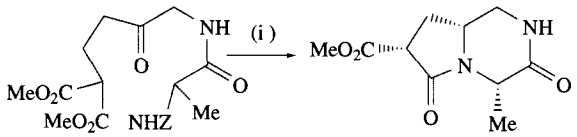
(71)



Tr = Ph_3C

(208)

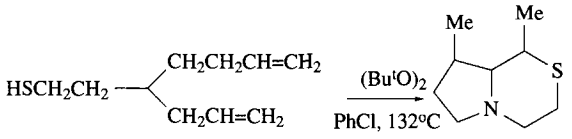
(72)



(i) H_2, Pd/C, 30 psi

(209) 79%
Epimer at 8a 15%

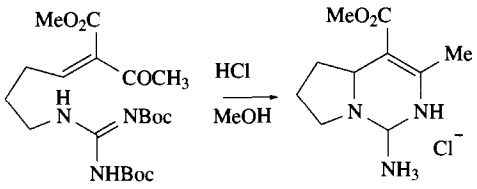
(73)



(210)

35%

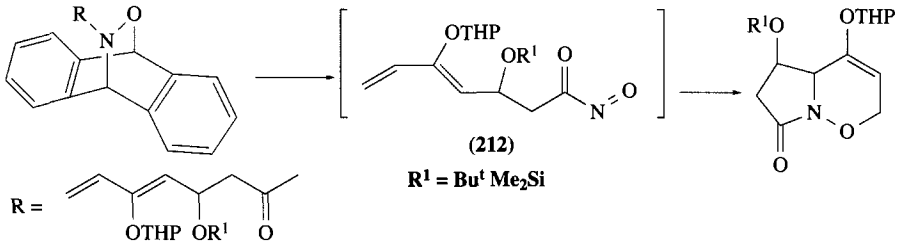
(74)



(75)

(211)

Thermal elimination of a nitroso compound from a dihydroanthracene is followed by cyclization of the intermediate (**212**) to pyrrolooxazinones (Scheme 20) ⟨78TL4767, 80JA3632⟩.



(212)

$R^1 = Bu^t Me_2Si$

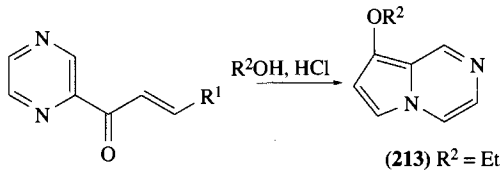
Scheme 20

8.11.9.1.2 Syntheses in which the five-membered ring is formed from derivatives of an existing six-membered ring

The major sub-divisions of this section concern the position of the newly formed bond, the first being N—C^{α} formation, then C^{β}—C^{γ}, and finally C^{γ}-ring carbon.

(i) Bond formation N—C^{α}

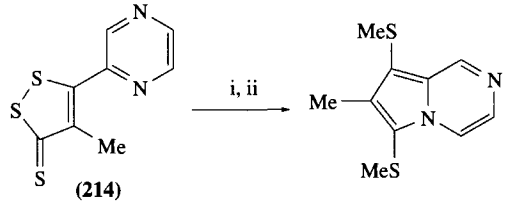
There are two routes to fully conjugated pyrrolopyrazines. In the first, cyclization of an unsaturated side chain by acid gives (**213**) (Equation (76)) ⟨81CPB2442⟩. In the second, cleavage of the dithiazole ring in a compound such as (**214**) gives, after methylation of the initial cyclized product, the bismethylthio derivative (**215**) (Equation (77)) ⟨89JCS(P2)391⟩. Cleavage can also be by thiolate ⟨85T3705, 87T3421⟩, or polarography ⟨86T409⟩.



(76)

(213) R^2 = Et : 44%
R^2 = Me : 21%

R^1 = 2-furyl



(77)

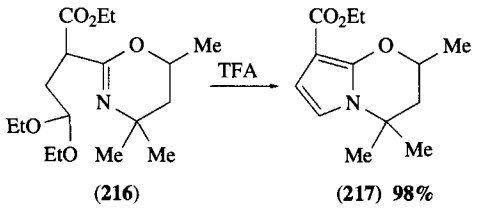
(214)

(215) 40%

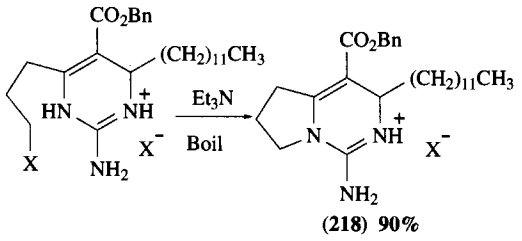
i, Electrochem. reduction
ii, NaH , MeI

Acid treatment of acetals (**216**) gives the dihydropyrrolooxazine (**217**) (Equation (78)) (⟨71JHC875, 73JOC1974, 74JOC2572⟩). Cyclization by displacement of a leaving group from the side chain has

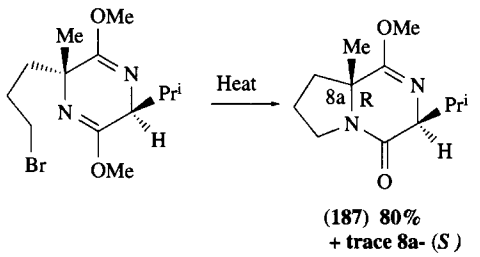
given cytotoxic compounds (**218**) (Equation (79)) ⟨92JOC2526, 93JOC3828⟩, (**187**) (Equation (80)) ⟨87AG(E)137⟩, and (**219**) (Equation (81)) ⟨88MI 811-02⟩.



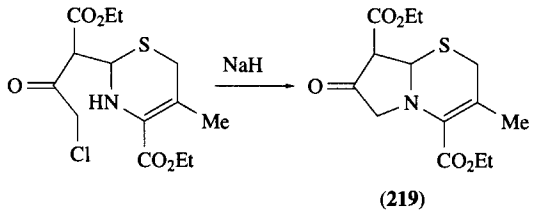
(78)



(79)



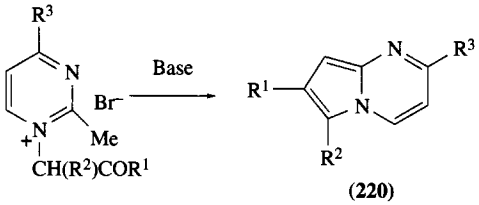
(80)



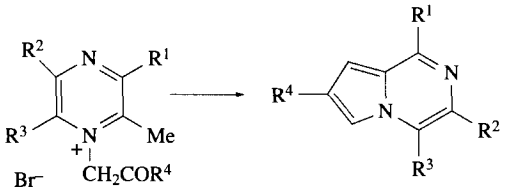
(81)

(ii) Bond formation C^{β} to C^{γ}

Condensation between a carbonyl group and an adjacent activated methyl or methylene group (a modification of the Tchichibabin synthesis of indolizines) has been used to make pyrrolopyrimidines (**220**) (Equation (82)) ⟨77JOC2448⟩ and pyrrolopyrazines (**221**) (Equation (83)) ⟨85JOC1324⟩, mostly in small yields; in the latter case the 3,4-benzo derivative was also prepared. Higher yields are reported for a two stage process with isolation of an intermediate (**222**) (Scheme 21) ⟨91H(32)85⟩, and for cyclizations with triethylamine as base ⟨92MI 811-04⟩. In the production of pyrrolopyrimidinones (**223**) yields from 3% ⟨78JOC3544⟩ to 93% ⟨83IZV2364⟩ have been reported.

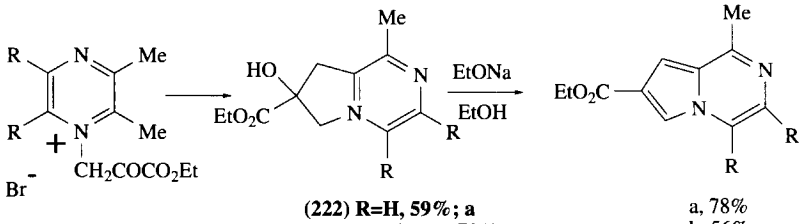


(82)



(83)

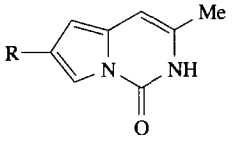
(221)



(222) R=H, 59%; a
R=$(CH_2)_4$, 72%; b

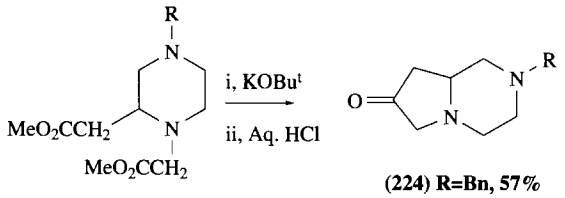
a, 78%
b, 56%

Scheme 21



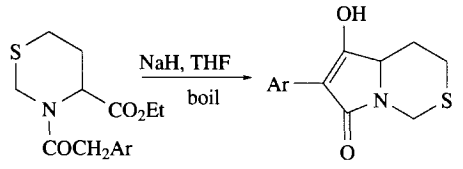
(223)

A few reduced systems have been prepared by conventional condensations. A Dieckman cyclization gave pyrrolopyrazinone (**224**) (Equation (84)) ⟨92JCS(P1)1035⟩, a similar condensation the pyrrolothiazinone (**225**) (Equation (85)) ⟨91EUP415211⟩, and treatment of the dibromide (**226**) with sulfinate caused cyclization to pyrrolopyrimidinones (**227**) (Equation (86)) ⟨88CPB3887⟩.



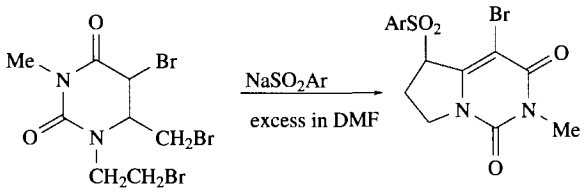
(84)

(224) R=Bn, 57%
R=2-$MeOC_6H_4$, 55%



(85)

(225) Ar=mesityl, 85%



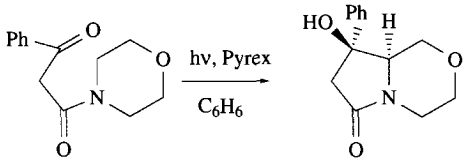
(86)

(226)

(227) Ar=Ph, 49%
Ar=*p*-tolyl, 57%

(iii) Bond formation between C^{γ} and ring carbon

Only one example of this type of synthesis is reported, a photochemical cyclization of an *N*-(oxazinyl) β-diketone (**228**) (Equation (87)) ⟨76JCS(P1)2054⟩.



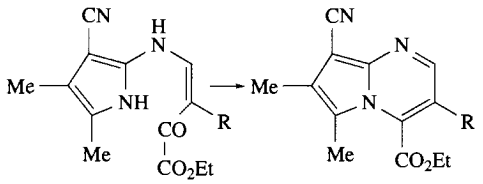
(228) 80% (87)

8.11.9.1.3 Syntheses in which the six-membered ring is formed from a pyrrole or pyrrolidine derivative

This section is again divided into subgroups depending on which bond is formed, starting with bonds to N.

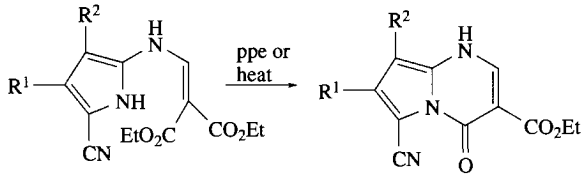
(i) Formation of a bond to N

The fully conjugated pyrrolopyrimidines (**229**) are formed by heating an appropriate ketoester (Equation (88)) ⟨83JHC81⟩; the corresponding esters give pyrrolopyrimidinones (**230**) (Equation (89)) ⟨87JHC297, 90IJC(B)47⟩.



(88)

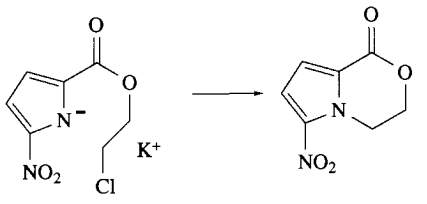
(229) **R=Ac, 60%**
R=CO_2Et, 81%



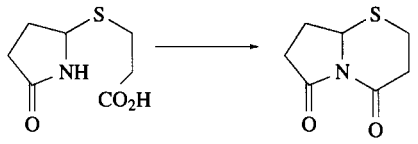
(89)

(230) **45-79%**

A pyrrolo[1,4]oxazinone has been prepared by cyclization of the β-chloroethyl pyrrolecarboxylate anion (**231**) (Equation (90)) ⟨70FRP1502066⟩, and a pyrrolo[1,3]thiazinedione (**232**) by lactam formation (Equation (91)) ⟨87JMC498⟩.



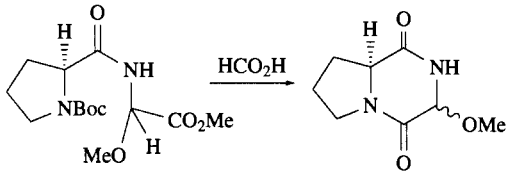
(231) (90)



(91)

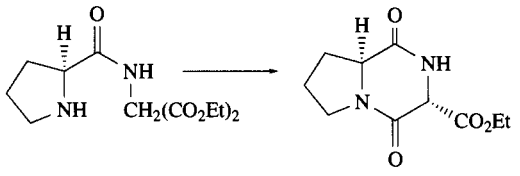
(232) 56%

Very many *cyclo*(Pro–X) dipeptides have been prepared by cyclization of linear peptides and it is beyond the scope of this review to give more than a few examples. The 3-methoxy derivative (**233**) can act as a chiral cationic glycine derivative (Equation (92)) ⟨91T563⟩, and the 3-methoxycarbonyl derivative (**234**) has been used as an intermediate in a brevianamide synthesis (Equation (93)) ⟨80JA3974, 81JCS(P1)959, 81T4295⟩, and the 3-*s*-butyl derivative (**235**) in an alkaloid synthesis (Equation (94)) ⟨87E1125⟩. Enantioselectivity is illustrated by the synthesis of the alcohol (**236**) in 3-(*R*) and 3-(*S*) forms with ≥95% *de* (Equation (95)) ⟨93TA2389⟩. A number of other syntheses are reported; R = substituent at C-3, R = H ⟨56JCS3642, 93JMC2311⟩; R = 1-methylpropyl ⟨86CZP232319⟩; R = 2-methylpropyl ⟨87TL1285⟩; R = Bn ⟨63T1675⟩; R = 4(5)-imidazolylmethyl ⟨85JMC1745⟩; R = 3-indolylmethyl ⟨78TL539, 89CPB23, 90MI 811-04⟩; various 3-R substituents ⟨81CPB233⟩.



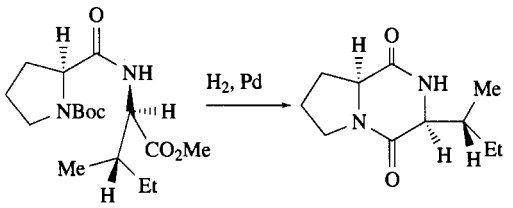
(92)

(233)



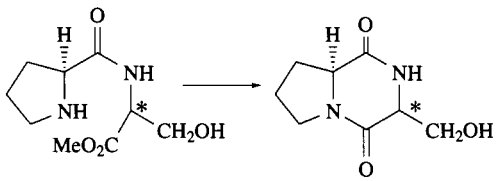
(93)

(234)



(94)

(235) 60%



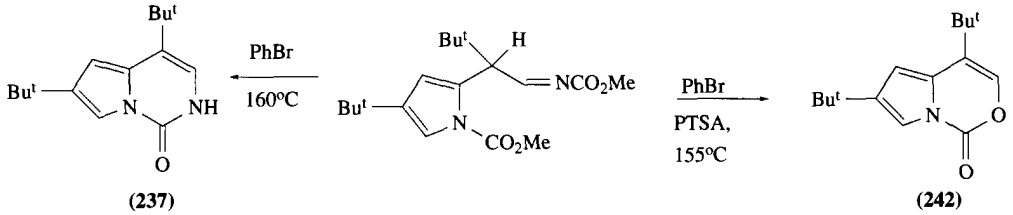
(95)

(236) 3-(*R*) or 3-(*S*)

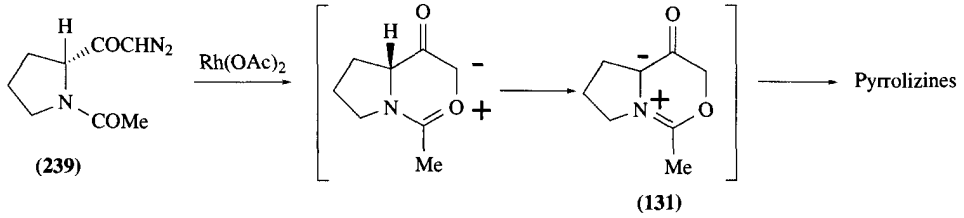
(ii) Formation of a bond on the next atom to N

The only examples of a fully conjugated system thus prepared are pyrrolopyrimidinone (**237**) and -oxazinone (**238**) prepared from a common precursor (Scheme 22) ⟨83CL743⟩. Diazoketone (**239**) gives an intermediate (**131**), not isolated, trapped by alkenes or alkynes (Scheme 23) ⟨92JA593⟩,

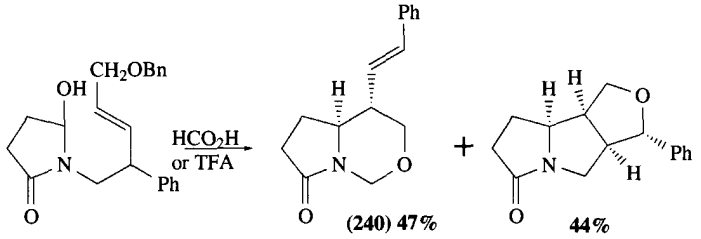
and a reaction in which the final bond forms between C^{α} and C^{β} leads to compound (**240**) (Equation (96)), ⟨90H(30)501⟩.



Scheme 22

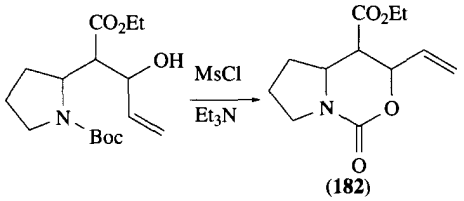


Scheme 23

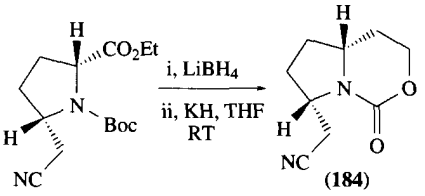


(96)

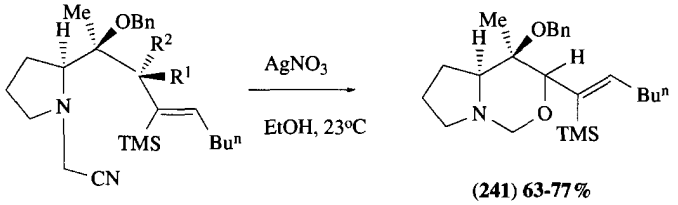
Other reactions involve lactonization, as in the synthesis of compound (**182**) (Equation (97)) ⟨88CPB1597, 90H(30)885⟩ and (**184**) (Equation (98)) ⟨81TL4197⟩, or S_N2 displacement, as in the synthesis of compound (**241**) (Equation (99)) ⟨88TL6541⟩.



(97)



(98)

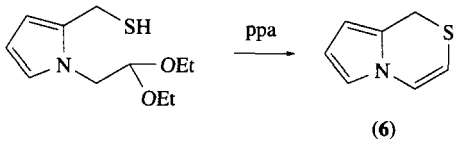


R^1=H, R^2=OH *or*
R^1=OH, R^2=H

(99)

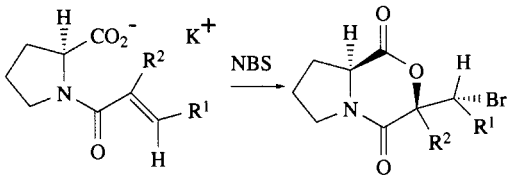
(iii) Formation of a bond two atoms from nitrogen

The parent pyrrolo[1,4]thiazine (**6**) has been obtained from a pyrryl acetal (Equation (100)) ⟨93JPR(335)101⟩. In many cases the bond is formed between the oxygen of a proline carboxylic acid and an adjacent electrophilic center generated by bromination of a double bond (intramolecular bromolactonization). This method has been extensively studied by Terashima and co-workers, with particular interest in the mechanism ⟨77TL1005, 79T2345⟩. The stereochemistry at C-3 is used in syntheses of α-hydroxyacids (see Section 8.11.6.4). Some examples showing high yields and high *ee* values are compounds (**242**) (Equation (101)) (⟨80TL2733, 81T2797⟩; other examples are in ⟨78JAP(K)78108997, 87TL2801, 88JMC885, 89CL465, 91JCS(P2)53⟩). In some cases reaction is sluggish with the free acid but much faster with the potassium salt ⟨77CL1109⟩. The bromolactonization has been used in the reverse direction, to give compound (**243**) (Equation (102)) ⟨83JA654⟩ and also to produce the unsaturated compound (**244**) with the bromo derivative (**245**) (Equation (103)) ⟨72T1113⟩. A cyclization between the proline carboxylic acid group and a benzylic methylene is produced by ddq, giving compounds (**190**) with reasonable *de* values (Equation (104)) ⟨86CC741, 91NJC379⟩.



(100)

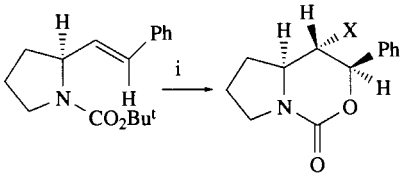
(6)



(242)

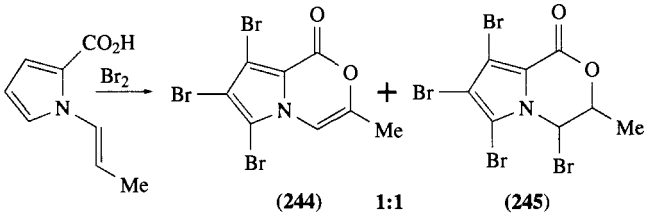
R^1	Ph			n-C_6H_{13}
R^2	Me			Me
Yields	95	88	78	93
Ratio of epimers at C-3	99:1	96:4	99:1	92:8

(101)



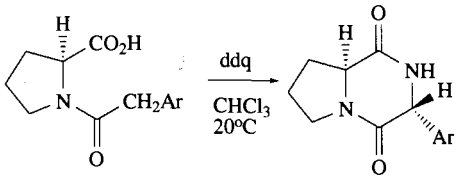
(102)

i, Br^+, $(collidine)_2\ ClO_4^-$ (**243**)



(**244**) 1:1 (**245**)

(103)

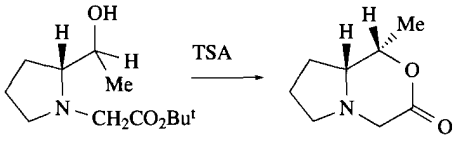


(104)

(**190**)

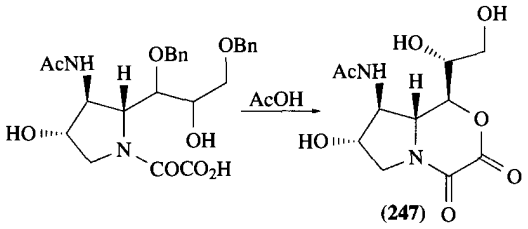
Simple lactonization gives the unsubstituted compound (**28**) ⟨72OMR(4)509, 74CC395⟩ and its derivative (**246**) (Equation (105)); a more complex example is (**247**) (Equation (106)) ⟨90HCA1338⟩. Lactamization has given the unsubstituted compound (**248**; R = H) ⟨92T4985⟩ and the N-substituted

derivative (**248**, R = CH_2CO_2Et) (Equation (107)) ⟨79ACS(B)125⟩, and the imide (**249**) (Equation (108)) ⟨87CR(2)441⟩. A cyclization of the amide (**250**) was achieved with dbn or hydroxide, giving either enantiomer at C-8a (Scheme 24) and an aldol condensation of the related amide (**251**) gave the cyclic dipeptide analogue (Equation (109)) ⟨77CB921⟩.



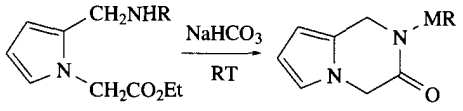
(105)

(246)



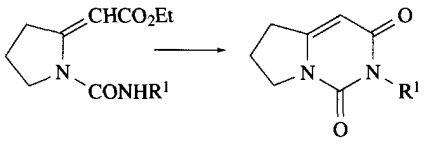
(106)

(247)



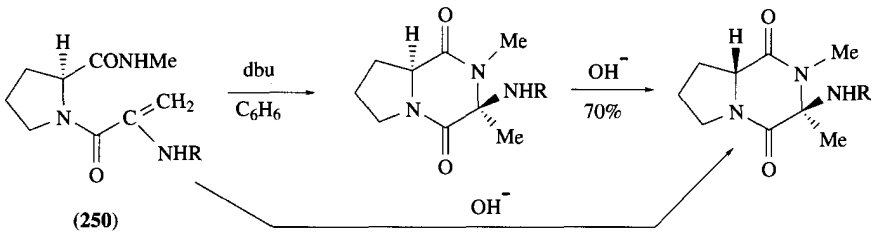
(107)

(248)



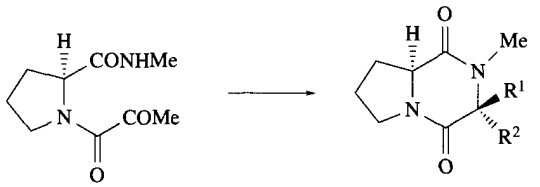
(108)

(249) R^1= Me, Ph



(250)

Scheme 24



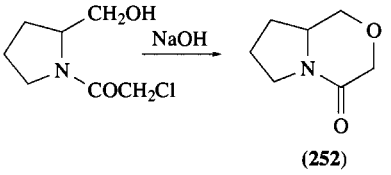
(109)

(251)

R^1=OH, R^2=Me
R^1=Me, R^2=OH
Ratio = 4:9

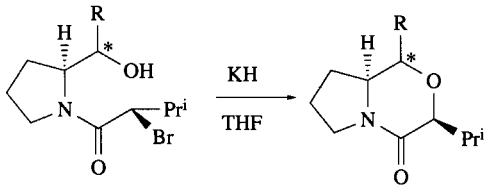
Simple pyrrolooxazines are available by intramolecular S_N2 attack by alkoxide on an alkyl halide, as in the synthesis of compound (**252**) (Equation (110)) ⟨86JMC859, 86USP4596819⟩. More complex stereochemistry is shown in the syntheses of compounds (**175**) (Equation (111)) ⟨91JOC2624⟩ and

(**253**) (Equation (112)) ⟨87JOC418⟩. Transacetalation gives methoxylated derivative (**158**) (Equation (113)) ⟨94JA5469⟩. Intramolecular N-alkylation gives pyrrolopyrazine-1,4-dione (**254**) (Equation (114)) ⟨88JA5927⟩.



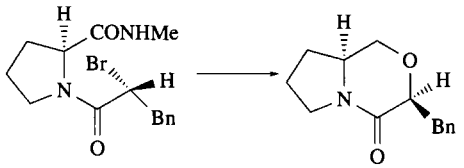
(110)

(**252**)



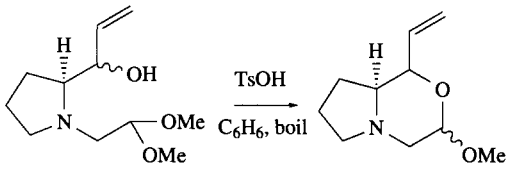
(111)

(**175**) 1-(*R*) 88%
1-(*S*) 86%



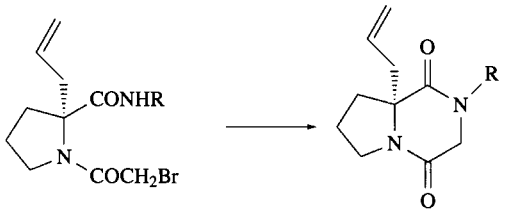
(112)

(**253**) 74%



(113)

(**158**) 58%

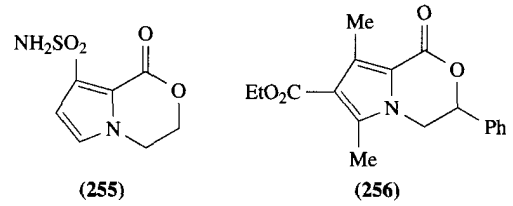


(114)

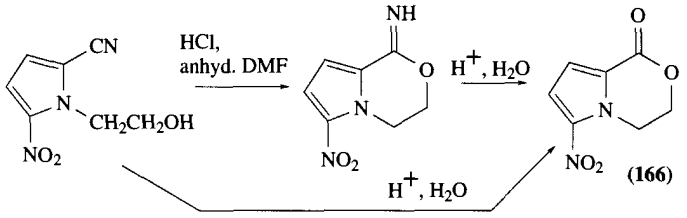
(**254**) 97% R=4-MeOBn

(iv) Formation of a bond three atoms from N

Lactonization to a proline or pyrrole-2-carboxylic acid gives pyrrolo[1,4]oxazinones (**166**) ⟨68MI 811-01⟩, (**255**) ⟨91MIP9110668⟩, and (**256**) ⟨71TL4321⟩ (Scheme 25). In the first case, cyclization using anhydrous HCl allows isolation of the intermediate imine. In the cyclization of a mixture of diastereomers only one gives a lactone (**257**) (Equation (115)), the other being recovered unchanged ⟨86JOC3290⟩. Thiols can also be used, giving pyrrolothiazinediones, such as (**258**) (Equation (116)) ⟨79USP4209617, 86JMC784⟩. A variant involves reaction of the enols of ketones (**259**) to produce cyclic lactones (Equation (117)) ⟨88JOC4650⟩.

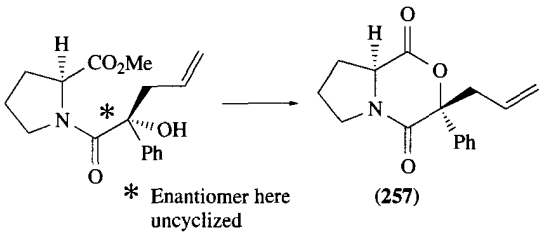


(255) (256)



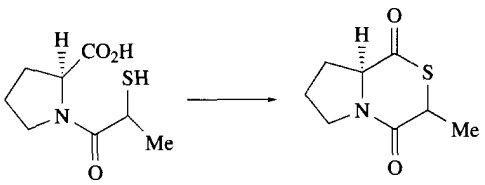
(166)

Scheme 25

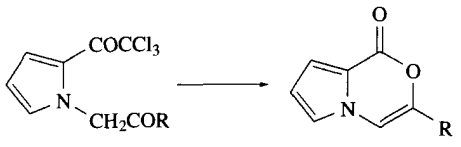


* Enantiomer here uncyclized

(257) (115)



(258) 32% (116)

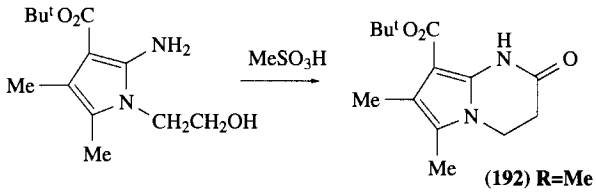


(259) (117)

R=Me, 58%
R=$(CH_2)_3Cl$, 62%

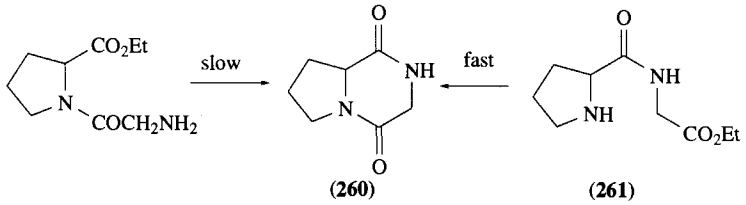
A similar route leads, by lactamization, to pyrrolopyrimidines or pyrrolopyrazines, mainly 1,4-diones (cyclic dipeptides or analogues). In the former case, an α-amino pyrrole gives the dihydro derivative (**192**; R = Me) (Equation (118)) ⟨87JHC661⟩. In the pyrrolopyrazine series much effort has been directed to inhibit cyclization during peptide synthesis. A selection of methods where cyclization has been achieved is given. In the simplest case, cyclization to give compound (**260**) was found to be much slower with the ethyl prolinate than with the prolinamide (**261**) (Scheme 26) ⟨56JCS3642⟩. Other mechanism studies relate to the cyclization stage in the production of *cyclo*(Pro–His) (**262**) in buffered solutions, showing strictly first order kinetics ⟨90JPP7⟩, and in the metabolism of thyrotropine-producing hormone in rat brain (Equation (119)) ⟨77NAT142⟩. Rates of cyclization in protected ⟨81TL3779⟩ and unprotected ⟨85S181, 86TL743⟩ dipeptides linked to polystyrene resins have been measured. Over all, basic treatment, particularly with ethyldiisopropylamine, was most effective. N-substituted derivatives such as (**263**) have been cyclized in acetic anhydride ⟨88AF647,

94G103〉 to the free carboxylic acid group (Equation (120)). Experiments where the amino group was freed 〈87TL4275〉 or generated 〈89TL4597, 91CC372〉 by reduction have given compounds (**264**) (Equation (121)), (**265**) (Equation (122)), and (**266**) (Equation (123)), respectively. Other syntheses are reported 〈83MI 811-01, 85TL5481, 88TL2539, 93JCS(P1)2391〉.



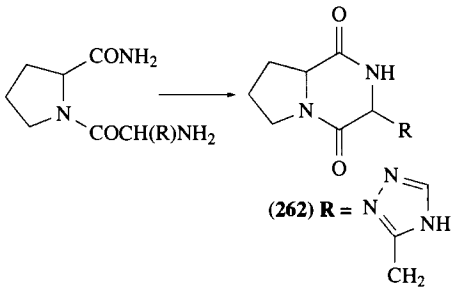
(118)

(**192**) **R=Me**



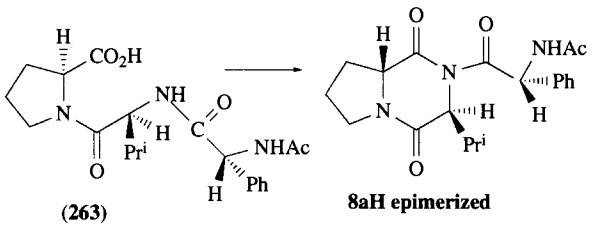
(**260**) (**261**)

Scheme 26



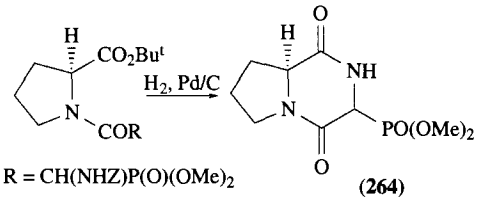
(119)

(**262**) **R =**



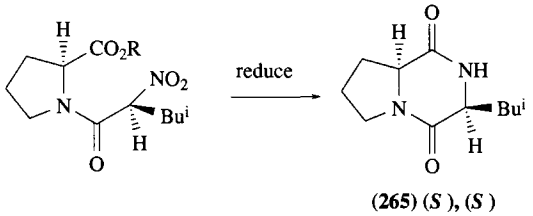
(120)

(**263**) **8aH epimerized**



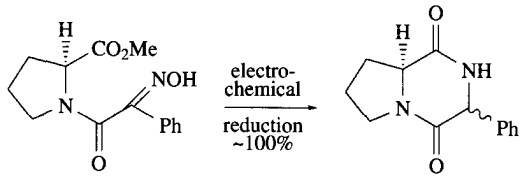
(121)

R = CH(NHZ)P(O)(OMe)$_2$ (**264**)



(122)

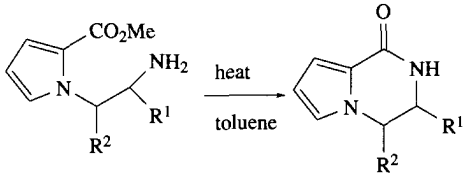
(**265**) (*S*), (*S*)



(123)

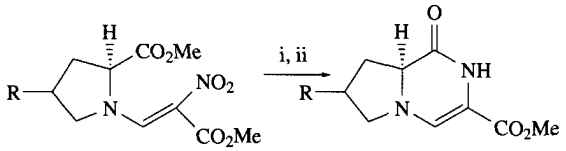
(266)

Related lactamizations give the pyrrolopyrazinones (**267**) ⟨90JCS(P1)311⟩, (**113**) (Equation (124)) ⟨88AJC1583⟩, (**268**) (Equation (125)) ⟨94T4887⟩, and (**269**) (Equation (126)) ⟨92T4985⟩. The route to (**268**) can also be used to prepare the 6,7-benzo derivative. The compound formulated as (**270a**) was found to have no NMR aldehyde signal, and hence is (**270b**) (Equation (127)) ⟨86CPB2931⟩.



(124)

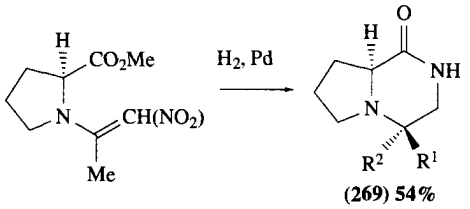
(267) R^1=CO_2Me, R^2=OEt
(113) R^1=R^2=H after methylation



(125)

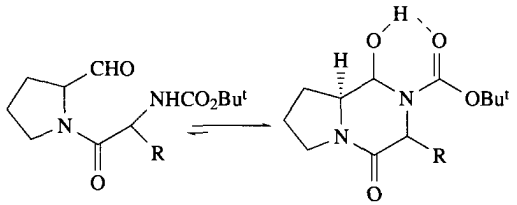
(268) R=H, 38%
R=α-OH, 71%

i, H_2, Pd/C, RT; ii, Mg, $HgCl_2$, $TiCl_4$, THF, Bu^tOH



(126)

(269) 54%
Ratio R^1=Me:R^2=Me is 7:3



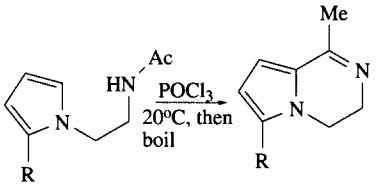
(127)

(270a) **R=Me, Bn** **(270b)**

(v) Bond formation to the α-carbon of the five-membered ring

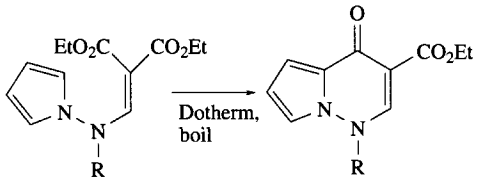
The most obvious cyclization is caused by an electrophilic centre in the N-substituent of a pyrrole. Thus are formed the dihydropyrrolopyrazines (**91**) ⟨81S481⟩ and (**271**) (Equation (128))

⟨93EUP521368⟩. The pyrrolopyridazines (**272**) are obtained by a Conrad–Limpach synthesis (Equation (129)) ⟨94JHC409⟩.



(128)

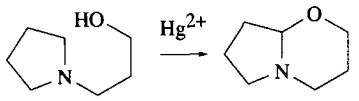
(91) R=H, 95%
(271) R=3-ClC$_6$H$_4$



(129)

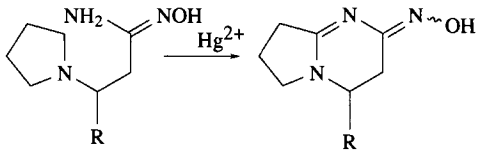
(272) R=H, 58%
R=Me, Et, Ph, 4-24%

A number of compounds have been prepared via cyclization to iminium ions. Generation of the iminium ion by mercuric acetate oxidation of an N-substituted pyrrolidine gives perhydropyrrolo-[1,2]oxazine (**273**) (Equation (130)) ⟨60JA5148, 88JA4829⟩ and pyrrolopyrimidine (**274**) (Equation (131)) ⟨92AP(325)23⟩. Iminium ions generated by elimination of a group in the α-position provides excellent yields of compounds (**275**) (Equation (132)) ⟨92JOC7010⟩ and (**276**) (Equation (133)) ⟨92JOC2641⟩, and moderate yields of the 3,4-benzopyrrolopyrimidines (**277**) (Equation (134)) ⟨96TL485⟩. The methylated thiones (**278**) are converted into the pyrrolopyrimidines (**279**) in an acid-catalyzed reaction with subsequent elimination of methanethiol (Equation (135)) ⟨96TA515⟩.



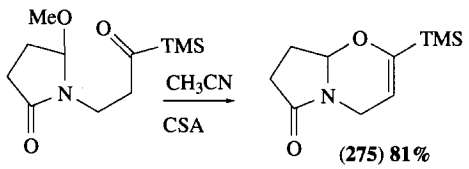
(130)

(273)



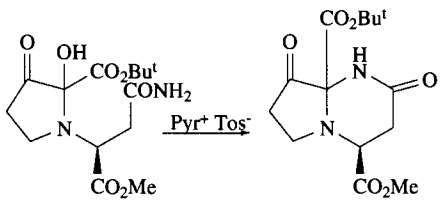
(131)

(274)



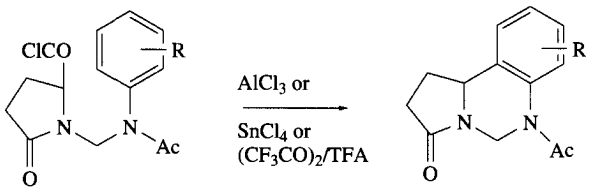
(132)

(275) 81%



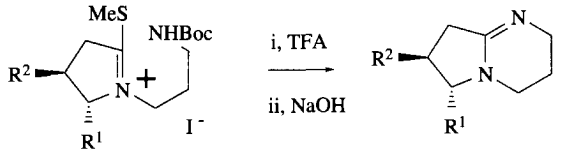
(133)

(276) 81%



(134)

(277) Various R, 23-77%

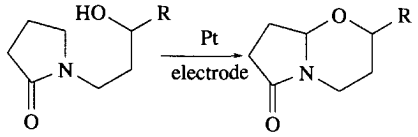


(135)

(278) R^1=$CH_2OSiThexylMe_2$, R^2=H
R^1=H, R^2=$CH_2OSiThexylMe_2$

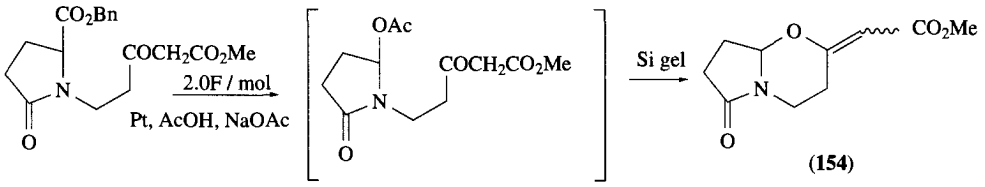
(279)

The other popular route to cyclized products is via a radical in the α-position of the pyrrolidine ring, generated by electrochemical oxidation or photochemically. Examples of the former route are pyrrolooxazines (**280**) (Equation (136)) ⟨80H(14)1089⟩ and (**273**) and (**154**) (Scheme 27) ⟨89H(29)2089⟩, and of the latter (**273**) ⟨94TL1715⟩, (**281**) (Equation (137)) ⟨91TL5147, 92T8295⟩, and (**282**) (Equation (138)) ⟨82H(19)2057, 86CPB3142⟩. In the case of compound (**281**) there is high regio- and stereoselectivity.



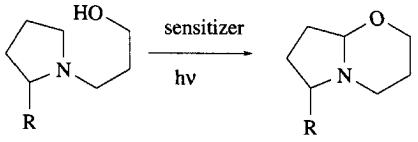
(136)

(280) R=H, 74%



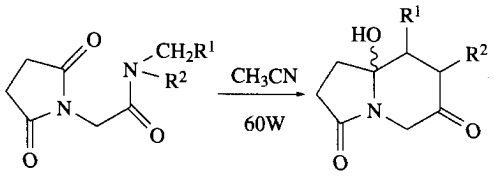
(154)

Scheme 27



(137)

(273) R=H, 50%
(281) R=Bu^n, 88%
β -isomer at 8a; 93:7



(138)

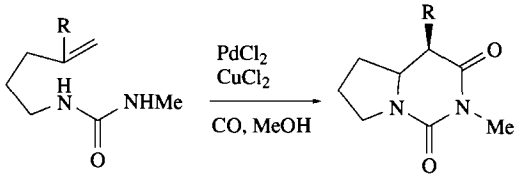
(282) Various R^1, R^2, 7-60%

8.11.9.2 Syntheses From Two Precursor Molecules

In this section the sub-divisions are as follows:
(i) from two acyclic precursors (8 + 1, 7 + 2, 5 + 4);
(ii) formation of the five-membered ring from a six-membered ring derivative (4 + 1, 3 + 2);
(iii) formation of the six-membered ring from a pyrrole or pyrrolidine derivative (5 + 1, 4 + 2, 3 + 3).

8.11.9.2.1 From two acyclic fragments

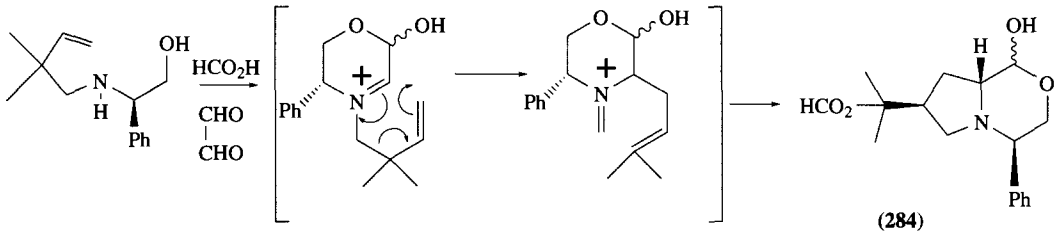
There is only one example of an (8 + 1) synthesis, the carbonylation of the imides (**283**) (Equation (139)) ⟨88JA3994⟩. The syntheses of type (7 + 2) can involve glyoxal and an aminoalcohol, as in the formation of pyrrolooxazine (**284**) (Scheme 28) ⟨92SL847, 93T7239⟩, or hydrazine and a triketone, as in the formation of pyrrolopyridazine (**285**) (Equation (140)) ⟨79JHC839⟩. The synthesis of (**101**) described in section 8.11.9.1.1, can be performed using a hydrazine and an α-haloketone, without isolation of the intermediate ⟨83S153⟩.



(283)

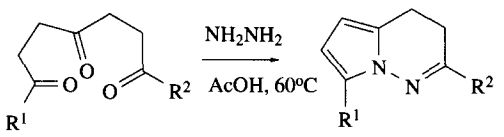
R=H, 95%
R=Me, 69%

(139)



(284)

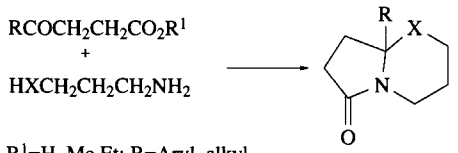
Scheme 28



(285) R^1=R^2=alkyl or R^1=Me,R^2=Ph; 69–85%

(140)

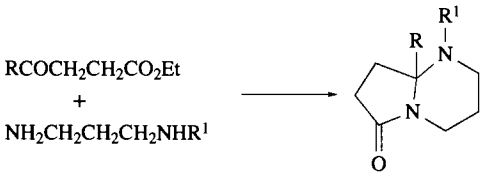
Almost all the syntheses of type (5 + 4) involve the condensation of a dicarbonyl compound with an aliphatic diamine or aminoalcohol or -thiol. These divide conveniently into two classes, those using 3-aminopropan-ols or -thiols or 1,3-diaminopropanes, and those using ethylenediamines. Examples of the former class are provided by the synthesis of compounds (**155**) ⟨65BEP659529, 69JOC165, 76JMC436⟩ and (**286**) (Equation (141)) ⟨67USP3334091, 91JCS(P2)735, 92LA29⟩); diamines give compounds (**30**) (Equation (142)) ⟨71AP774, 93MI P9324489⟩. Use of a γ-chlorocarbonyl compound gives perhydro derivatives such as (**287**) ⟨79AF983⟩ or (**288**) (Equation (143)) ⟨83TL1559⟩.



$RCOCH_2CH_2CO_2R^1$ + $HXCH_2CH_2CH_2NH_2$ → (141)

R^1=H, Me Et; R=Aryl, alkyl

(155) X=O, R=Ph
(286) X=S



$RCOCH_2CH_2CO_2Et$ + $NH_2CH_2CH_2CH_2NHR^1$ → (142)

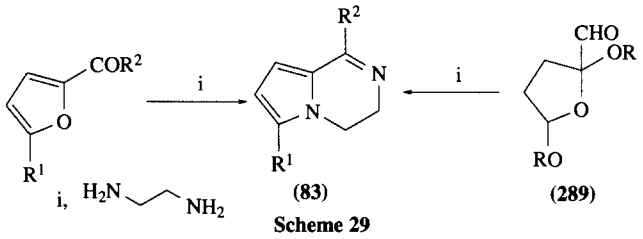
(30) various R,R^1,57-95%



$RCOCH_2CH_2CH_2Cl$ + $NH_2CH_2CH_2CH_2XH$ → (143)

(287) R=4-BrC_6H_4, X=NH
(288) R=H, X=O

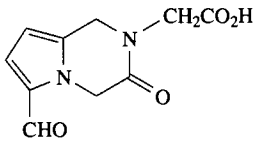
Syntheses using ethylene diamine derivatives have been used only for the preparation of pyrrolopyrazines, and the second component is a masked dicarbonyl compound, either a furyl ketone as in the synthesis of 1,6-disubstituted derivatives (**83**) ⟨86ZOR2610, 91KGS763⟩ or the cyclic acetal (**289**) as in the preparation of the parent (**83**; $R^1 = R^2 = H$) (Scheme 29) ⟨80URP765268⟩. A similar route may be involved in the production of Amadori compounds (**290**) obtained by heating together sugars and aminoacids, in this case D-glucose and glycine ⟨78ACS(B)249⟩.



i, H_2N–NH_2

(83) **(289)**

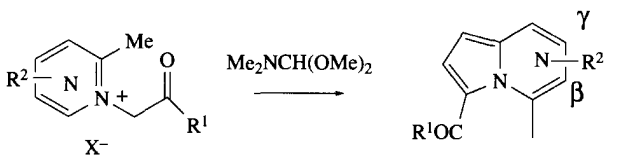
Scheme 29



(290)

8.11.9.2.2 Formation of the five-membered ring from an existing six-membered ring derivative

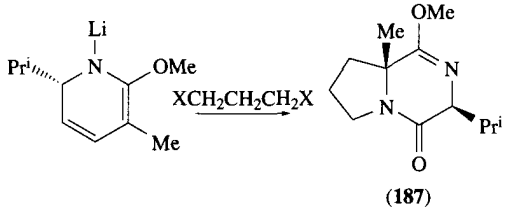
There are two major divisions of this section (4 + 1, 3 + 2) the latter sub-divided according to the bonds formed during the cyclization. In the only example of (4 + 1) cyclization the single carbon is provided by DMF acetal, in the production of azaindolizines (**291**) (Equation (144)) ⟨93JHC1577⟩.



(144)

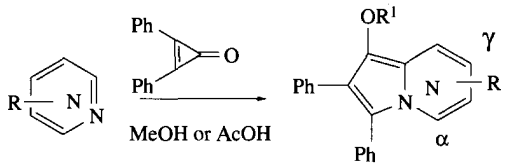
(291) R^1= Ph
N at β or γ

The smallest subsection of (3 + 2) syntheses is that where a three atom acyclic fragment adds to the nitrogen and the α-carbon of an azine. A lithiated pyrazine and a 1,3-dihaloalkane gives compound (**187**) (Equation (145)) ⟨88LA1025⟩. Diphenylcyclopropenone provides the three carbon fragment in the synthesis of compounds (**292**) and (**293**) (Equation (146)); in both cases benzo derivatives can also be prepared ⟨91JOC5594⟩. Pyrimidine gives a mixture of isomeric pyrrolopyrimidines (**294**) and (**295**) (Equation (147)). Palladium-catalyzed coupling of pyridazines and propargyl alcohol gives pyrrolopyridazines (**296**) (Equation (148)) ⟨80BCJ3273⟩. Palladium coupling also provides a route to pyrrolooxazine (**297**) (Equation (149)) ⟨93JA6636⟩. while an imine is intermediate in the synthesis of tricycle (**298**) (Equation (150)) ⟨93TL539⟩.



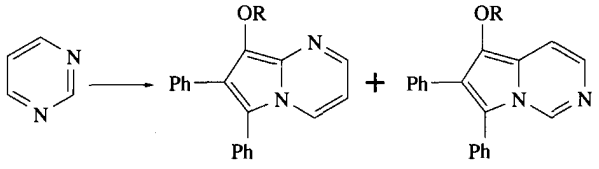
(145)

(**187**)



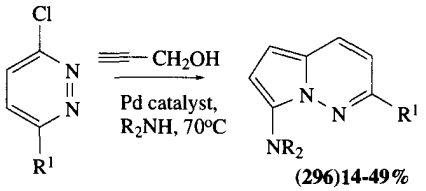
(146)

(292) α N, R^1=H 70%, Ac 78%
(293) γ N, R=Me, R^1=Ac, 90%



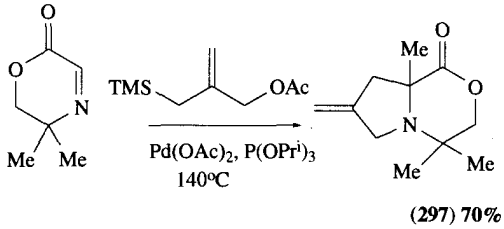
(147)

(**294**) **57:32** (**295**)



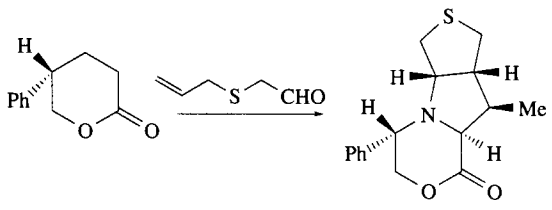
(148)

(296)14-49%



(149)

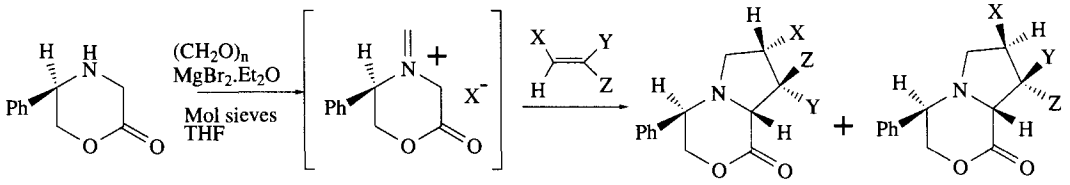
(297) 70%



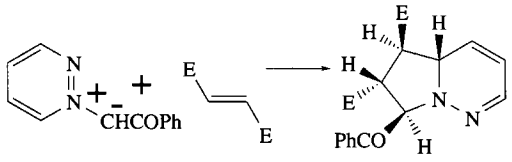
(150)

(298)

More commonly, a preformed imine reacts with a dipolarophile, added subsequently. The reaction is illustrated by the production of pyrrolooxazinones (**299**) and (**300**), where Lewis acids were found to improve the yields (Scheme 30) ⟨91TA169, 91TA1343, 93SL777⟩. Regioselectivity and stereochemistry of the addition are discussed in terms of HOMO dipole/LUMO dipole. Another example is the synthesis of precursors of compounds such as (**173**) ⟨92JOC6527⟩. A popular route to azaindolizines is by dipolar cycloaddition to a preformed ylide, usually with ketomethylene or dicyanomethylene stabilization. The synthesis of pyrrolopyridazines (**301**) illustrates the use of an alkene as dipolarophile (Equation (151)) ⟨79MI 118-04, 85BCJ137, 89MI 118-03⟩, and of pyrrolopyrimidines (**302**) the use of alkynes (Equation (152)) (⟨81RRC879, 86MI 118-02⟩). Dicyanomethylene ylides allow the preparation of a pyrrolopyridazine (**303**) ⟨83H(20)1009⟩ or its 3,4-benzo derivative. By using phenylsulfinylethene the cyano derivative (**304**) ⟨87BCJ3645⟩ can be made available by removal of TMS groups from (**303**) (Scheme 31). Pyrrolopyrazine (**73**) is available by the same route ⟨83H(20)1009⟩.

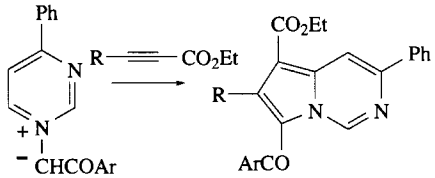


Scheme 30 (299) (300)



(151)

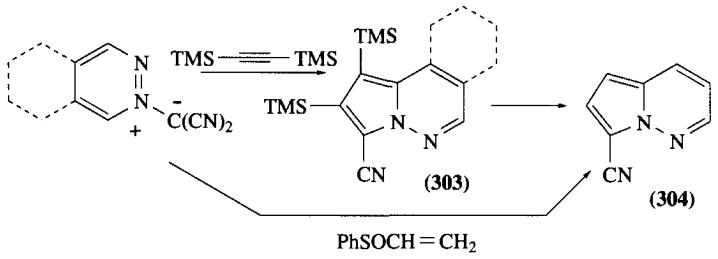
E = CO_2Me or CO_2Bu^t (301) 99-100%



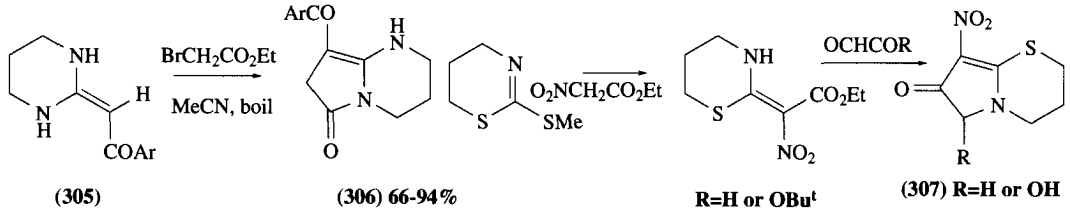
(152)

(302)

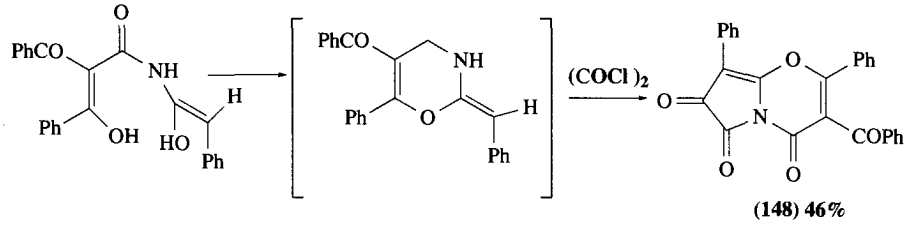
The second mode of (3 + 2) cyclization uses a three atom fragment which includes a nitrogen and one carbon of the six-membered ring. The oldest is a modified indolizine synthesis, where the nitrogen is quaternized by an α-haloketone and the resulting salt cyclizes on treatment with base to an adjacent active methyl or methylene group; examples are in Section 8.11.9.1.2 (compounds (**220**)–(**223**)). Ethyl bromoacetate reacts with the pyrimidine derivative (**305**) to give compound (**306**) ⟨89CB95⟩, and ethyl nitroacetate with a thiazine to give an adduct which with glyoxal ⟨77USP4033955⟩ or a glyoxylate ⟨77USP4033954⟩ give pyrrolothiazinones (**307**) (Scheme 32). Oxalyl chloride is the two carbon component in the synthesis of (**148**) (Scheme 33) ⟨77LA1964⟩, while DMAD gives pyrrolo[1,4]oxazine (**308**) (Scheme 34) ⟨94T7075⟩.



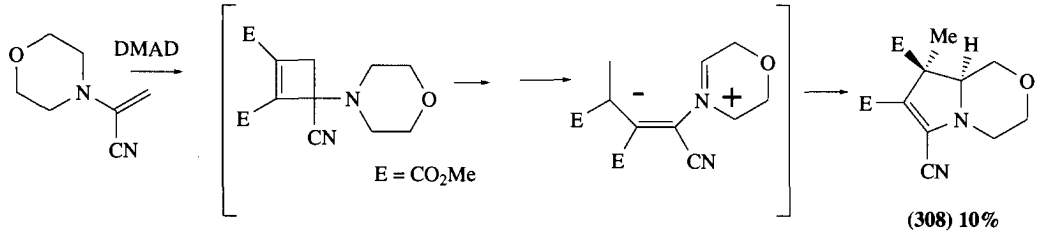
Scheme 31



Scheme 32



Scheme 33

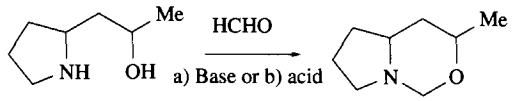


Scheme 34

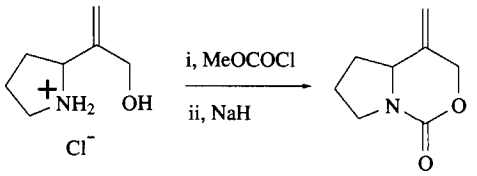
8.11.9.2.3 Formation of a six-membered ring from a derivative of pyrrole or pyrrolidine

The sub-divisions in this section are based on the size of fragments (5 + 1, 4 + 2, 3 + 3), and within each sub-division grouped according to bonds formed.

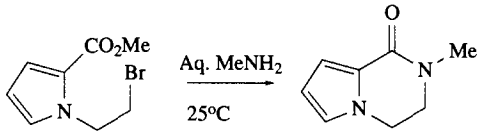
In the (5 + 1) category, the inserted atom can be carbon or nitrogen. Formaldehyde reacts with the pyrrolidinylpropan-2-ol (**309**) under basic ⟨60CCC483⟩ or acidic ⟨60JOC2028⟩ conditions to give compound (**181**) (Equation (153)). A similar alcohol with methyl chloroformate, followed by base, provides compound (**183**) (Equation (154)) ⟨91TL7119⟩. Insertion of N-2 has been used to prepare pyrrolpyrazinones (**113**) (Equation (155)) ⟨88AJC1583⟩ and (**106**) (Equation (156)) ⟨90JHC2181⟩, and various aryl aldehydes provide C-1 in the synthesis of compounds (**310**) (Equation (157)) ⟨81S481⟩.



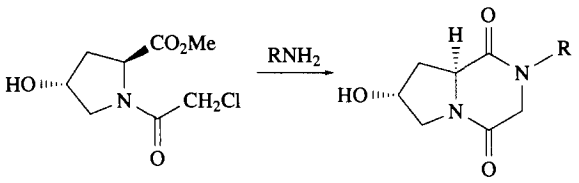
(309) (181) a) 100% b) 67% (153)



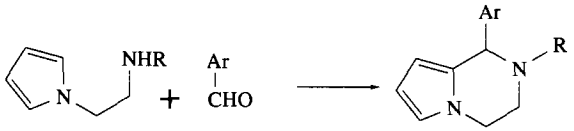
(183) 60% (154)



(113) (155)

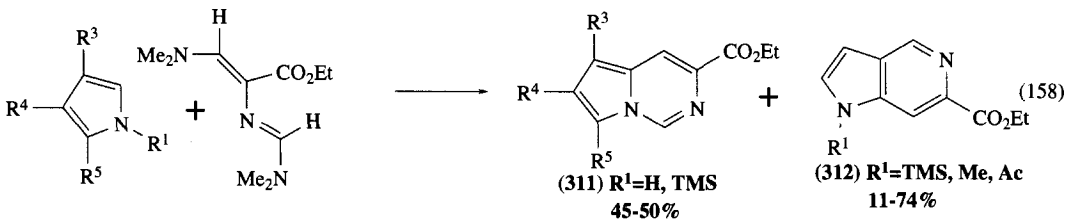


(106) 30-80% (156)

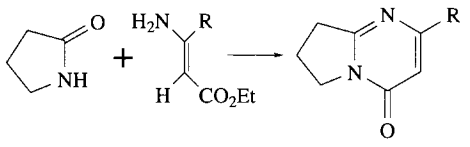


(310) R=H, Et, 44-63% (157)

Of the four possible modes of (4 + 2) synthesis, two are known. Most reports are of a four atom acyclic fragment adding to an activated pyrrolidine or pyrrole. One fully conjugated system (**311**) is formed as one of two products from a pyrrole and a 2-azadiene ⟨87LA491⟩; with an *N*-methylpyrrole only the isomeric compound (**312**) is formed (Equation (158)). Reaction between 2-pyrrolidinone and aminoacrylates gives pyrrolopyrimidinone (**313**) (Equation (159)) ⟨91KPS394⟩. A pyrrolidone lactim ether gives with diketene predominantly pyrrolooxazinone (**314**) (Equation (160)) ⟨75H(3)927⟩, with a β-aminoester the pyrrolopyrimidinone (**104**; R^1 = H) ⟨87H(26)85⟩, and with propargylamine the pyrrolopyrimidine (**315**) (Scheme 35) ⟨83JHC393⟩. With the acetyl Meldrum's acid (**316**) a pyrrolidine lactim ether can give either pyrrolooxazinedione (**317**) or -oxazinone (**318**) (Equation (161)) ⟨86MI 811-04⟩. Pyrroline (**319**) is used to give a poor yield of a pyrrolothiazinone (Equation (162)) ⟨87AP799⟩.

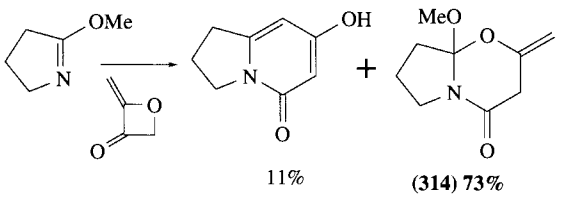


(311) R^1=H, TMS 45-50% (312) R^1=TMS, Me, Ac 11-74% (158)



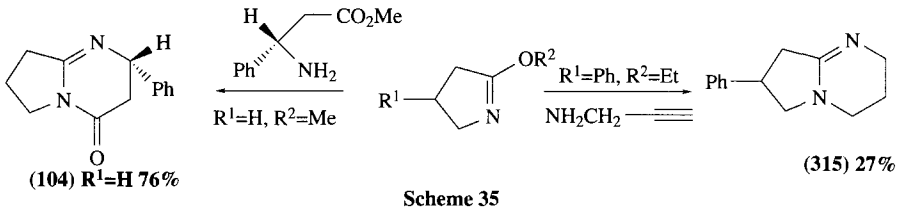
(159)

(313) R=Me, 32%
R=Ph, 56%



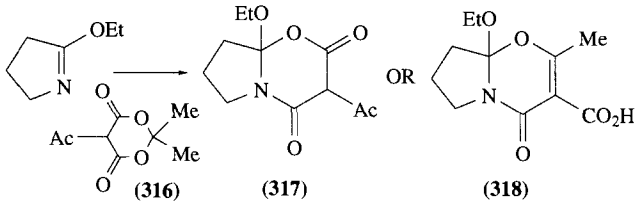
(160)

11% **(314) 73%**



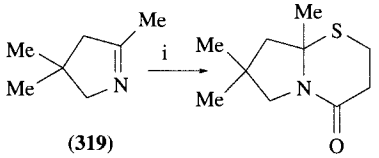
(104) R^1=H 76%

Scheme 35



(161)

(316) **(317)** **(318)**

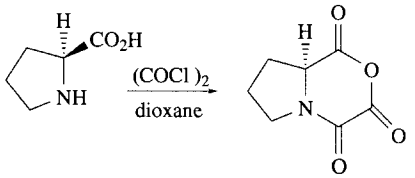


(162)

(319)

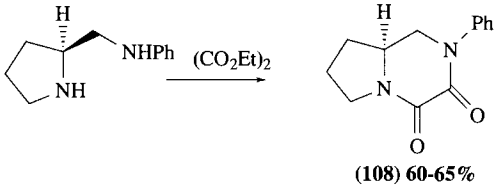
i, $HSCH_2CH_2CO_2Me$

The second mode of (4 + 2) addition uses an α-dicarbonyl compound to form C-3 and C-4. This can be oxalyl chloride ⟨67JOC4072⟩ or diethyl oxalate ⟨89TL3551⟩, as in the synthesis of compounds **(170)** (Equation (163)) and **(108)** (Equation (164)) or pyruvoyl chloride, as in the synthesis of compound **(320)** (Equation (165)) ⟨86EUP180544⟩.



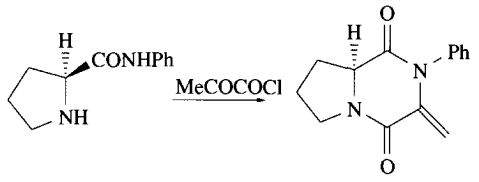
(163)

(170) 74%



(164)

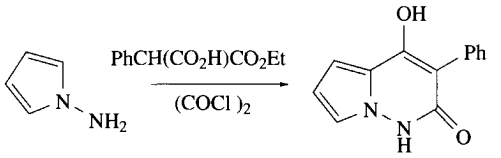
(108) 60-65%



(165)

(320)

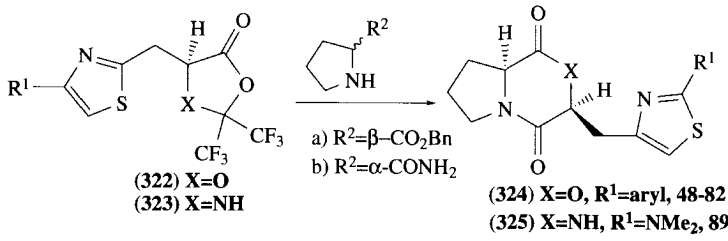
Most syntheses in this section involve (3 + 3) addition. Here there are only two possible modes, involving a five-membered ring with a single active substituent, either on N or on the α-carbon. Of the former, the only significant examples start from an *N*-aminopyrrole, reacting with a malonic acid derivative to give compound (**321**) (Equation (166)) ⟨93BRP2265372⟩, or with ethoxymethylenemalonate with subsequent thermal cyclization ⟨94JHC409⟩ (see Section 8.11.9.1.3.v, compound (**272**)).



(166)

(321)

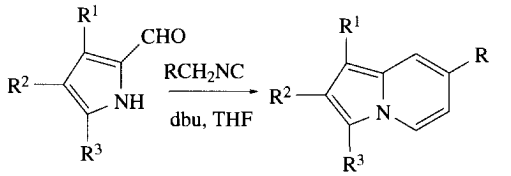
In the second mode, a further subdivision is possible into those where the α-atom is carbon, and those where it is a heteroatom. In the first class would come all *cyclo*(Pro–X) dipeptides mentioned in Section 8.11.9.1.3.i. In a similar synthesis the protected hydroxyacids (**322**) ⟨93M453⟩ and aminoacids (**323**) ⟨92S1145⟩ react with proline derivatives to give pyrrolo[1,4]oxazinediones (**324**) or -pyrazinedione (**325**) respectively (Equation (167)). Pyrrole-2-carboxaldehydes react with activated isocyanides and a base to give pyrrolopyrimidines (**326**) ⟨76JOC1482, 77JAP(K)7723093⟩ and (**327**) (Equation (168)) ⟨79CPB793⟩. Oxiranes provide two carbons and an oxygen in the synthesis of pyrrolooxazine derivatives, often in excellent yield, as in the synthesis of compounds (**168**) (Equation (169)) ⟨68SAP6800809, 73JCS(P1)911, 83AP(316)339, 83JOC3234⟩. Other three atom fragments are the isocyanates in the synthesis of compounds (**328**) (Equation (170)) ⟨91CB2126⟩ and the oxazolone (**329**) used in the synthesis of pyrrolpyrazinedione (**330**) (Equation (171)) ⟨89TL3101⟩.



(322) X=O
(323) X=NH

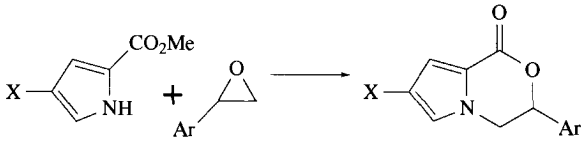
(324) X=O, R¹=aryl, 48-82%
(325) X=NH, R¹=NMe₂, 89%

(167)



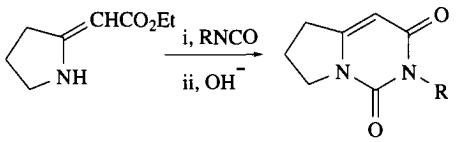
(325) R=CO₂Me, 50-69%
(327) R=Ts, 20%

(168)

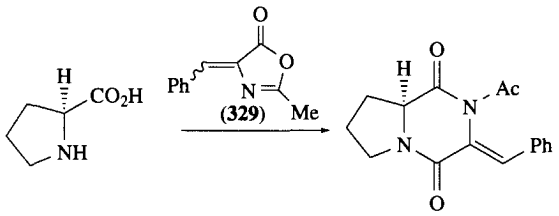


(166) 73-90%

(169)

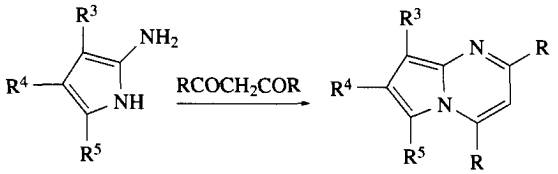


(328) (170)

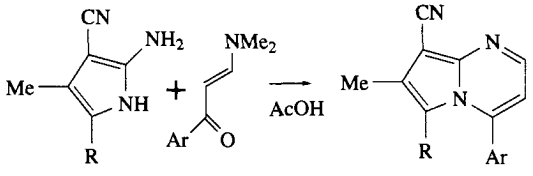


(330) 72% (171)

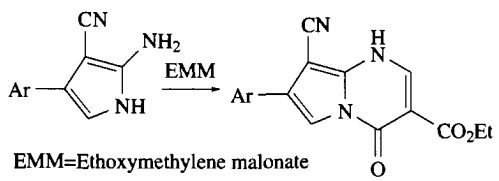
The majority of syntheses involving pyrroles or pyrrolines with α-heteroatom substituents involve amines. These are condensed with β-diketones as in the synthesis of compounds (**331**) (Equation (172)) ⟨76CB2983, 88IJC(B)1046, 89ZC100⟩; the reactions can be acid- or base-catalyzed. One report includes the use of acetals instead of the free β-ketoaldehydes, and another the sodium salt of ethyl formylacetate ⟨87FES787⟩; an enaminoketone or -aldehyde has been used to make compounds such as (**332**) (Equation (173)) ⟨94EJM393⟩. Pyrrolopyrimidinones (**333**) can be prepared by using ethoxymethylene malonates (Equation (174)) ⟨87FES717, 87JHC297, 89PHA814, 91MI 811-02⟩. There is one report of cyclization with the opposite regiochemistry when an ethoxyethylene malonate was used ⟨93JAP(K)0570705⟩. DMAD has been used to give a low yield of compound (**334**) (Equation (175)) ⟨92AP(325)545⟩. Aminopyrrolines react with γ-bromopropylamine hydrobromide to give compound (**335**) ⟨84BSB191⟩ and with α,β-unsaturated ketones or diketene to give compounds of type (**87**) (Scheme 36) ⟨83JHC393⟩.



(331) (172)

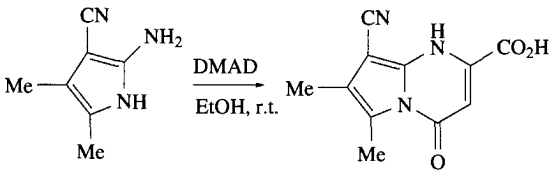


Ar=3-FC$_6$H$_4$ (332) (173)



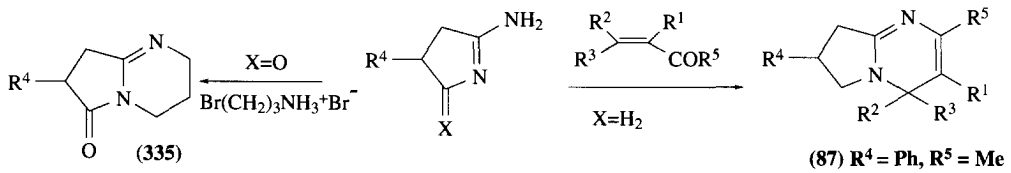
EMM=Ethoxymethylene malonate

(333) (174)



(175)

(334) 20%

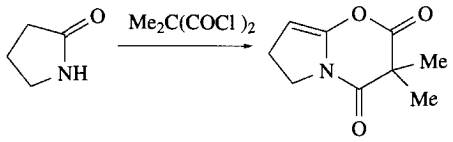


(335)

(87) R^4 = Ph, R^5 = Me

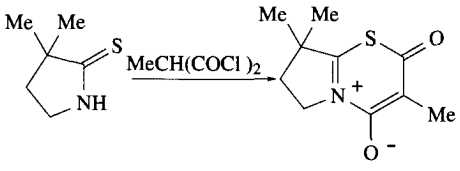
Scheme 36

A malonyl chloride with 2-pyrrolidone gives pyrrolooxazinedione (**336**) (Equation (176)) ⟨68USP3373159⟩; a similar reaction with a pyrrolidine-2-thione gives the mesoionic compound (**132**) (Equation (177)) ⟨93TL5405⟩. When the 5-oxopyrrolidine-2-thione (**337**) reacts with ethoxymethylene derivatives, the products are pyrrolothiazines (**338**) (Equation (178)) ⟨89SUL175⟩.



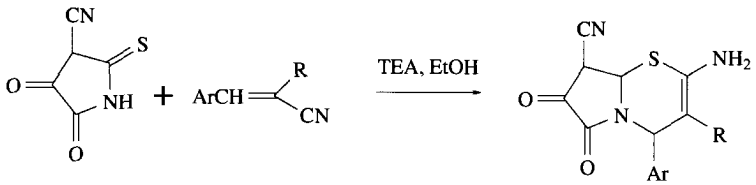
(176)

(336) 26%



(177)

(132)



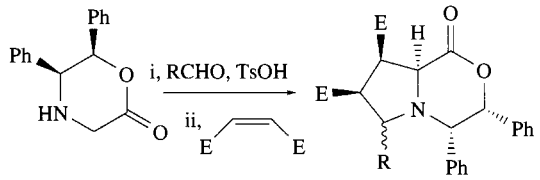
(178)

(337)

(338) R=CN, CO_2Et, $CSNH_2$, 55-85%

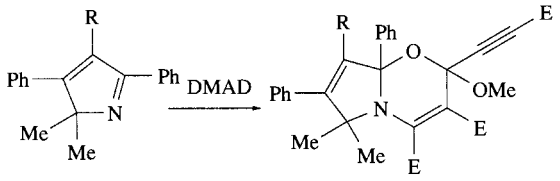
8.11.9.3 Formation from Three or More Precursor Molecules

There are only four examples in this section. An oxazinone reacts with aldehydes and dimethyl maleate to give pyrrolooxazine precursor of (**173**) (Equation (179)) ⟨92JOC6527⟩; this may be another variant of the imine synthesis described in Section 8.11.9.2. Two molecules of DMAD are involved in the synthesis of pyrrolooxazine (**339**) (Equation (180)) ⟨89JCR(S)126⟩. A one-pot reaction which might be considered as (4 + 1) involves ethyl nitroacetate and subsequently formaldehyde to give (**340**) (Equation (181)) ⟨78BRP1526620⟩. A four component reaction between ethyl 2-pyrrolidinylideneacetate, formaldehyde, and amines, gives compound (Equation (182)) (**341**) ⟨91CPB2126⟩.



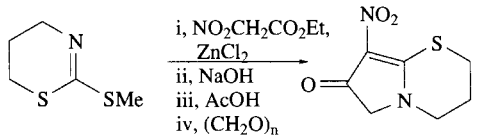
(179)

(173) 32-71%



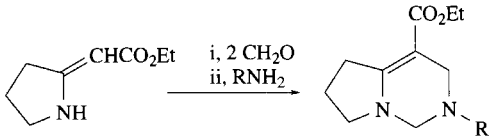
(180)

(339)



(181)

(340)

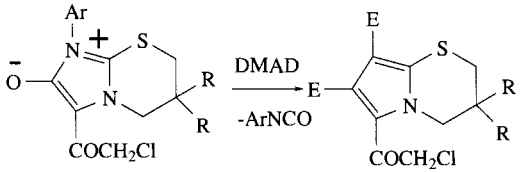


(182)

(341)

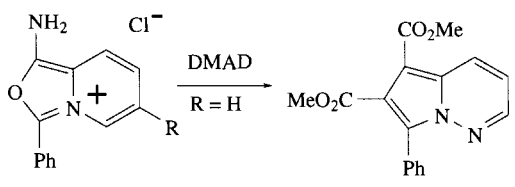
8.11.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Dipolar addition of DMAD to the mesoionic species (**342**) (Equation (183)) ⟨88H(27)227⟩ or to the quaternary salt (**343**) (Equation (184)) give a pyrrolo-thiazine and -pyridazine, respectively. Nucleophilic attack on salt (**344**) by active methylene anions gives pyrrolopyridazines (Equation (185)) ⟨77YZ422⟩.



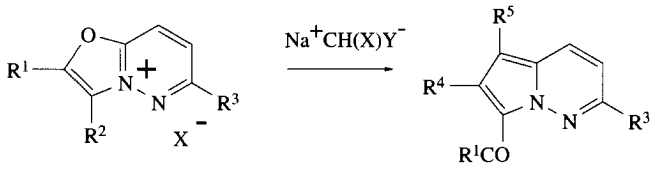
(183)

(342) **45-96%**



(184)

(343)

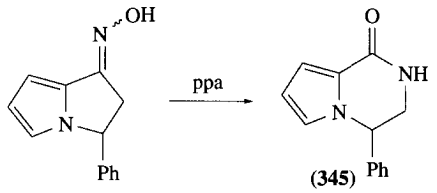


(344)

e.g. R^4=NH_2, R^5=CN or CO_2Et
R^4=OH, R^5=CO_2Et

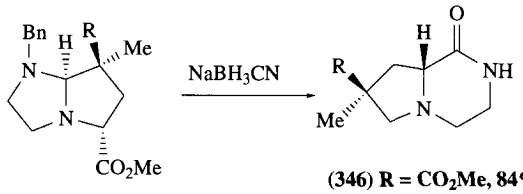
(185)

Expansion of a five-membered ring can provide the six-membered ring, as in the synthesis of compound (**345**) by Beckmann rearrangement (Equation (186)) ⟨93H(36)2129⟩. Reduction and recyclization of the monocyclic intermediate give compound (**346**) (Equation (187)) ⟨93JCS(P1)2391⟩. A tricyclic intermediate is involved in the synthesis of compound (**347**) (Scheme 37) ⟨89AG(E)1381⟩.



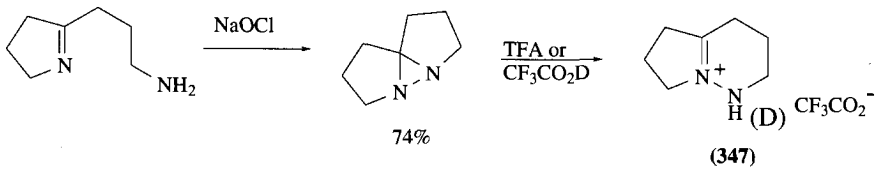
(345)

(186)



(346) **R = CO_2Me, 84%**

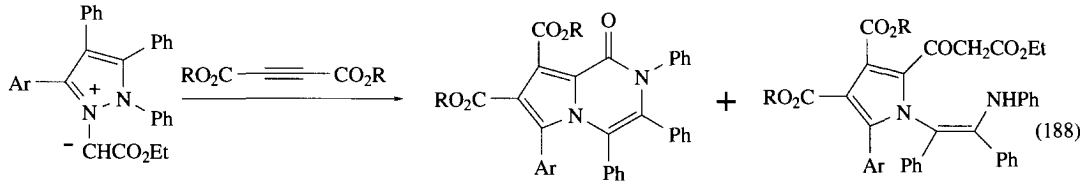
(187)



(347)

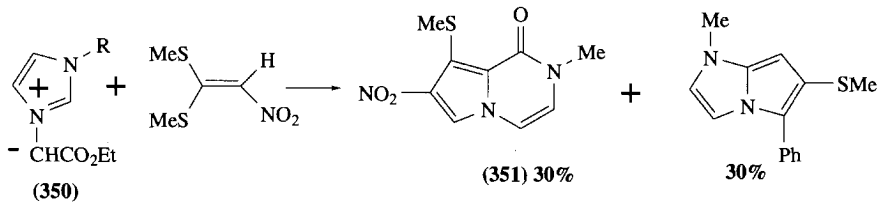
Scheme 37

Various azole ylides react with alkynes or alkenes with subsequent ring opening and recyclization. Thus pyrazolium ylide (**348**) gives compound (**349**) (Equation (188)) ⟨93JCS(P1)883⟩, imidazolium ylide (**350**) gives (**351**) (Equation (189)) ⟨91H(32)2217⟩, and thiazolium ylide (**352**) gives (**353**) (Equation (190)) ⟨76JOC187⟩.



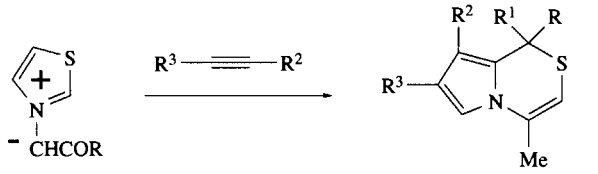
(348) (349) **14-56%** **9-78%**

(188)



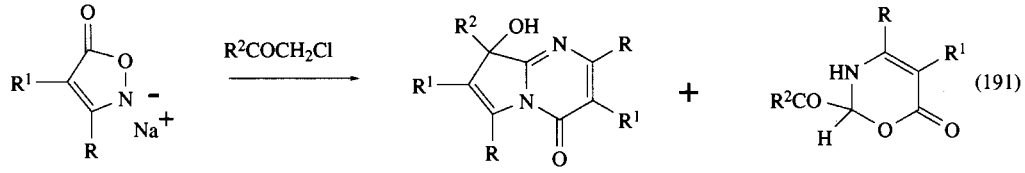
(350) (351) **30%** **30%**

(189)

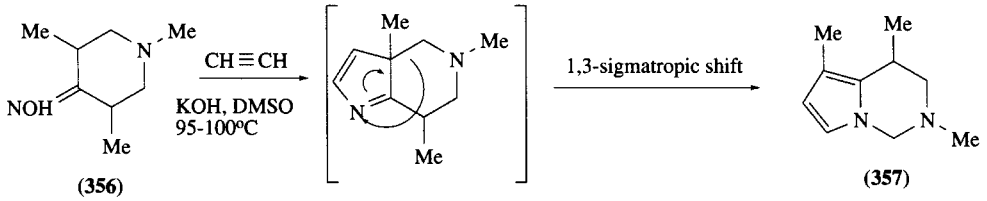


(352) (353) R=Aryl, R^1=OH or $OCH{=}CHCO_2R^5$ (190)

Alkylation of isoxazolone anion (**354**) gives pyrrolopyrimidinone (**355**) (Equation (191)) ⟨88T6225⟩. The oxime (**356**) reacts with ethyne to give pyrrolopyrimidine (**357**) via an intermediate pyrrolopyridine (Scheme 38) ⟨87KGS1286⟩, and the sulfoxide (**358**) gives two quite different products when heated in a solvent ⟨91CR(B)885⟩ or treated with diethyl cyanophosphate (Scheme 39) ⟨91CR(B)989⟩.

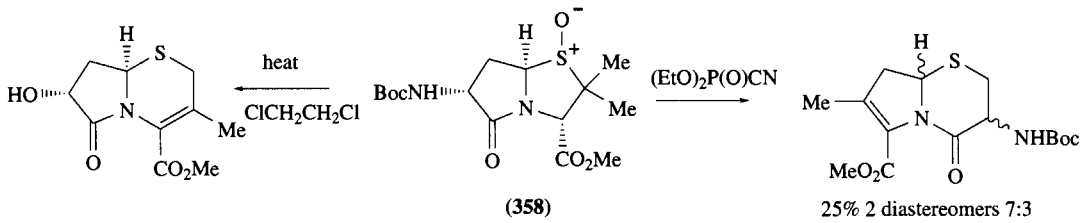


(354) (355) 3-36% 24-88% (191)



(356) (357)

Scheme 38



(358) 25% 2 diastereomers 7:3

Scheme 39

8.11.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

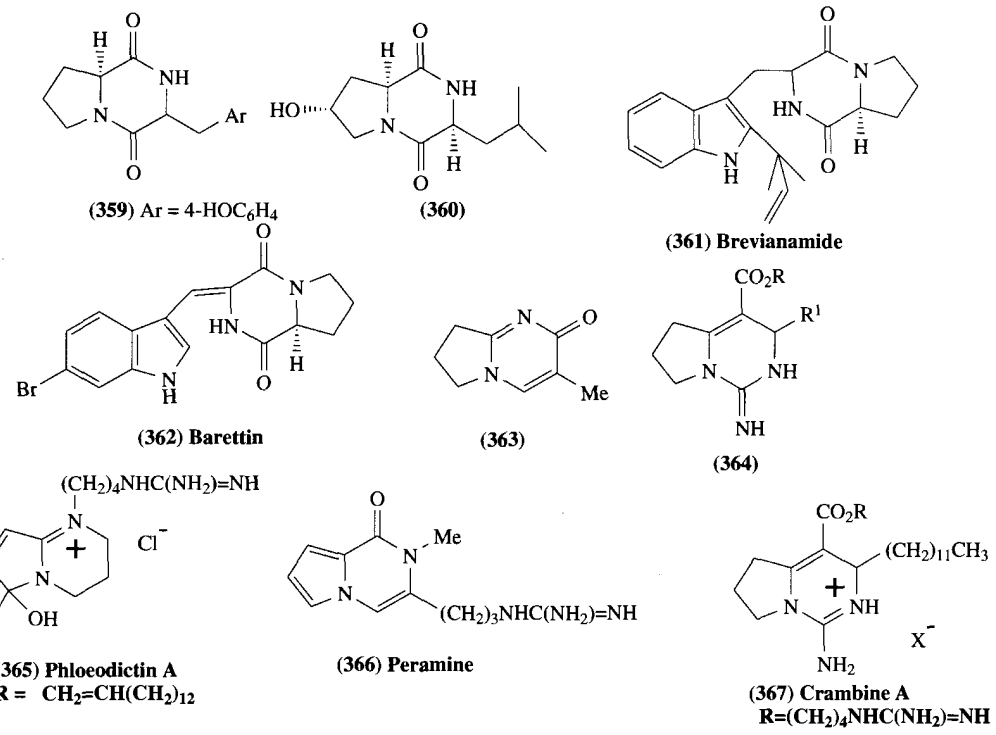
The systems are so diverse that no brief and meaningful discussion is possible.

8.11.12 IMPORTANT COMPOUNDS AND APPLICATIONS

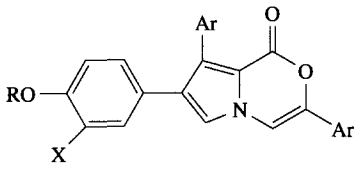
Most of the importance of compounds dealt with in this chapter is biological or medicinal. There are virtually no industrial applications except for flavour chemistry. As a strong base dbn has many applications.

There are many recorded isolations of *cyclo*(Pro–X) dipeptides, the most intensively studied being

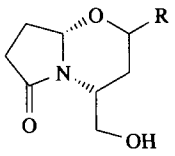
cyclo(Pro–His) which is a metabolic product of TRH (thyrotropin releasing hormone) ⟨88MI 811-01, 89ANY553⟩. In view of the ubiquity of α-aminoacids in nature, and their use in fermentation broths, it is not surprising that many *cyclo*(Pro–X) dipeptides have been isolated ⟨51JA2947, 79JAP(K)157598, 81ABC2613, 81MI 811-01, 81P815, 83JOC3941, 84FES718, 85MI 811-02, 89JA647, 91EGP287272, 94MI 811-01, 94MI 811-02⟩. Specific mention can be made to maculosin, (**359**) host specific phytotoxin (knapweed) ⟨88PNA8008, 93MI 811-02, 94MI 811-01, 94P101⟩; analogues are reported to have selective herbicidal activity against knapweed ⟨90USP4929270⟩. Compound (**360**) isolated from rabbit skins ⟨87TL1285, 88E356⟩ used as a pretreatment for rice seeds enhances drought resistance. Related compounds are plant growth regulators ⟨88JAP(K)63135386⟩ and fungicides ⟨78JAP(K)78121930⟩. Another well known source of *cyclo*(Pro–X) dipeptides are the ergot alkaloids, where pyrolysis was found to produce simple compounds of type (**38**) ⟨37JCS396, 83H(20)2229, 85HCA724⟩, subsequently shown by synthesis to be present in many of the alkaloids (see ⟨81JPR869, 81ZC148, 87E1125⟩; also ⟨76CCC3415, 76MI 811-04⟩). Other synthetic analogues with pharmaceutical interest are reported ⟨84FES718, 86CPB2931, 88AF647⟩. Brevianamide (**361**) and many derivatives and analogues have been synthesized ⟨B-86MI 811-05⟩; barettin (**362**) has been isolated from a sponge ⟨86TL3283⟩. Examples of pyyrolopyrazine and pyrimidine alkaloids are compound (**363**) ⟨90MI 811-06⟩ and the batzella alkaloids containing the group (**364**) ⟨93MIP9324489⟩ and said to inhibit infection by the HIV virus, phloeodictins A (**365**) and B ⟨92JOC3832⟩, crambines (**366**) ⟨92JOC2526, 93JOC3828⟩, and peramine (**367**) an insect feeding deterrent ⟨88AJC1583, 88JOC4650, 90MI 811-05⟩.



Among pyrrolooxazines of natural origin and medicinal interest are lukianols (**368**) from a tunicate ⟨92HCA1721⟩ and compound (**369**) ⟨92P3757⟩. Agropine (**43**) was originally isolated from crown gall tumors ⟨79MI 811-01, 79MI 811-03, 80PNA(77)2693, 80TL495, 81CR(C)153⟩. Many pyrrolo[1,4]oxazin-3-ones, such as (**44**) are important flavors and odors in food and tobacco ⟨76USP3996941, 76MI 811-01, 76MI 811-02, 78MI 811-01⟩; it is therefore unsurprising that they are found when sugars and aminoacids are heated together ⟨71ABC2097, 77ABC2377, 93MI 811-05⟩. Similarly found ⟨77HCA1872, 77MI 811-01, 78ABC607⟩ and formed ⟨78ACS(B)249, 79ACS(B)125, 92MI 811-03⟩ are pyrrolopyrazines. A few pyrrolothiazines have reported activity as insecticides e.g. compound (**340**) ⟨78BRP1526620⟩, also ⟨91EUP415211⟩, or in medicine ⟨86JMC784, 91EUP425134⟩. Compounds mentioned elsewhere in the text which have reports of pharmaceutical or insecticidal activity are (**71**), (**86**), (**194**), (**252**), (**255**), (**271**), (**286**), and (**321**).



(368) Lukianol A, X=R=H
B, R=H, X=I
Ar=4-HOC$_6$H$_4$



(369)

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8.12
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 1 : 1

DRAGO ROBERT SLISKOVIC
Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA

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8.12.1 INTRODUCTION

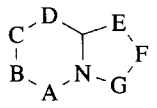
This chapter reviews those systems composed of a bicyclic system containing fused five- and six-membered rings with one ring junction nitrogen atom and two extra heteroatoms, one in the five-membered ring and one in the six-membered ring. The heteroatoms are primarily nitrogen, oxygen, and sulfur; however, a limited number of phosphorus and selenium-containing systems have been described. The total number of different ring systems falling within the scope of this definition, which have been reported in the literature, is 74, so a comprehensive treatment of each system is impossible within the confines of this Chapter (some ring systems have been reviewed in ⟨61CHE749⟩, which covers literature prior to 1961). As has been noted previously, the amount of literature for each of these ring systems varies greatly. Ring systems (**1**)–(**62**) have received scant coverage in the primary literature, some of these systems being covered by a single reference. These systems are shown in Table 1 with pertinent references and comments. The only exception to this statement is the thiazolo[3,2-*a*] pyrimidine (**42**) ring system, which has received a lot of attention in the literature mainly due to the interesting biological properties associated with this ring system. Ritanserin (**75**) has stimulated a lot of interest mainly due to its atypical antipsychotic activity (see Section 8.12.11). Reviews have appeared on the synthesis and biological properties ⟨89MI 812-01⟩ of the parent system and on the synthesis of polycyclic condensed thiazolo[3,2-*a*]pyrimidines ⟨91SR143⟩. The imidazodiazines (**63**)–(**70**) and the pyrazolodiazines (**71**)–(**74**) have attracted most attention in the literature because these compounds are the only representatives in this section which can form electronically neutral, fully delocalized 10 π-electron systems (Table 2).

Based on an analysis of those ring systems attracting the greatest attention in the literature, this chapter will focus on the imidazodiazines (**63**)–(**70**) and the pyrazolodiazines (**71**)–(**74**). The other systems known (**1**)–(**62**), which fall within the scope of this chapter, are noted and the most relevant references are provided in Table 1, with pertinent comment when necessary. The imidazodiazines (**63**)–(**70**) have been the subject of extensive review prior to 1982 ⟨84CHEC-I(5)607⟩, a thorough review covering the imidazopyrimidines (**67**) and (**68**), and related benzo analogues covers literature up to 1977 ⟨77RCR634⟩ and a more recent review, in the early 1990s, on the imidazo[1,2-*c*]pyrimidine (**68**) ring system has appeared covering both syntheses and chemical properties ⟨91MI 812-01⟩. The pyrazolodiazines (**71**)–(**74**) have also been extensively reviewed prior to 1982 ⟨84CHEC-I(5)305⟩. The pyrazolopyrimidines (**73**)–(**74**) have been the subject of a review covering the literature up to 1987 ⟨87AHC(41)319⟩, and a review has appeared covering a series of aminovinyl pyrazolo[1,5-*a*]pyrimidines as precursors to a series of tricyclic derivatives which bind to the benzodiazepine receptor ⟨93MI 812-01⟩. As can be seen, the literature on systems (**63**)–(**74**) is extensive and thus in the interest of saving space, this review will concentrate on the more recent literature which has appeared since the mid-1980s.

8.12.2 THEORETICAL METHODS

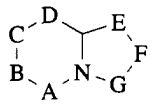
INDO/S–SOS molecular orbital calculations have been used to estimate the electric field gradients at the various nitrogen nuclei of systems (**65**) and (**67**). These calculations are in good agreement with the data obtained from ^{15}N NMR ⟨84OMR(22)209, 87BAP301⟩.

Table 1 Ring systems (**1**)–(**62**).



Compound name and number	*Heteroatom location*	*References (Comments)*
Isoxazolo[2,3-*b*][1,2]oxazine (**1**)	A=G=O	70IZV2641
Isoxazolo[3,2-*c*][1,4]oxazine (**2**)	C=G=O	92T5273, 93JPO326 (^{13}C NMR)
Isoxazolo[3,2-*b*][1,3]oxazine (**3**)	D=G=O	80JHC299
Isoxazolo[2,3-*c*][1,3]oxazine (**4**)	B=G=O	89T233, 89AX(C)1838 (x ray)
Oxazolo[2,3-*c*][1,4]oxazine (**5**)	C=E=O	86USP4595751
Oxazolo[4,3-*c*][1,4]oxazine (**6**)	C=F=O	64AP(297)632, 74JCS(P1)1419 (NMR)
Oxazolo[3,4-*c*][1,3]oxazine (7)	B=F=O	73JCS(P1)1379 (NMR), 91JST(263)157 (*Theor. Chem.*)
Oxazolo[3,2-*c*][1,3]oxazine (**8**)	B=E=O	73JOC4465
Oxazolo[2,3-*b*][1,3]oxazine (**9**)	D=E=O	91TL597
Oxazolo[2,3-*c*][1,4]thiazine (**10**)	C=S, E=O	88JOC447
Oxazolo[4,3-*c*][1,4]thiazine (**11**)	C=S, F=O	76JCS(P1)584, 76JCS(P2)203 (NMR)
Oxazolo[3,4-*b*][1,2]thiazine (**12**)	A=S, F=O	84JA7861, 86TL4885
Oxazolo[3,2-*c*][1,3]thiazine (**13**)	B=S, E=O	76M183
Oxazolo[2,3-*b*][1,3]thiazine (**14**)	D=S, E=O	66AG(E)894
Isoxazolo[2,3-*a*]pyrazine (**15**)	C=N, G=O	81CB2536
Isoxazolo[2,3-*a*]pyrimidine (**16**)	D=N, G=O	77ZN(B)311, 83JOC575, 90OPP532
Isoxazolo[2,3-*c*]pyrimidine (**17**)	B=N, G=O	82LA2223
Oxazolo[3,4-*a*]pyrazine (**18**)	C=N, F=O	62HCA2383
Oxazolo[3,2-*a*]pyrazine (**19**)	C=N, E=O	81USP4251529
Oxazolo[3,4-*b*]pyridazine (**20**)	A=N, F=O	68MI 812-01
Oxazolo[3,2-*b*]pyridazine (**21**)	A=N, E=O	77YZ422
Oxazolo[3,4-*c*]pyrimidine (**22**)	B=N, F=O	91KGS855
Oxazolo[3,2-*a*]pyrimidine (**23**)	D=N, E=O	87JCR(S)158, 88S816
Oxazolo[3,2-*c*]pyrimidine (**24**)	B=N, E=O	66AP(299)107, 76M171, 84H(22)2505
[1,3]Azaphospholo[1,2-*a*] pyrazine (**25**)	C=N, E=P	92TL1049
[1,3]Azaphospholo[1,5-*a*] pyrazine (**26**)	C=N, F=P	91CB475 (NMR)
[1,3]Azaphospholo[1,2-*b*] pyridazine (**27**)	A=N, E=P	92TL1049 (x ray)
[1,3]Azaphospholo[1,5-*b*]pyridazine (**28**)	A=N, F=P	92TL1049
Thiazolo[2,3-*c*][1,4]oxazine (**29**)	C=O, E=S	67KGS1043
Thiazolo[4,3-*b*][1,3]oxazine (**30**)	D=O, E=S	91HCA297
Thiazolo[3,4-*c*][1,3]oxazine (**31**)	B=O, F=S	83TL4503
Thiazolo[3,2-*c*][1,3]oxazine (**32**)	B=O, E=S	79LA334, 84H(22)2341
Thiazolo[2,3-*b*][1,3]oxazine (**33**)	D=O, E=S	86JCS(P1)2187 (x ray)
Thiazolo[2,3-*c*][1,4]thiazine (**34**)	C=E=S	64M1335
Thiazolo[4,3-*c*][1,4]thiazine (**35**)	C=S, F=S	80USP4181799
Thiazolo[4,3-*b*][1,3]thiazine (**36**)	D=S, F=S	92T10277
Thiazolo[2,3-*b*][1,3]thiazine (**37**)	D=S, E=S	82CC76 (x ray)
Isothiazolo[2,3-*a*]pyrimidine (**38**)	D=N, G=S	84JCS(P1)1631 (x ray)
Thiazolo[3,4-*a*]pyrazine (**39**)	C=N, F=S	77H(8)461, 80TL1803, 84MI 812-01
Thiazolo[3,2-*a*]pyrazine (**40**)	C=N, E=S	69JCS(C)2270
Thiazolo[3,2-*b*]pyridazine (**41**)	A=N, E=S	69JOC996, 77CPB299, 90CCC2795
Thiazolo[3,2-*a*]pyrimidine (**42**)	D=N, E=S	91SR143 (Review), 89MI 812-01 (Review)
Thiazolo[3,2-*c*]pyrimidine (**43**)	B=N, E=S	84UKZ81 (MS), 85UKZ987 (UV), 87MRC550 (^{13}C NMR), 69JMC227
Thiazolo[3,4-*a*]pyrimidine (**44**)	D=N, F=S	73JHC479 (*Theor. Chem.*), 83KGS936
Selenazolo[3,2-*a*]pyrimidine (**45**)	D=N, E=Se	73UKZ956, 75JHC675
Imidazo[2,1-*c*][1,4]oxazine (**46**)	B=O, E=N	72USP3676439
Imidazo[5,1-*c*][1,4]oxazine (**47**)	C=O, F=N	66JOC806, 75OMS885 (MS)
Imidazo[5,1-*b*][1,3]oxazine (**48**)	D=O, F=N	75CB372
Imidazo[1,2-*c*][1,3]oxazine (**49**)	B=O, E=N	75JOC252, 89CJC1560 (NMR)
Imidazo[1,5-*c*][1,3]oxazine (**50**)	B=O, F=N	83JA2382
Imidazo[2,1-*b*][1,3]oxazine (**51**)	D=O, E=N	87JOC2355
Pyrazolo[5,1-*c*][1,4]oxazine (**52**)	C=O, G=N	80S875, 82SC381, 87JOC3681
Pyrazolo[5,1-*b*][1,3]oxazine (**53**)	D=O, G=N	84AP(317)198, 84CPB930
Pyrazolo[1,5-*c*][1,3]oxazine (**54**)	B=O, G=N	84S71, 79S440
Imidazo[2,1-*c*][1,4]thiazine (**55**)	C=S, E=N	82JHC1375, 83S481
Imidazo[5,1-*c*][1,4]thiazine (**56**)	C=S, F=N	81JOC3026 (x ray), 83OMR(21)328 (NMR)
Imidazo[5,1-*b*][1,3]thiazine (**57**)	D=S, F=N	87JCS(P1)1437
Imidazo[1,2-*c*][1,3]thiazine (**58**)	B=S, E=N	79TL1281
Imidazo[1,5-*c*][1,3]thiazine (**59**)	B=S, F=N	83JHC483
Imidazo[2,1-*b*][1,3]thiazine (**60**)	D=S, E=N	72JOC1464, 80JCS(P1)1352, 81T409, 88IJC(B)570 (x ray)
Pyrazolo[5,1-*c*][1,4]thiazine (**61**)	C=S, G=N	82JOC4429
Pyrazolo[5,1-*b*][1,3]thiazine (**62**)	D=S, G=N	82GEP157803

Table 2 Imidazodiazines (**63**)–(**70**) and pyrazolodiazines (**71**)–(**74**).



Compound name and number	*Heteroatom location*
Imidazo[1,5-*a*]pyrazine (**63**)	C=F=N
Imidazo[1,2-*a*]pyrazine (**64**)	C=E=N
Imidazo[1,2-*b*]pyridazine (**65**)	A=E=N
Imidazo[1,5-*b*]pyridazine (**66**)	A=F=N
Imidazo[1,2-*a*]pyrimidine (**67**)	D=E=N
Imidazo[1,2-*c*]pyrimidine (**68**)	B=E=N
Imidazo[1,5-*a*]pyrimidine (**69**)	D=F=N
Imidazo[1,5-*c*]pyrimidine (**70**)	B=F=N
Pyrazolo[1,5-*a*]pyrazine (**71**)	C=G=N
Pyrazolo[1,5-*b*]pyridazine (**72**)	A=G=N
Pyrazolo[1,5-*c*]pyrimidine (**73**)	B=G=N
Pyrazolo[1,5-*a*]pyrimidine (**74**)	D=G=N

8.12.3 EXPERIMENTAL STRUCTURAL METHODS

8.12.3.1 NMR Studies

There are miscellaneous collections of chemical shift data available for examples of all these systems but nothing deserves special comment. Studies since the mid-1980s have focused on answering specific questions and they are detailed below.

8.12.3.1.1 Proton spectra

Proton NMR spectra, in combination with ^{13}C and ^{15}N NMR data, has been used to determine the protonation sites of (**67**) and a number of cardiotonic 2-aryl derivatives, derived from sulmazole. The increases in ^{1}H–^{1}H couplings that occur on protonation of a heterocyclic nitrogen have helped in showing that 2-aryl substitution has no effect on the protonation site since (**67**) and its 2-aryl derivatives all undergo protonation at N-1. In addition, the effect of an *N*-methyl substituent on the ^{1}H chemical shifts is very similar to that of a hydrogen ⟨91MI 812-02⟩. This study was also expanded to include (**64**) and (**65**) and related 2-aryl derivatives. Again, protonation for the parent systems was confirmed as occurring at N-1. However, the 2-aryl substituted analogues of (**64**) protonated primarily at N-7 ⟨91MRC468⟩. Interproton distances for (**67**) have been determined using the NMR SNIDE (Selective NonInversion for Dipolar Effects) method ⟨93MI 812-02⟩.

8.12.3.1.2 ^{13}C and ^{15}N spectra

The ^{13}C chemical shifts and coupling constants for (**63**), (**64**), and (**67**) have been reported and used to study the nucleophilic substitution of the 3,5-dibromo- and 6,8-dibromo derivatives of (**64**) by a methoxy group. This study showed that nucleophilic substitutions only occurred on the pyrazine ring ⟨84AJC1357⟩. In another study, ^{13}C NMR has been used to provide a clear distinction between *O*-methyl and nuclear *N*-methyl groups attached to systems (**64**) and (**65**) ⟨84AJC2391⟩. ^{13}C NMR shift data has also been reported for (**65**) (in addition to (**64**) and (**67**)) ⟨87JHC805, 89BAP313⟩.

^{15}N NMR chemical shifts have also been reported for systems (**64**), (**65**), and (**67**) ⟨82OMR87, 84OMR209, 87BAP301⟩.

8.12.3.2 Mass Spectrometry Studies

The use of mass spectrometry in this series of compounds has been mainly confined to molecular ion determination and structure determination. There have been no recent systematic studies on the fragmentation patterns for these systems.

8.12.3.3 Electronic, IR, and Photoelectron Spectroscopy

There have been no systematic studies for systems (**63**)–(**74**). Derivatives of (**68**), containing the acyl guanidine moiety of fixed conformation have been prepared, and UV and IR have been used to examine the conformational and tautomeric preference of acylguanidines ⟨85JCS(P2)1255, 85JCS(P2)1265⟩.

8.12.3.4 X-ray Studies

X-ray crystallography has essentially only been used as a method of structure determination/confirmation and the results are unexceptional.

8.12.3.5 Magnetic Circular Dichroism Studies

The MCD spectra of 14 azaindolizines (including (**64**) and (**65**)) in the neutral and protonated forms have been determined. The protonation of (**64**) was found to occur either at N1 or N4, whereas for (**65**) protonation at the 1-position was the only choice consistent with the calculations ⟨85JOC302⟩.

8.12.4 THERMODYNAMIC ASPECTS

From the point of view of systems (**1**)–(**74**), these aspects have been very much neglected. Most references contain some boiling and melting points but there has been no consideration of these values from the point of view of intermolecular forces between molecules. The pK_a values for the parent systems (**64**), (**65**), (**67**), $pK_a = 3.59, 4.57, 4.81$, respectively) and some 2-aryl analogues have been determined spectroscopically. The basicity of the aryl substituted compounds was lower than that of the parent heterocycle ⟨91MRC468⟩. The pK_a values for a number of oxo analogues of (**67**), have been reported in a study to determine the conformational and tautomeric preferences of acylguanidines ⟨85JCS(P2)1255⟩.

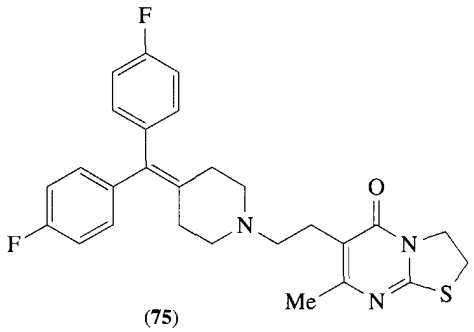
8.12.5 REACTIVITY OF FULLY CONJUGATED RINGS

The imidazodiazines (**63**)–(**70**) and the pyrazolodiazines (**71**)–(**74**) are the only representatives in this section which can form electronically neutral fully delocalized 10 π-electron systems. The chemistry of the fully conjugated systems can best be understood by assuming that the system consists of a five-membered π-excessive heterocyclic ring that is fused to a six-membered π-deficient ring. Thus, electrophilic reagents are expected to attack the five-membered ring carbons, and nucleophilic reagents are expected to attack the six-membered ring. The reactivity of these systems has been reviewed extensively; ⟨84CHEC-I(5)607⟩ covers literature for the imidazodiazines prior to 1982, ⟨84CHEC-I(5)305⟩ covers literature for the pyrazolodiazines prior to 1982, ⟨87AHC319⟩ covers pyrazolopyrimidines and ⟨91MI 812-01⟩ imidazo[1,2-*c*]pyrimidine (**68**). This section will deal collectively with systems (**63**)–(**74**) and concentrate on literature describing novel chemical reactivity, appearing since 1982.

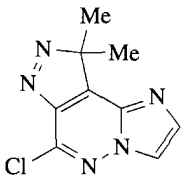
8.12.5.1 Thermal and Photochemical Reactions

There have been few reports on this topic in the literature. Photolysis of (**76**) led to ejection of nitrogen from the 3*H*-pyrazole moiety and the formation of the alkene (**78**). The intermediate 1,3-

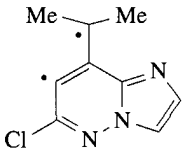
diradical (**77**) can be trapped by the addition of methanol, furan or 1,3-butadiene ⟨86TL1309⟩. Decomposition of the azide (**79**) at 160 °C in bromobenzene gave (**80**) in 52% yield, while photolysis in dry dichloromethane gave the same product in only 12% yield ⟨92JHC691⟩.



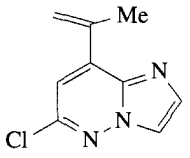
(**75**)



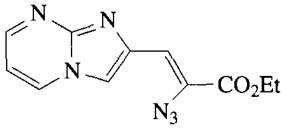
(**76**)



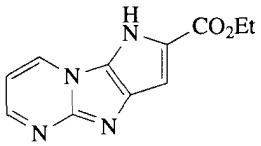
(**77**)



(**78**)



(**79**)



(**80**)

8.12.5.2 Electrophilic Attack at Nitrogen (and/or Carbon)

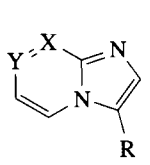
There are some reports on the protonation sites of some of these systems. Proton NMR, in combination with ^{13}C and ^{15}N NMR data, has been used to determine the protonation sites of (**64**), (**65**), and (**67**) as occurring at N-1 (see Section 8.12.3.1.1) ⟨91MI 812-02, 91MRC468⟩. Using magnetic circular dichroism studies (see Section 8.12.3.5), the protonation of (**64**) was found to occur either at N-1 or N-4, whereas for (**65**), protonation at the 1-position was the only choice consistent with the calculations ⟨85JOC302⟩.

It is well documented in these systems that electrophilic attack at carbon always occurs in either the imidazole or pyrazole rings ⟨84CHEC-I(5)607, 84CHEC-I(5)305⟩. Hydroxyalkylation of (**64**) and (**67**) with formaldehyde in acetic acid has been shown to yield the corresponding C-3 hydroxymethyl compounds, (**81**) and (**82**), respectively ⟨86JCR(S)202⟩. Bromination of (**83**) with bromine or iodination with iodine chloride caused dehydrazination as well as halogenation and led to good yields of the respective 3-bromo-(**84**) and 3-iodo-(**85**) compounds. Nitration gave a mixture of (**86**) and (**87**) ⟨93JCR(S)292⟩.

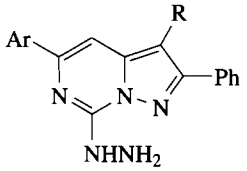
8.12.5.3 Nucleophilic Attack at Carbon

Reaction of (**67**) with phenyllithium in diethyl ether and then propionaldehyde at 0 °C gave the addition product (**88**), compound (**64**) gave two addition products (**89**) and (**90**) using the same conditions. Treatment of the quinazoline (**91**) gave a number of products depending on the solvent choice; in THF, phenyllithium followed by propionaldehyde gave (**92**) as the major addition product; in diethyl ether, (**93**) (ring opening) and (**94**) (ring opening–ring closure) were isolated ⟨94H(38)551⟩.

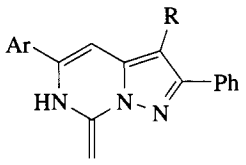
Many reports of the nucleophilic displacement of halogens and methylthio groups from most of these systems have appeared ⟨83CPB2540, 84CHEC-I(5)607, 84CHEC-I(5)305, 86JHC981⟩. Mesoionic analogues of (**68**) have also been shown to undergo such displacement ⟨94JOC2473⟩.



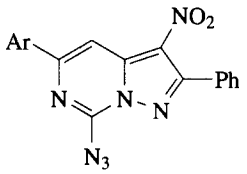
(**81**) X = CH, Y = N, R = CH_2OH
(**82**) X = N, Y = CH, R = CH_2OH



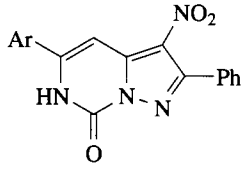
(**83**) R = H



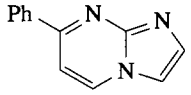
(**84**) R = Br
(**85**) R = I



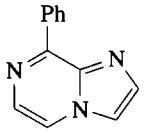
(**86**)



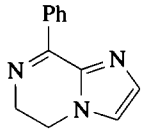
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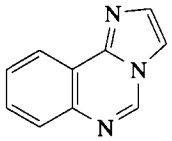
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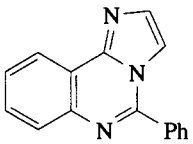
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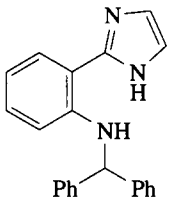
(**90**)



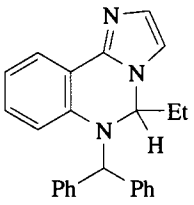
(**91**)



(**92**)



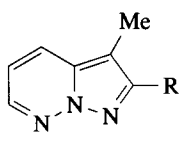
(**93**)



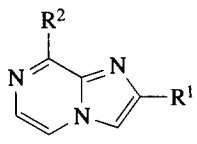
(**94**)

8.12.5.4 Reactions at Surfaces

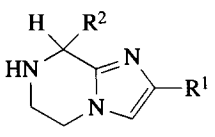
Hydrogenolysis of (**95**), using Pd–calcium carbonate in alkaline methanol, gave (**96**) in 80% yield ⟨86CPB1023⟩. Similar reactions have been reported for analogues of system (**69**) ⟨83CPB2540⟩. Hydrogenation of (**97**) using platinum oxide catalysis gave (**98**) ⟨84JCR(S)28⟩.



(**95**), R=Cl
(**96**), R=H



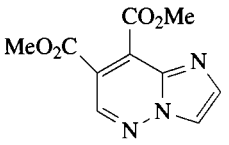
(**97**)



(**98**)

8.12.5.5 Reactions with Radicals

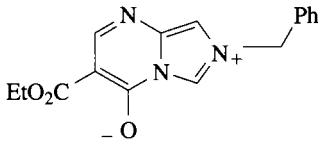
Regioselective homolytic alkoxycarbonylation of (**65**) with radicals derived from methyl pyruvate gave (**99**) in 37% yield ⟨89JHC1751⟩.



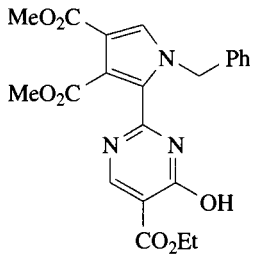
(**99**)

8.12.5.6 Reactions with Cyclic Transition States

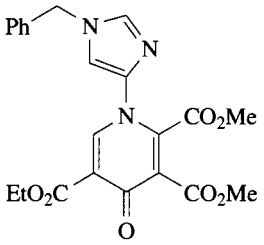
The mesomeric betaine (**100**) underwent 1,3-dipolar cycloaddition, with DMAD in toluene at 100°C, to give a mixture of two products (**101**) and (**102**). Compound (**101**) was formed by initial 1,3-dipolar cycloaddition of DMAD to the azomethine ylid fragment of (**100**) to yield a tricyclic intermediate which fragmented to (**101**). Compound (**102**) was formed via ring opening of (**100**) to a ketene intermediate which underwent a hetero Diels–Alder reaction with DMAD to give (**102**) ⟨92JCS(P1)2789⟩.



(**100**)



(**101**)



(**102**)

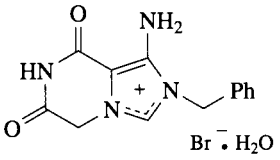
8.12.6 REACTIVITY OF NONCONJUGATED RINGS

The reactivity of nonconjugated systems has not been the subject of great scrutiny in the literature. The majority of references dealing with nonconjugated systems primarily deal with those systems which contain oxo groups (either one or two) in the six-membered ring and thus can be considered to be in equilibrium with the corresponding hydroxy compound. Most of the systems covered behave as cyclic amides and are thus weakly basic.

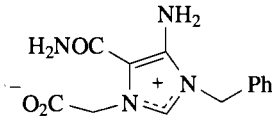
8.12.6.1 Nucleophilic Attack at Carbon

Nucleophiles typically attack in the six-membered ring and this usually results in ring opening. Treatment of the salt (**103**) with Amberlite 400 (hydroxy form) or with one equivalent of sodium hydroxide led to the formation of betaine (**104**); however, treatment of (**103**) with excess base led to the Dimroth rearrangement product (**105**) ⟨83IJC(B)30⟩. Treatment of the thione (**106**) with KOH resulted in ring opening followed by ring closure to the pyrazolopyridinone (**107**) ⟨93BCJ1172⟩. Base hydrolysis of (**108**) followed by acidification gave the imidazole (**109**) ⟨93EJM201⟩. Treatment of the inner salt (**110**) with excess NaOH gave a small amount (5%) of the corresponding acid, and the imine acid (**111**) in 88% yield, which was subsequently cyclized by thermal methods to (**112**) ⟨90JHC531⟩. Heating (**113**) at 180–190°C with PPA led to pyrimidine ring fission and the formation of a ketene intermediate, which cyclized to (**114**) ⟨83CPB2288⟩. Nucleophilic

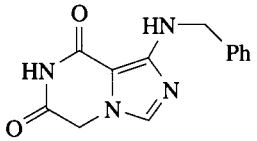
attack of hydrazine on the thione (**115**) gave the fully aromatic hydrazine derivative (**83**) ⟨93JCR(S)292⟩.



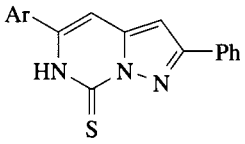
(**103**)



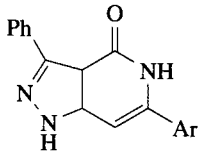
(**104**)



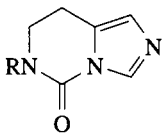
(**105**)



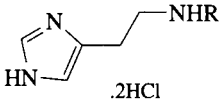
(**106**)



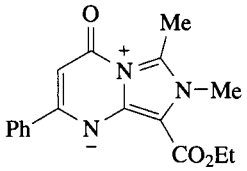
(**107**)



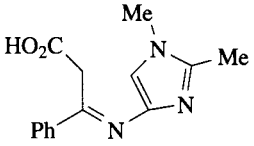
(**108**) R = alkyl
(**121**) R = H



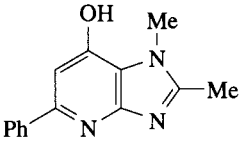
(**109**)



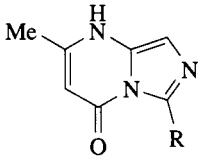
(**110**)



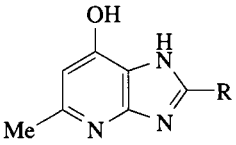
(**111**)



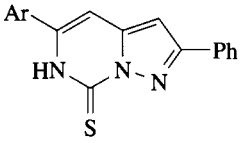
(**112**)



(**113**)



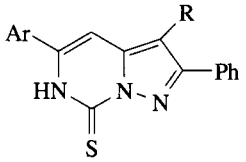
(**114**)



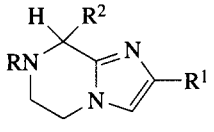
(**115**)

8.12.6.2 Electrophilic Attack at Carbon

Bromination of (**115**) with bromine or iodination with iodine monochloride gave the respective 3-bromo (**116**) and 3-iodo (**117**) derivatives, while nitration with nitric and sulfuric acids in glacial acetic acid led to the formation of the corresponding 3-nitro (**118**) derivative ⟨92BCJ3419⟩. Nitration of (**98**) with nitric and sulfuric acids gave a mixture of the nitroso (**119**, 85%) and nitro (**120**, 15%) derivatives. No nitration occurred on the imidazole ring ⟨84JCR(S)28⟩.



(**116**) R = Br
(**117**) R = I
(**118**) R = NO_2



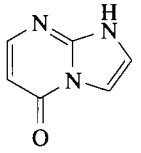
(**119**) R = NO
(**120**) R = NO_2

8.12.6.3 Nucleophilic Attack at Hydrogen

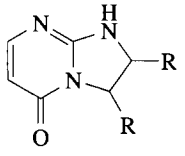
Deprotonation of (**121**) with sodium hydride and subsequent alkylation gave alkylated derivatives (**108**) ⟨93EJM201⟩.

8.12.6.4 Reaction with Radicals and at Surfaces

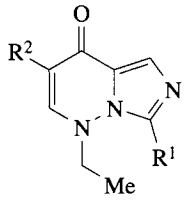
Diacetoxylation (probably a radical process) of the cyclic enamine (**122**) with lead tetraacetate in glacial acetic acid gave (**123**), which was readily hydrolyzed to the diol (**124**) ⟨92CPB235⟩. Treatment of (**125**) with Raney nickel led to desulfurization and the formation of (**126**) ⟨94JHC409⟩.



(**122**)



(**123**) R = OAc
(**124**) R = OH



(**125**) R^1 = SMe, R^2 = CO_2Et
(**126**) R^1 = H, R^2 = CO_2Et
(**127**) R^1 = H, R^2 = CO_2H

8.12.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Substituent reactivity has been covered in previous reviews ⟨84CHEC-I(5)607, 84CHEC-I(5)305, 87AHC319, 91MI 812-01⟩. The few novel reactions appearing in the literature since 1983 will be presented in this section. Hydrolysis of the ester (**126**) (aliphatic nucleophilic substitution) gives the corresponding acid (**127**) ⟨94JHC409⟩. Likewise, hydrolysis of the *gem*-dihalide (**128**) gave the corresponding aldehyde (**129**) which was reduced to the alcohol (**130**) using LAH. Alternatively, (**128**) can be dechlorinated (aliphatic nucleophilic substitution), using tri-*n*-butyl tin hydride and AIBN to yield (**131**) ⟨86CPB1023⟩. Alkylation (aliphatic nucleophilic substitution) of (**132**) with diazomethane gave the fully aromatic derivative (**133**) ⟨83AJC1215⟩. Treatment of the hydrazine derivative (**83**) with nitrous acid (aliphatic electrophilic substitution) gave (**134**) ⟨93JCR(S)292⟩. Reduction of the nitroso derivative (**135**) with either Sn/HX or Zn/AcOH gave the corresponding amine (**136**) ⟨91EJM13⟩. A similar reduction has been achieved using triethylphosphite; this reaction is thought to proceed via a ring-opened intermediate ⟨83JCS(P1)2663⟩. Deformylation of (**137**) with aqueous ammonia gave the amide (**138**) ⟨85H(23)2669⟩.

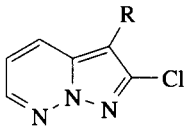
8.12.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

This area has received little attention in the literature.

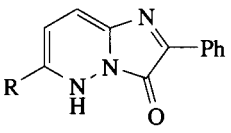
8.12.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

8.12.9.1 Imidazo[1,5-*a*]pyrazine (63)

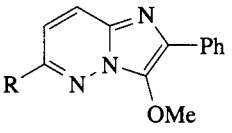
The known preparative methods for the synthesis of imidazo[1,5-*a*]pyrazines prior to 1983 have been extensively reviewed ⟨84CHEC-I(5)607⟩. This section will review new methods of syntheses published since 1983. The most common syntheses of this ring system involve closure of the imidazole ring, usually by the conversion of 2-aminomethyl pyrazines, by means of acids or anhydrides, into amides, which are then cyclized to the target heterocycle. The newer methods all involve ring closure of the pyrazine ring.



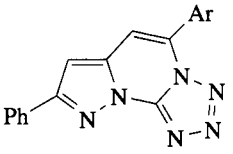
(**128**) R = $CHCl_2$
(**129**) R = CHO
(**130**) R = CH_2OH
(**131**) R = Me



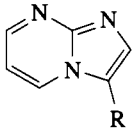
(**132**)



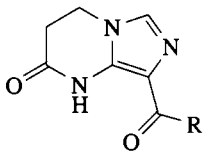
(**133**)



(**134**)



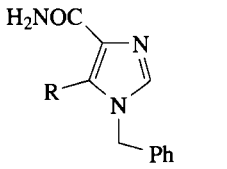
(**135**) R = NO
(**136**) R = NH_2



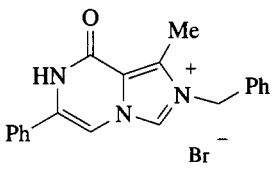
(**137**) R = NHCHO
(**138**) R = NH_2

8.12.9.1.1 Closure of the pyrazine ring

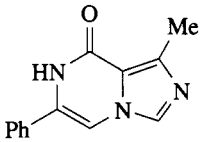
Treatment of the imidazole (**139**) with ethyl bromoacetate in refluxing DMF gave the salt (**103**) ⟨83IJC(B)30, 86MI 812-01⟩. Reaction of the imidazole (**140**) with phenacyl bromide in DMF/acetonitrile gave (**141**), which was subsequently debenzylated upon treatment with imidazole to yield (**142**) ⟨87JOC4379⟩. Refluxing the salt (**143**) in ethanolic hydrazine gave (**144**) via an azomethine ylid ⟨92JCR(S)170⟩.



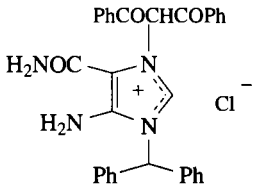
(**139**) R = NH_2
(**140**) R = Me



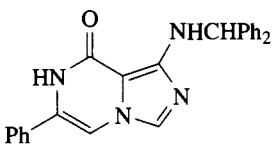
(**141**)



(**142**)



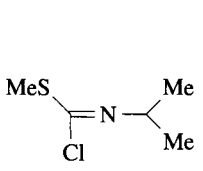
(**143**)



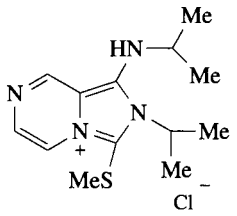
(**144**)

8.12.9.1.2 Closure of the imidazole ring

A mixture of the iminochlorosulfide (**145**), pyrazine, and an isocyanide (R—NC) underwent a three-component cyclocondensation to give the salt (**146**). Initial reaction gave a *N*-imidoylpyrazinium salt, which was then trapped by the nucleophilic isocyanide to form the desired product ⟨93TL2319⟩.



(145)



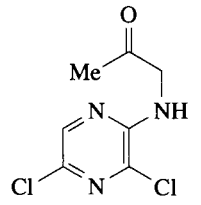
(146)

8.12.9.2 Imidazo[1,2-*a*]pyrazine (64)

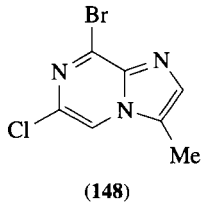
The known preparative methods for the synthesis of imidazo[1,2-*a*]pyrazines prior to 1983 have been reviewed extensively ⟨84CHEC-I(5)607⟩. This section will review new methods of syntheses published since 1983. The most common syntheses of this ring system involve closure of the imidazole ring by cyclization of an appropriately substituted aminopyrazine using a variety of reagents, or by the reaction of bifunctional agents (such as α-ketoacids, α-ketoaldehydes, α-halocarbonyl compounds), with 2-aminopyrazines.

8.12.9.2.1 Closure of the imidazole ring

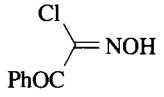
Trifluoroacetic anhydride has been used to cyclodehydrate (**147**), followed by Cl–Br exchange to give (**148**) ⟨83JMC357⟩. A number of new bifunctional agents have appeared. The α-keto hydroximoyl chloride (**149**) has been condensed with 2-aminopyrazine to produce the nitroso derivative (**150**) ⟨84JHC1029⟩. Treatment of the heteroarylacetamidines (**151**) with α-haloketones gave (**152**) in low yields ⟨84S263⟩. Treatment of the iminoether (**153**) with propargylamine gave (**154**) ⟨92TL4443⟩.



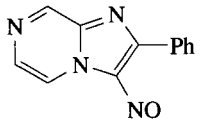
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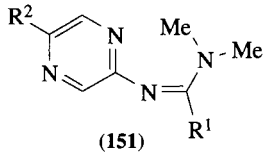
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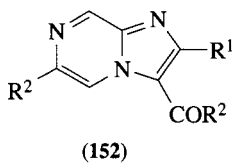
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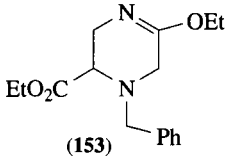
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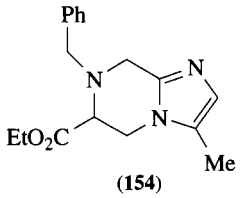
(151)



(152)



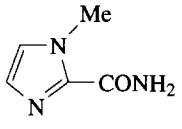
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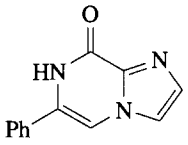
(154)

8.12.9.2.2 Closure of the pyrazine ring

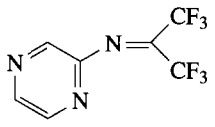
Treatment of the imidazole (**155**) with phenacyl bromide in DMF/acetonitrile followed by subsequent dealkylation with imidazole gave (**156**) ⟨87JOC4379⟩. Reaction of the hetero-1,3-diene (**157**) with tin(II) chloride gave (**158**) in low yield ⟨88S199⟩. Thermolysis of the imidazolium *N*-allylide (**159**) in refluxing 1,2,4-trimethylbenzene, resulted in 1,6-cyclization and debenzylation to give (**160**) ⟨91H(32)2217⟩. Reaction of (**161**) with an isocyanide (R—NC) gave the phosphono substituted derivative (**162**) ⟨94JPC29⟩.



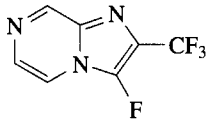
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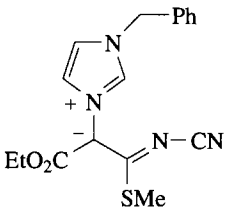
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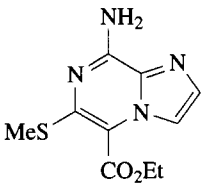
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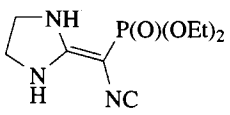
(158)



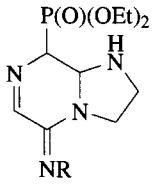
(159)



(160)



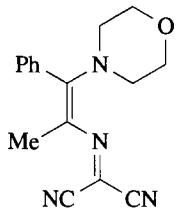
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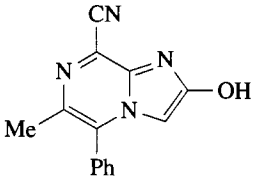
(162)

8.12.9.2.3 Formation of both rings simultaneously

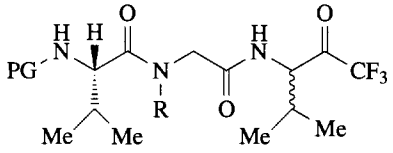
Nucleophilic attack of ethyl glycinate on the 2-aza-1,3-diene (**163**) in TEA/EtOH gave (**164**) ⟨87HCA187⟩. Deprotection of the tripeptide (**165**) gave directly (**166**) as a mixture of diastereomers in >85% yield ⟨91BMC69⟩.



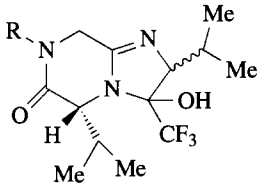
(163)



(164)



(165), PG=tBOC or CBZ



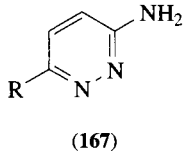
(166)

8.12.9.3 Imidazo[1,2-*b*]pyridazine (65)

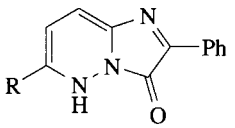
The known preparative methods for the synthesis of imidazo[1,2-*b*]pyridazines prior to 1983 have been extensively reviewed ⟨84CHEC-I(5)607⟩. This section will review new methods of syntheses published since 1983. The most common synthesis of this ring system is closure of the imidazole ring via the Tschitschibabin cyclization between a 3-aminopyridazine and an α-halocarbonyl compound.

8.12.9.3.1 Closure of the imidazole ring

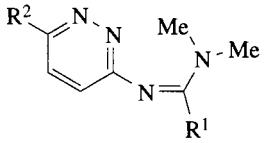
In a newer variation of the standard synthesis, treatment of (**167**) with ethanolic phenylglyoxal gave (**168**) in 62% yield ⟨83AJC1215⟩. Treatment of the heteroarylacetamidines (**169**) with α-haloketones gave (**170**) in low yield ⟨84S263⟩.



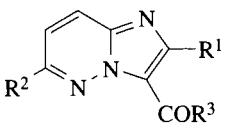
(167)



(168)



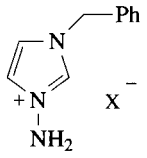
(169)



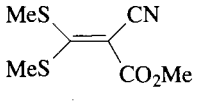
(170)

8.12.9.3.2 Closure of the pyrazine ring

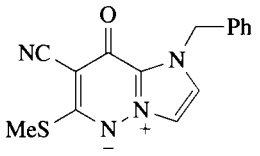
Treatment of the salt (**171**) with the ketene dithioacetal (**172**) and potassium carbonate in DMSO gave the mesomeric betaine (**173**) via the corresponding *N*-allylide, ⟨90H(31)977⟩.



(171)



(172)

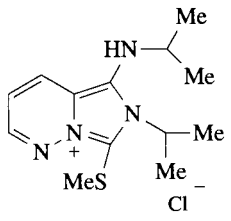


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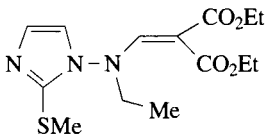
8.12.9.4 Imidazo[1,5-*b*]pyridazine (66)

This is one of the least studied imidazodiazine ring systems. Prior to 1983, there were only two previous reports on this ring system ⟨84CHEC-I(5)607⟩.

A mixture of the iminochlorosulfide (**145**), pyridazine and an isocyanide (R—NC) undergoes a three-component cyclocondensation to give the salt (**174**) ⟨93TL2319⟩. Cyclization of (**175**) in PPA gave (**125**) in 10% yield ⟨94JHC409⟩.



(174)



(175)

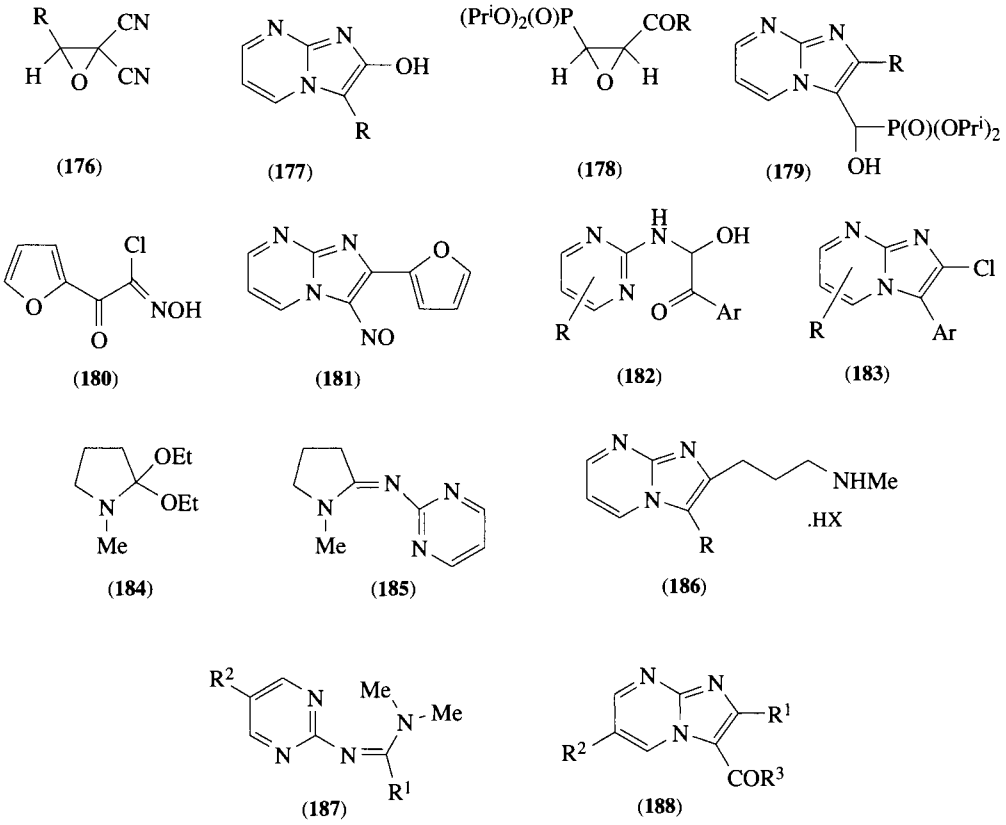
8.12.9.5 Imidazo[1,2-*a*]pyrimidine (67)

The known preparative methods for the synthesis of imidazo[1,2-*a*]pyrimidines prior to 1983 have been reviewed extensively ⟨84CHEC-I(5)607⟩. By far the most common synthetic method for the preparation of this system involves closure of the imidazole ring by the condensation of 2-aminopyrimidine with an α-halocarbonyl compound and closure of the pyrimidine ring by the condensation of a 2-aminoimidazole (or imidazoline) with a β-dicarbonyl compound. New methods of syntheses will be considered in this section.

8.12.9.5.1 Closure of the imidazole ring

The epoxide (**176**) reacts with 2-aminopyrimidine in acetonitrile containing HBr to yield an initial enaminoimidazole. The two carbons of the epoxide then act as electrophilic centers allowing cyclization to (**177**) in 54% yield ⟨86T1169⟩. Condensation of epoxide (**178**) with 2-aminopyrimidine gave the phosphonate (**179**) ⟨85CB4099⟩. Condensation of the furoylhydroximoyl chloride (**180**) with 2-aminopyrimidine in ethanol gave (**181**) ⟨84JHC1029, 88AP(321)913, 92MI 812-01⟩. Intramolecular condensation of (**182**) in the presence of thionyl chloride in carbon tetrachloride gave (**183**) in a

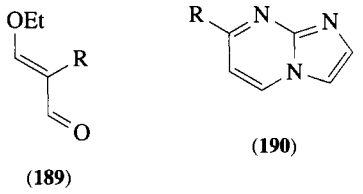
totally regioselective one-pot procedure ⟨90S485⟩. Reaction of 2-aminopyrimidine with lactam acetal (**184**) gave the 2-pyrrolidine imine (**185**) which was then treated with CH—acidic methyl halides to yield (**186**) via a ring-chain transformation of the resulting *N*-alkylation product ⟨93S521⟩. The heteroarylacetamidines (**187**) reacted with α-haloketones to give (**188**) in low yield ⟨84S263⟩.



(176) (177) (178) (179) (180) (181) (182) (183) (184) (185) (186) (187) (188)

8.12.9.5.2 Closure of the pyrimidine ring

Reaction of 3-alkoxyacroleins (**189**) with 2-aminoimidazole gave (**190**) in 60–68% yields ⟨83S161⟩.



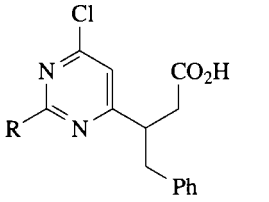
(189) (190)

8.12.9.6 Imidazo[1,2-*c*]pyrimidine (68)

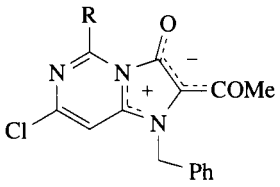
The known preparative methods for the synthesis of imidazo[1,2-*c*]pyrimidines prior to 1983 have been extensively reviewed ⟨84CHEC-I(5)607⟩. A number of miscellaneous chemical syntheses were reported between 1983 and 1991, but they possessed little generality and have been reviewed recently ⟨91MI 812-01⟩. This section will review new methods of synthesis published since 1991.

The most common synthesis of this ring system is the condensation of a 4-aminopyrimidine with an α-halocarbonyl compound or treatment of a 4-halopyrimidine with 2-chloroethylamine, to yield a 4-(2-chloroethyl)amino derivative which can be easily cyclized. Since the mid-1980s, there have

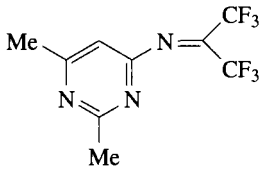
only been two new syntheses reported which are worthy of note. Cyclodehydration of (**191**) with acetic anhydride and triethylamine at 50°C gave the mesoionic compound (**192**) in high yields. The use of a more reactive anhydride (e.g., TFAA) allowed cyclizations to occur at lower temperatures and in higher yields ⟨94JOC2473⟩. Reaction of the hetero-1,3-diene (**193**) with tin(II) chloride gave (**194**) in low yield ⟨88S199⟩.



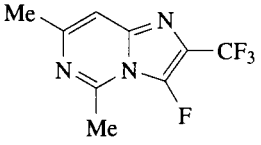
(**191**)



(**192**)



(**193**)



(**194**)

8.12.9.7 Imidazo[1,5-*a*]pyrimidine (69)

The known preparative methods for the synthesis of imidazo[1,5-*a*]pyrimidines prior to 1983 have been reviewed ⟨84CHEC-I(5)607⟩. This ring system has been sparsely reported in the literature, most syntheses reported involve annulation of a 4-aminoimidazole with a three-carbon unit. Some more recent methods are described below.

8.12.9.7.1 Closure of the pyrazine ring

Some variations on the classical synthesis have involved condensation of ethyl benzoylacetate with (**195**) to give the inner salt (**110**) ⟨90JHC531⟩ and the condensation of the *o*-aminocarboxamide (**196**) with a β-diketone to give (**197**), whose structure was confirmed by x-ray crystallography ⟨92H(34)1133⟩. Cycloaddition of DMAD, in refluxing acetonitrile, with (**198**) gave two products, (**199**) and (**200**) ⟨83JOC3⟩. Intramolecular base-catalyzed cyclization of (**201**) gave (**202**) in 57% yield ⟨87JHC1155⟩. Acid-catalyzed cyclization of (**203**) gave a mixture of two products which were separated by pH-controlled selective precipitation and identified as (**204**) and the betaine (**100**) ⟨92JCS(P1)2789⟩.

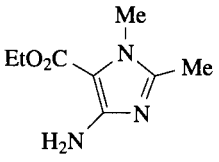
8.12.9.7.2 Closure of the imidazole ring

Treatment of the pyrimidone (**205**) with PPA at 100–110°C gave (**113**) in 58% yield ⟨83CPB2288⟩. Similar cyclizations have been shown to occur using $POCl_3$ ⟨83CPB2540⟩.

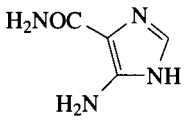
In a rare example of the simultaneous formation of both rings, treatment of (**206**) with propylenediamine gave (**207**) in 42% yield ⟨94JPC29⟩.

8.12.9.8 Imidazo[1,5-*c*]pyrimidine (70)

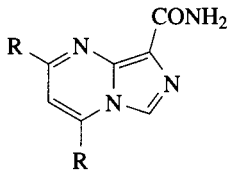
The known preparative methods for the synthesis of imidazo[1,5-*c*]pyrimidines prior to 1983 have been reviewed ⟨84CHEC-I(5)607⟩ and it is evident that closure of the pyrimidine ring onto a suitably substituted histidine derivative is the major synthetic route to these rare systems.



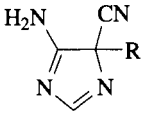
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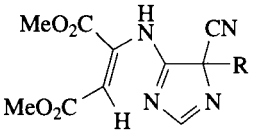
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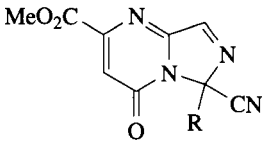
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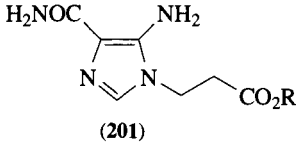
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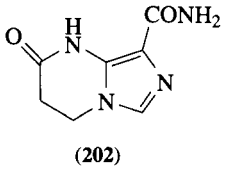
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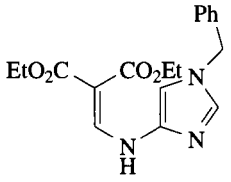
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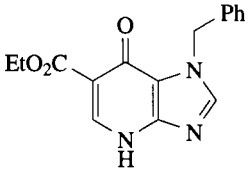
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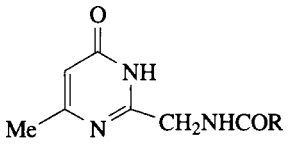
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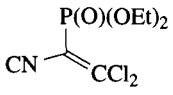
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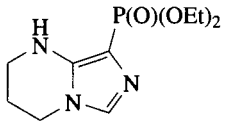
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(205)

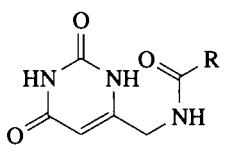


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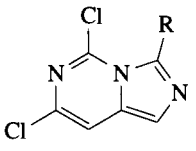


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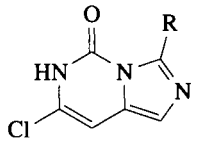
The cyclodehydration of amides (**208**), derived from 6-aminomethyluracil, using $POCl_3$ has been shown to give a readily separable mixture of (**209**) and (**210**) ⟨86JHC981⟩. *N*-Protected histidine azides (**211**) reacted at room temperature, via a Curtius rearrangement, to give the corresponding isocyanate, which then underwent an intramolecular cyclization to give (**212**) ⟨90JMC1688, 93JCR(S)118⟩.



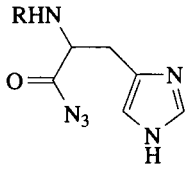
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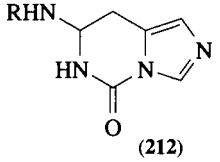
(209)



(210)



(211)



(212)

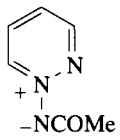
8.12.9.9 Pyrazolo[1,5-*a*]pyrazine (71)

This is one of the least studied systems. Previous reviews on the pyarazolodiazines ⟨84CHEC-I(5)305⟩ contained no material on this system and a review of the literature since 1983 revealed no new material.

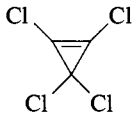
8.12.9.10 Pyrazolo[1,5-*b*]pyridazine (72)

This is also one of the least studied pyrazolodiazine ring systems. Prior to 1983, there was only one previous report on this ring system, which was synthesized by reaction of *N*-iminopyridazine with DMAD or ethyl propiolate ⟨84CHEC-I(5)607⟩.

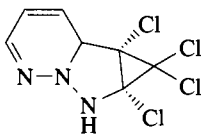
Pyridazinium *N*-ylide (**213**) underwent 1,3-dipolar cycloaddition with the perhalocyclopropene (**214**) to give the cycloadduct (**215**) which was thermolysed in refluxing xylene to give (**128**) ⟨86CPB1023⟩. Flash vacuum pyrolysis, at temperatures between 450 °C and 700 °C, of the *N*-pyrazolyl derivative (**216**) gave a mixture of two products (**217**) and (**218**). The relative proportions of these two products were shown to be temperature dependent. The major product at higher temperature was shown to be (**217**), whereas at lower temperatures (**218**) predominated ⟨93CC840⟩.



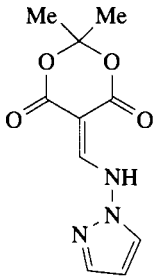
(**213**)



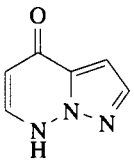
(**214**)



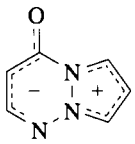
(**215**)



(**216**)



(**217**)

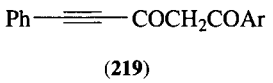


(**218**)

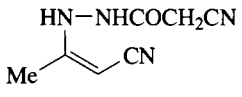
8.12.9.11 Pyrazolo[1,5-*c*]pyrimidine (73)

The pyrazolopyrimidines (**73**) and (**74**) have been reviewed extensively in terms of synthetic methods and chemical and physical properties; ⟨84CHEC-I(5)305⟩ covers literature up to 1982, ⟨87AHC(41)319⟩ covers literature up to 1987. Of these systems, pyrazolo[1,5-*c*]pyrimidine (**73**) is the less studied. There is no general synthetic route to these systems which offers versatility.

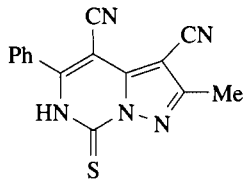
Condensation of the 1,3-dione (**219**) with thiosemicarbazide in refluxing ethanol gave (**115**), this being one of the few synthetic routes which provides aryl substituted analogues ⟨92BCJ3419⟩. Thione (**221**) was obtained when (**220**) was allowed to react with benzoyl isothiocyanate ⟨93JCR(S)352⟩. Amidrazone (**222**) condenses with 1,3-dicarbonyl compounds to yield (**223**) by addition, oxidation, and condensation ⟨94JHC1157⟩.



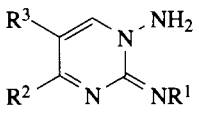
(**219**)



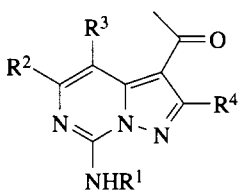
(**220**)



(**221**)



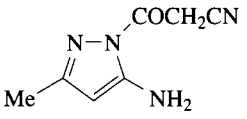
(**222**)



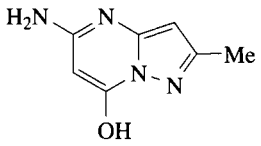
(**223**)

8.12.9.12 Pyrazolo[1,5-*a*]pyrimidine (74)

The pyrazolopyrimidines (**74**) have been reviewed extensively in terms of synthetic methods and chemical and physical properties; ⟨84CHEC-I(5)305⟩ covers literature up to 1982, ⟨87AHC(41)319⟩ covers literature up to 1987). The cyclocondensation of 1,3-dicarbonyl compounds with 1-unsubstituted 3(5)-aminopyrazoles is the most general approach for the synthesis of this system. Other 1,3-bifunctional reagents, such as malondialdehyde tetramethylacetal, 3-oxoalkanonitriles and 3-ketiminonitriles, have also been used in this condensation. Another popular route to this system is the condensation of 3(5)-aminopyrazoles with acrylic acid derivatives. The only new synthesis appearing since 1987 was the following: compound (**224**) was readily cyclized to (**225**) when refluxed in acetic acid ⟨93JCR(S)352⟩.



(**224**)



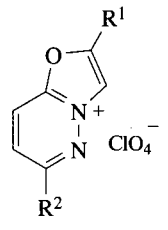
(**225**)

8.12.10 RING SYNTHESES BY TRANSFORMATION OF ANOTHER RING

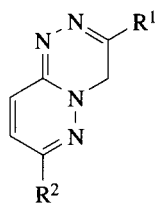
Unless discussed below, there have been no new syntheses of these systems by transformation of other heterocycles.

8.12.10.1 Imidazo[1,2-*b*]pyridazine (65)

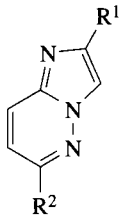
Treatment of the salt (**226**) with hydrazine hydrate in acetonitrile at room temperature, gave (**227**) and (**228**). Isolation of (**227**) and treatment with excess hydrazine hydrate gave (**228**) ⟨82CPB1557⟩. Treatment of the monooxime (**229**) with acetic anhydride gave (**230**) ⟨83CPB3811⟩. Intramolecular ring transformation of the γ-keto-oxazole (**231**) with hydrazine gave (**232**). Reaction is thought to occur via initial hydrazone formation and cyclization to a spiro derivative which collapses to a ketone and then cyclizes to the product (**232**) ⟨83JCS(P1)3027⟩.



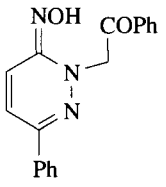
(**226**)



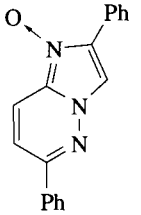
(**227**)



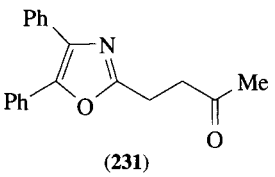
(**228**)



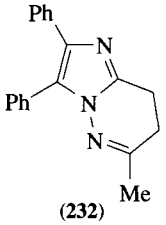
(**229**)



(**230**)



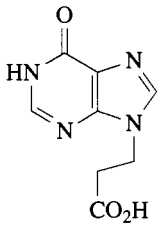
(**231**)



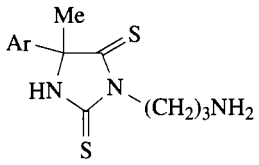
(**232**)

8.12.10.2 Imidazo[1,5-*a*]pyrimidine (69)

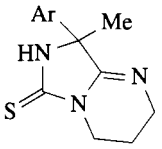
Reaction of (**233**), or its 6-mercapto analogue, with a water soluble carbodiimide resulted in an intramolecular acylation at N-3 followed by a spontaneous hydroxylation at C-2 and opening of the pyrimidine ring to give (**137**) in 67% yield ⟨85H(23)2669⟩. Treatment of (**234**) in refluxing ethanol gave (**235**) ⟨90JCS(P1)3003⟩.



(233)



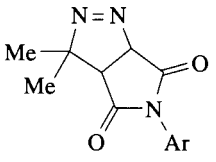
(234)



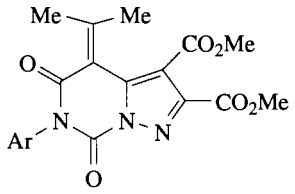
(235)

8.12.10.3 Pyrazolo[1,5-*c*]pyrimidine (73)

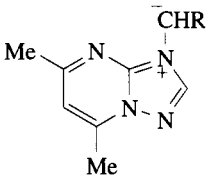
Addition of DMAD to the pyrrolo[3,4-*c*]pyrazole (**236**) gave (**237**) in quantitative yield. This reaction proceeded via a vinyldiazo intermediate ⟨89JOC5912⟩. Double cycloaddition of the *N*-ylide (**238**) with activated acetylenes gave (**239**) in 26% yield ⟨87JCS(P1)2531⟩.



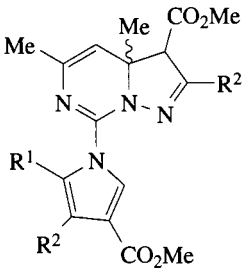
(236)



(237)



(238)



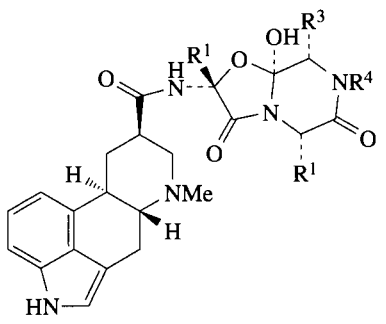
(239)

8.12.11 IMPORTANT COMPOUNDS AND APPLICATIONS

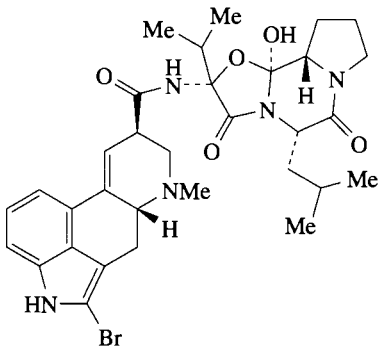
Of all the ring systems containing a bridgehead nitrogen atom and two extra heteroatoms, compounds in this chapter are by far the most biologically active. The many references to new synthetic methods and chemical reactivities are due mainly to the diverse array of biological activities found within these systems. Some of the more important biological active series will now be discussed.

One of the most important biological analogues of the thiazolo[3,2-*a*]pyrimidine (**42**) ring system is ritanserin (**75**). This compound has stimulated a lot of interest because it is an atypical anti-psychotic agent with reduced EPS liability. It is a potent 5-HT_2 antagonist and has moderately high potencies at $alpha_1$ and $alpha_2$ adrenergic binding sites, which may contribute to its atypical profile ⟨B-86MI 812-01⟩. The ergopeptide alkaloid (**240**) contains the oxazolo[3,2-*a*]pyrazine ring system (**19**) and has been shown to be efficacious in the treatment of cerebral insufficiency ⟨81USP4251529⟩. The closely related bromocriptine (**241**) has been shown to be useful in the treatment of Parkinsonism ⟨83MI 812-01⟩.

By far the greatest amount of biological activity has been found to associate with the imidazodiazines (**63**)–(**70**) and to a lesser extent, the pyrazolodiazines (**71**)–(**74**). In an extensive series of papers, analogues of the imidazo[1,2-*b*]pyridazine (**65**) have been shown to compete effectively with diazepam for benzodiazepine receptors in rat brain synaptic plasma membranes. One of these compounds, (**242**), has been shown to possess anxiolytic activity *in vivo* ⟨94AJC609⟩ and references cited herein). Other analogues, possessing this biologically active ring system, have been shown to have analgesic and anti-inflammatory activity ⟨92MI 812-02⟩, antibacterial activity against both Gram

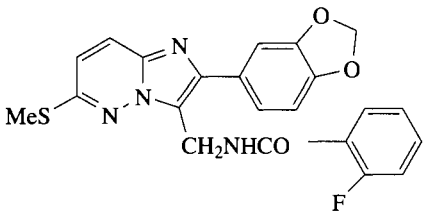


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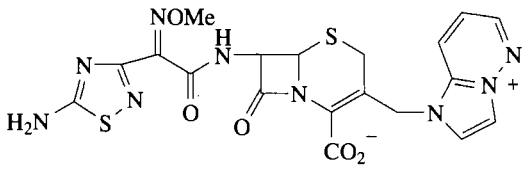


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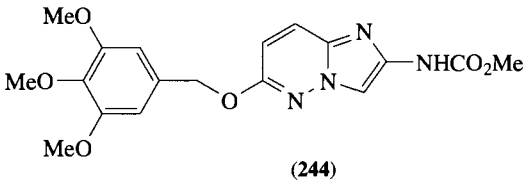
positive and negative bacteria (e.g., (**243**, cefozopran)) ⟨92JAN709, 93MI 812-03⟩, antitumor activity via disruption of the microtubules (e.g., (**244**, ⟨92BMC1257⟩, and potent AT_1 selective AII antagonistic activity, effective in the treatment of hypertension ⟨94BMC219⟩. Analogues of (**64**) have been shown to possess affinity for *in vitro* α-adrenergic receptor subtypes ⟨83JMC357⟩, antibronchospastic activity with more potency than theophylline and no CNS stimulation ⟨92JMC3353⟩, gastric antisecretory and cytoprotective activity (**245**) ⟨87JMC2047⟩, antiinflammatory activity ⟨93EJM337, 93JHC1213⟩, and hypoglycemic activity ⟨92JMC3845⟩. The chromophore (**246**, coelenterazine) from the photogenic organs of various marine bioluminescent organisms has been shown to contain the imidazo[1,2-*a*]pyrazine (**64**) ring system ⟨90BCJ3132, 92TL5771⟩. Analogues of (**68**) have been shown to possess antinflammatory, analgesic, and antipyretic activities comparable to indomethacin ⟨91MI 812-03⟩. Derivatives containing the imidazo[1,2-*a*]pyrimidine ring system (**67**) have been shown to possess antiinflammatory, analgesic and antipyretic activities ⟨87FES657⟩, bronchodilator activity comparable to theophylline ⟨87EJM457⟩, and antifungal activity better than amphotericin B ⟨91EJM13⟩. Analogues of (**66**) have been shown to be inhibitors of HIV-1 reverse transcriptase ⟨93JMC3784⟩. The pyrazolo[1,5-*b*]pyridazine ring system (**72**) has been used as an indole bioisostere in the design and synthesis of potent and selective 5-HT_3 antagonists for the treatment of emesis, anxiety, schizophrenia, and memory disorders ⟨94BMC695⟩.



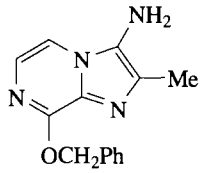
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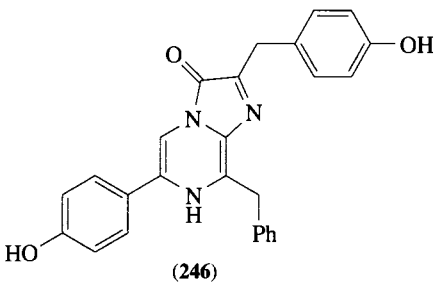
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(244)



(245)



(246)

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8.13
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 2 : 0

DRAGO ROBERT SLISKOVIC
Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA

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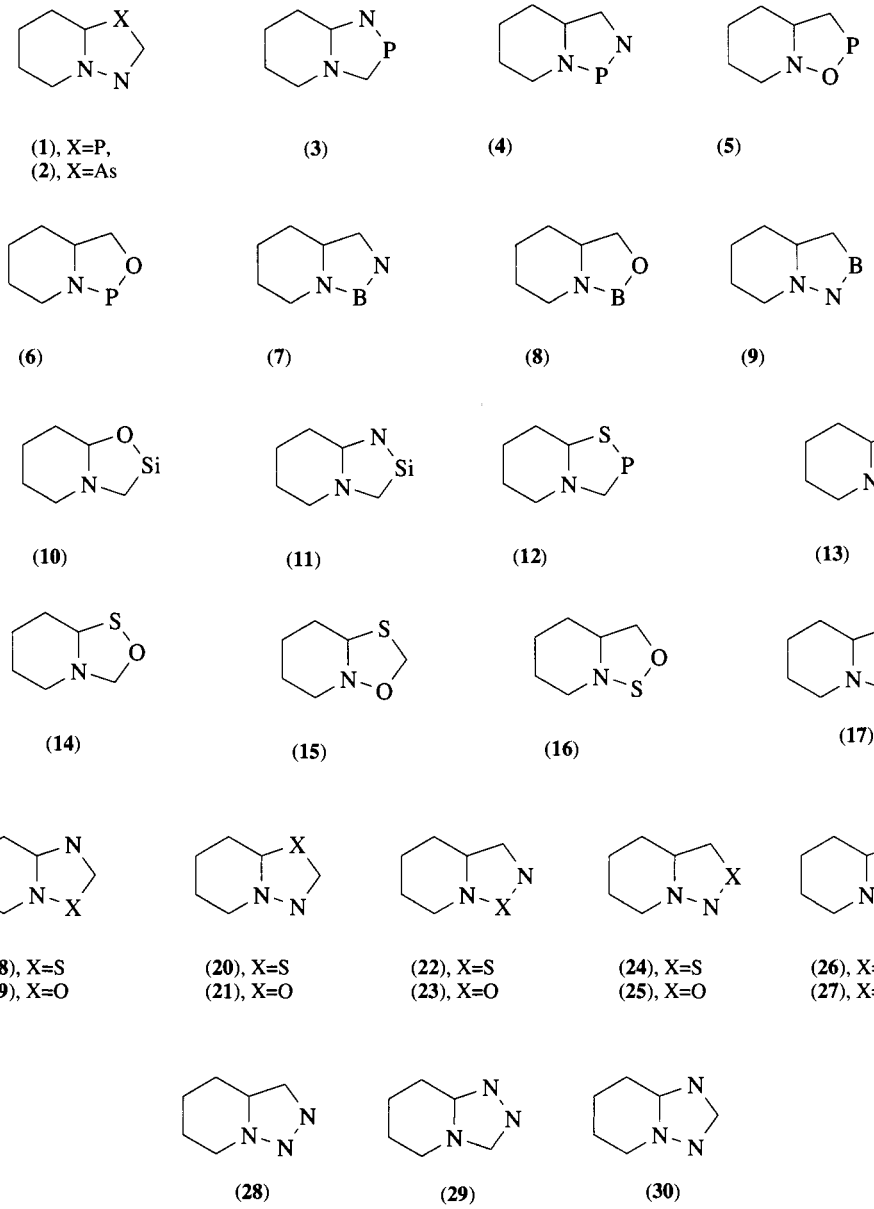
8.13.1 INTRODUCTION

This chapter reviews those systems composed of a bicyclic system containing fused 5- and 6-membered rings with one ring junction nitrogen atom and two extra heteroatoms in the five-membered ring. The heteroatoms are primarily nitrogen, oxygen, and sulfur; a limited number of boron, silicon, phosphorous, and arsenic containing systems have been described. The total number of different ring systems falling within the scope of this definition, which have been reported in the literature, is 30, so clearly a comprehensive treatment of each system is impossible within the confines of this chapter. The amount of literature for each of these ring systems varies greatly. The exotic ring systems (**1**)–(**16**) are represented by a single reference, while more literature exists for systems (**17**)–(**27**) mainly due to the potential of these systems to form mesoionic compounds (i.e., those systems containing "a five-membered heterocycle which cannot be represented satisfactorily by any one covalent or ionic structure and possesses a sextet of electrons in association with the five atoms comprising the ring" ⟨82T2965⟩. The triazolopyridines (**28**)–(**30**) have attracted the most attention in the literature because this series of compounds are the only representatives in this section which can form electronically neutral, fully delocalized 10 π-electron systems. In addition to this, the approval, by a number of regulatory agencies around the world, of trazodone hydrochloride (Desyrel in the USA), a 1,2,4-triazolo [4,3-*a*] pyridin3(2*H*)-one, for the treatment of depression has stimulated interest in the triazolopyridines in general (see Section 8.13.11).

Based on an analysis of those ring systems attracting the greatest attention in the literature, this chapter focuses on the triazolopyridines (**28**)–(**30**) and related benzo derivatives, as well as those ring systems capable of forming mesoionic compounds (**17**)–(**27**). The other known systems (**1**)–(**16**), which fall within the scope of this chapter, are noted and all of the limited number of references are provided with pertinent comment when necessary. These systems include [1,2,4]diazaphospholo[1,5-*a*]pyridine (**1**) ⟨87TL1511⟩, [1,2,4]diazaarsolo[1,5-*a*]pyridine (**2**) ⟨87TL1511⟩, [1,4,2]diazaphospholo[4,5-*a*]pyridine (**3**) ⟨91MRC1045⟩ (NMR studies), ⟨86PS(44)289, 91HAC369, 92ZN(B)373⟩, [1,3,2]diazaphospholo[4,5-*a*]pyridine (**4**) ⟨63MI 813-01⟩, [1,2,5]oxazaphospholo[2,3-*a*]pyridine (**5**) ⟨67AG(E)457⟩, [1,3,2]oxazaphospholo[3,4-*a*]pyridine (**6**) ⟨63MI 813-01⟩, [1,3,2]diazaborolo[1,5-*a*]pyridine (**7**) ⟨93TA2335⟩, [1,3,2]oxazaborolo[3,4-*a*]pyridine (**8**) ⟨78JOM(154)C3, 85JOM(294)1⟩, [1,2,3]diazaborolo[4,5-*a*]pyridine (**9**) ⟨81CB3801⟩, [1,4,2]oxazasilolo[4,5-*a*]pyridine (**10**) ⟨86IZV2156⟩ (x-ray studies), [1,4,2]diazasilolo[4,5-*a*]pyridine (**11**) ⟨90JOM(382)345⟩ (synthesis and x-ray studies), [1,4,2] thiazaphospholo[4,5-*a*]pyridine (**12**) ⟨89PS(44)249⟩, [1,2,4]dithiazolo[4,3-*a*]pyridine (**13**) ⟨74AP(307)828, 80CB3010⟩, [1,2,4]oxathiazolo [4,3-*a*]pyridine (**14**) ⟨92JCS(P1)621⟩ (synthesis and x-ray studies), [1,4,2]oxathiazolo[2,3-*a*]pyridine (**15**) ⟨69CB926, 83CC939⟩, [1,2,3]oxathiazolo[3,4-*a*]pyridine (**16**) ⟨72CPB1768, 72CPB2269⟩.

Ring systems (**1**)–(**16**) have received little attention in the review literature. Systems (**17**)–(**27**) have been covered partially in various reviews on mesoionic heterocycles (e.g., ⟨82T2965⟩). The triazolopyridines (**28**)–(**30**), and related benzo analogs, have been the subject of a number of reviews. One review covers literature up to 1961 ⟨61CHE749⟩, the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(5)847⟩ covers literature up to 1982, a fully comprehensive review on systems (**28**)–(**30**) up to 1981 ⟨83AHC(34)80⟩.

Thus, the remainder of this review will concentrate on systems (**17**)–(**27**) where the majority of



(1), X=P,
(2), X=As

(3)

(4)

(5)

(6)

(7)

(8)

(9)

(10)

(11)

(12)

(13)

(14)

(15)

(16)

(17)

(18), X=S
(19), X=O

(20), X=S
(21), X=O

(22), X=S
(23), X=O

(24), X=S
(25), X=O

(26), X=S
(27), X=O

(28)

(29)

(30)

the literature deals primarily with new synthetic methods, and there is little literature on the physical and chemical properties of these systems. The literature on systems (**28**)–(**30**) is extensive and thus in the interest of saving space, this review will concentrate on the most recent literature (after 1982).

8.13.2 THEORETICAL METHODS

Calculations of electron density and bond orders for compounds (**28**)–(**30**) have been performed using the SCF–LCAO–MO method, and this data has been reported ⟨83AHC(34)80⟩. Studies after this have been directed at determining the sites of alkylation of (**28**) using semiempirical and *ab initio* calculations. The underlying assumption was that SN_2 attack on the halide was related to the electron density at the nitrogen atoms, the most appropriate measure of nucleophilicity would be the electron density in the HOMO which is of σ-symmetry. *Ab initio* calculations were in accord with the semi-empirical calculations and confirm alkylation at N-2. For systems (**29**) and (**30**), both methods of calculation confirm alkylation at N-3 ⟨93T4307⟩. There is little data on theoretical chemistry associated with systems (**17**)–(**27**).

8.13.3 EXPERIMENTAL STRUCTURAL METHODS

8.13.3.1 NMR Studies

The ^{1}H, ^{13}C, ^{14}N, ^{15}N, and ^{19}F NMR spectral data has been thoroughly reviewed ⟨83AHC(34)80⟩ for systems (**28**)–(**30**) and only more studies since 1983 will be presented here. The ^{13}C shifts for (**28**) and some monodeuterated derivatives have been reported ⟨84OMR(22)192⟩. Proton NMR studies have also determined the sites of quaternization of (**28**). Using DIFNOE NMR, irradiation of the quaternary α-proton signal or that at C-3 confirmed that protonation occurred at N-2 ⟨89T7041, 90JCR(S)9⟩.

There have been no systematic NMR studies of systems (**17**)–(**27**). Isolated collections of chemical shift data do exist, but do not warrant special mention here. The existence of these scant details highlights the need for comprehensive collations of data for these systems.

8.13.3.2 Mass Spectrometry Studies

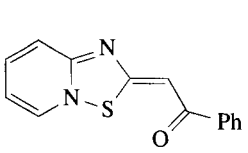
The use of mass spectrometry in these series of compounds has been mainly confined to molecular ion determination and structure determination and has been thoroughly reviewed ⟨83AHC(34)80⟩. [1,2,4]Triazolo[4,3-*a*]pyridine (**29**) has been used for the location of branched and double bonds containing fatty acids. The mass spectra of these derivatives provide a superior structure specific fragmentation pattern ⟨88OMS(23)566⟩.

8.13.3.3 Electronic, IR, and Photoelectron Spectroscopy

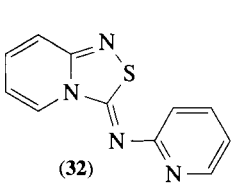
These have been thoroughly reviewed for systems (**28**)–(**30**) ⟨83AHC(34)80⟩. There has been no systematic study for systems (**17**)–(**27**).

8.13.3.4 X-ray Studies

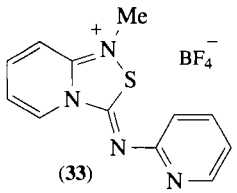
X-ray crystallography has essentially only been used as a method of structure determination/confirmation, and the results are unexceptional. For (**31**), the molecule was shown to be almost planar with an adopted position in which the oxygen and sulfur are brought within 2–2.07 Å of each other forming a potential O,S donor set ⟨88JCS(D)433⟩. In the methylation of (**32**) to yield (**33**), x-ray diffraction showed both molecules to be quasi planar and to exhibit a linear N(2)—S(1)—N(8) arrangement. In structure (**32**), the separation between the sulfur and pyridine nitrogen atom (2.61 Å) is larger than the Huggins constant energy distance (2.58 Å), suggesting little or no bonding ⟨92JHC1765⟩. For compound (**34**), the bond lengths in the two rings are shorter than sp^3–sp^3 bonds and longer than sp^2–sp^2 double bonds. The two fused rings are coplanar as shown by the torsion angles and this is in agreement with delocalization of the π-electrons. In the six-membered ring the distances and angles are consistent with those found in pyridine rings. The ethoxycarbonyl group is coplanar with the annular system ⟨83AX(C)391⟩.



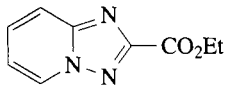
(**31**)



(**32**)



(**33**)



(**34**)

8.13.3.5 Magnetic Circular Dichroism Studies

The determination of the position of protonation in heterocycles with several basic sites by MCD spectroscopy is based on the notion that protonation increases the electronegativity of the aza nitrogen and therefore has a predictable effect on the ΔHOMO–ΔLUMO and thus on the MCD

spectrum. The MCD spectra of 14 azaindolizines (including (**28**) and (**30**)) in the neutral and protonated forms have been determined. The protonation pattern for (**28**) and (**30**) was found to be inconclusive with protonation possibly occurring at N-2 or N-3 ⟨85JOC302⟩.

8.13.4 THERMODYNAMIC ASPECTS

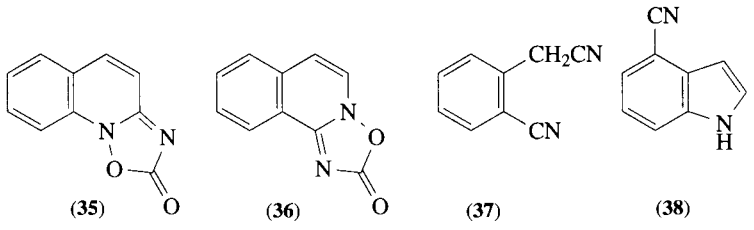
From the point of view of systems (**17**)–(**30**), these aspects have been very much neglected. Most references contain some boiling and melting points but there has been no consideration of these values from the point of view of intermolecular forces between molecules. The question of aromaticity in the mesoionic systems has been poorly studied. A number of dissociation constants for systems (**28**)–(**30**) have been reported ⟨65JCS2778⟩.

8.13.5 REACTIVITY OF FULLY CONJUGATED RINGS

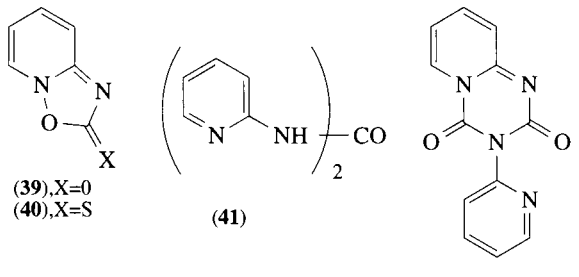
The triazolopyridines (**28**)–(**30**) are the only representatives in this section which can form electronically neutral fully delocalized 10 π-electron systems. The chemistry of the fully conjugated systems can best be understood by assuming that the system consists of a five-membered π-excessive heterocyclic ring that is fused to a six-membered π-deficient ring. Thus, electrophilic reagents are expected to attack the triazole carbons and nucleophilic reagents are expected to attack the six-membered ring. In general, the reactivity of the fully conjugated systems is similar to that found for indolizine and the reactivity of these ring systems, and their benzo derivatives, have been thoroughly reviewed prior to 1983 ⟨61CHE749, 83AHC(34)80, 84CHEC-I(5)847⟩. Thus, only developments since 1983 will be highlighted. Both the thiadiazolopyridines ((**17**), (**18**), (**20**), (**22**), (**24**), (**26**)) and oxadiazolopyridines ((**19**), (**21**), (**23**), (**25**), (**27**)) are capable of forming mesoionic compounds, so reactions of compounds of this type will be covered in this section. There have been no systematic studies on the reactivity of systems (**1**)–(**27**), and as a consequence the literature is sparse.

8.13.5.1 Thermal and Photochemical Reactions

Pyrolysis of both (**35**) and (**36**) at 600°C/0.1 mm over silica packing gave similar mixtures of (**37**) and (**38**), suggesting a common nitrene intermediate ⟨69JCS(C)795⟩. Subsequent studies using the same conditions showed that pyrolysis of (**39**) led to the elimination of carbon dioxide and the formation of 2-pyridylnitrene as an intermediate, which isomerized to form mixtures of cyanopyrroles and 1,3-dicyanopropene ⟨72AJC607⟩. In a similar fashion, pyrolysis of (**40**) at 140°C gave a mixture of (**41**), (**42**), and elemental sulfur, suggesting the intermediacy of 2-pyridylisocyanate ⟨80CPB3570⟩.



(**35**) (**36**) (**37**) (**38**)

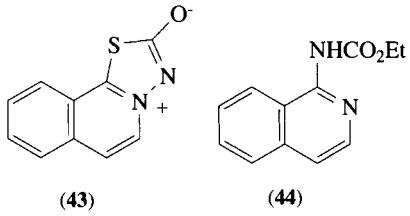


(**39**),X=O
(**40**),X=S

(**41**)

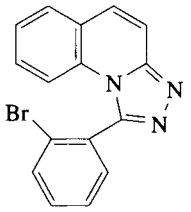
(**42**)

Photo induced 1,3 bridging in the mesoionic five-membered ring of (**43**) and subsequent addition of ethanol gave (**44**) ⟨79JCS(S)377, 80ACH259⟩. Since 1983, the only novel photochemical reaction involving the triazolopyridines is the photocyclization of (**45**) in acetonitrile to yield (**46**) ⟨89SC2345⟩.

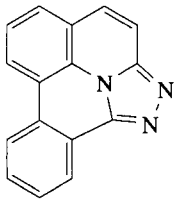


(**43**)

(**44**)



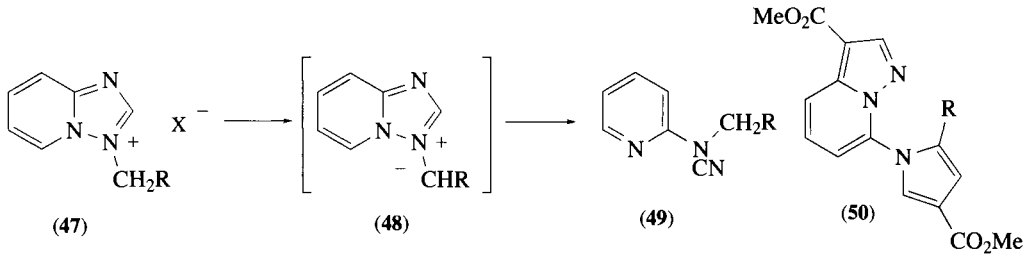
(**45**)



(**46**)

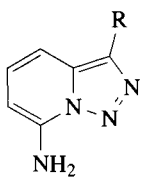
8.13.5.2 Electrophilic Attack at Nitrogen (and/or Carbon)

There has been little systematic study on the attack of electrophiles at the ring carbons or nitrogens of systems (**17**)–(**27**). Previous reviews ⟨83AHC(34)80, 84CHEC-I(5)847⟩ have covered this topic up to 1983 for systems (**28**)–(**30**). Reports covering this topic include the following: the site of quaternization of the [1,2,3]triazolo[1,5-*a*]pyridines (**28**) as N-2 was determined by NMR studies (see Section 8.13.3.1) ⟨89T7041⟩. Treatment of [1,2,4]triazolo[1,5-*a*]pyridine (**30**) with alkylating agents in acetone gave the salts (**47**), which when treated with base (TEA) gave the unstable ylides (**48**) which gave (**49**) on prolonged heating. These ylides (**48**) also underwent a cycloaddition reaction with two moles of methyl propiolate to yield (**50**) via a nonisolated tetracyclic intermediate ⟨86H(24)2563⟩.

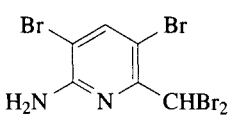


(**47**) (**48**) (**49**) (**50**)

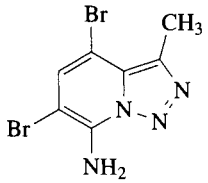
The directed lithiation of (**28**) and the subsequent reaction of the 7-lithio species with electrophiles has been the subject of a number of reports ⟨83AHC(34)80⟩. These observations have been extended to the [1,2,3]triazolo[1,5-*a*]quinoline ring system ⟨84JCR(S)140⟩ and (**30**) ⟨92JOC5538⟩. It has also been reported that the 7-lithio species derived from (**28**) reacts with the electrophilic nitrogen reagent, styryl azide, to give the 7-amino derivative in low yield. Bromination of (**51**) or (**52**) gives the brominated pyridine (**53**) or the triazolopyridine (**54**), this is a rare instance of electrophilic attack occurring in the pyridine ring ⟨89T7041⟩. In addition to these studies, it has been reported that (**28**) reacts with electrophiles in two distinct ways, either by substitution at the 3-position or triazole ring opening to yield a variety of substituted pyridine derivatives ⟨83AHC(34)80, 85JCS(P1)2719⟩. The ring opening reactions are interesting in that they appear to depend on the equilibrium between the triazolopyridine and the pyridyldiazoalkane. These hydrolytic ring opening reactions have now been extended to the [1,2,3]triazolo[5,1-*a*]isoquinoline ring system providing a new synthesis of 1,3-disubstituted isoquinolines ⟨85JCS(P1)1897⟩.



(**51**), R=H
(**52**), R=CH_3



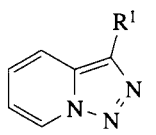
(**53**)



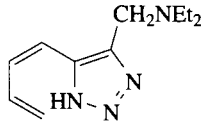
(**54**)

8.13.5.3 Nucleophilic Attack at Carbon

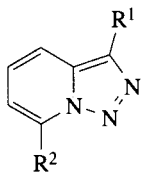
Direct nucleophilic substitutions on these systems have not been reported. The most common reaction with nucleophiles is the nucleophilic replacement of halogen (in the six-membered ring) ⟨83AHC(34)80⟩. However, there has been one report of direct nucleophilic attack. During the reduction of the amide (**55**) with LAH in THF, the triazole (**57**) was produced as well as the desired product (**56**) ⟨85JCS(P1)2719⟩. The bromo compounds (**58**) reacts with a variety of nucleophiles (OMe, SPh, $NHNH_2$, piperidine) to produce (**59**) which can be ring opened to yield a variety of 2,6-disubstituted pyridines. Similar synthetic transformations can be performed on the corresponding bromotriazoloisoquinolines ⟨86TL3543, 87JCS(P1)1865, 88T3005⟩.



(**55**), R^1=CONEt2
(**56**), R^1=CH_2NEt_2



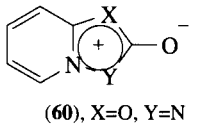
(**57**)



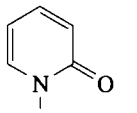
R^1=H, Me, $CONEt_2$

(**58**), R^2=Br
(**59**), R^2=nucleophile

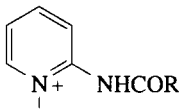
Mesoionic compounds, derived from systems (**17**)–(**27**), are attacked by various nucleophiles which usually result in ring opening. Thus, treatment of (**60**) or (**61**) with an alcohol yields (**62**) or (**63**), respectively, whereas treatment with an amine gives (**64**) or (**65**), respectively ⟨56JCS2063, 57JCS4385, 58HCA548, 76CB723⟩. Basic hydrolysis of (**66**) yields (**67**) ⟨74OPP243⟩, in contrast, hydrolysis of (**68**) yields (**69**) ⟨75CJC1973⟩.



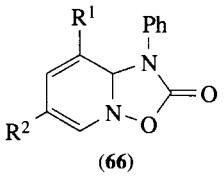
(**60**), X=O, Y=N
(**61**), X=N, Y=O



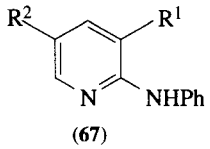
(**62**), R=Et
(**64**), R=NH_2



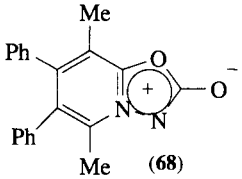
(**63**), R=Et
(**65**), R=NH_2



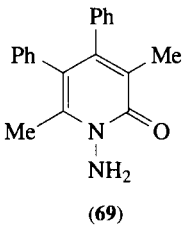
(**66**)



(**67**)



(**68**)



(**69**)

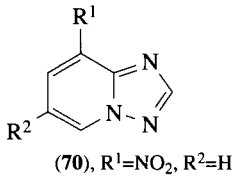
8.13.5.4 Reactions at Surfaces

The literature on this subject is sparse and what is available has been covered in reviews ⟨83AHC(34)80, 84CHEC-I(5)847⟩. Hydrogenation of (**70**) with palladium catalysis in ethanol at 95°C gave the corresponding amino derivative (**71**); continued hydrogenation fully reduced the pyridine ring ⟨90JHC1649⟩.

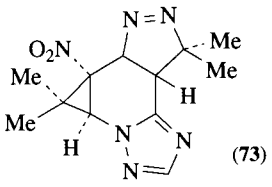
8.13.5.5 Reactions with Cyclic Transition States

1,3-Dipolar cycloaddition of the diazoalkane ($(CH_3)_2CN_2$) to (**72**) in acetone gave the tetracyclic compound (**73**). The unsubstituted compound did not react. The nitro group at the 6-position activates the C(5)—C(6) and C(7)—C(8) double bonds for cycloaddition ⟨89H(28)259⟩. It was originally reported that [1,2,4]triazolo[4,3-*a*]pyridine (**29**) reacted with DMAD in the presence of 5% Pd/C to give (**74**) ⟨81IJC(B)10⟩. It was subsequently shown that this reaction produces three products independent of the use of the palladium catalyst. Initial Michael addition of DMAD to (**29**) via its

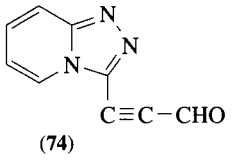
two nucleophilic centers C-3 and N-1 gives zwitterionic intermediates one of which can react with another mole of DMAD to give (**75**) or collapse to a cycloadduct which rearranges to form (**76**). The other zwitterionic intermediate undergoes intermolecular proton transfer with opening of the triazole ring to form the *N*-cyano compound which then undergoes a [1,5] favored shift of cyanide from nitrogen to carbon, with cyclization to (**77**) ⟨82CC1280⟩.



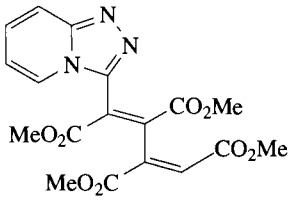
(**70**), R^1=NO_2, R^2=H
(**71**), R^1=NH_2, R^2=H
(**72**), R^1=H, R^2=NO_2



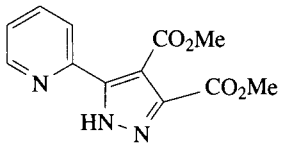
(**73**)



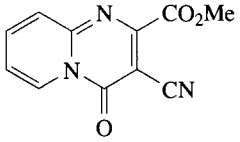
(**74**)



(**75**)



(**76**)



(**77**)

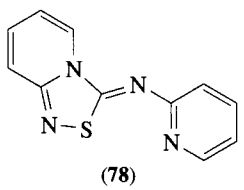
8.13.6 REACTIVITY OF NONCONJUGATED RINGS

8.13.6.1 Thermal and Photochemical Reactions

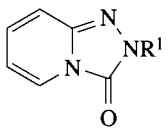
No new reactions for nonconjugated systems based on ring systems (**28**)–(**30**) have been reported since 1983 and studies on systems (**17**)–(**27**) are sparse.

8.13.6.2 Electrophilic Attack at Nitrogen (and/or Carbon)

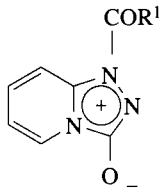
Experiments using a homonuclear double resonance NOE experiment have determined the site of quaternization of (**78**), using Meerwein's reagent, to be at the thiadiazole N-2 ⟨92JHC1765⟩. Compound (**79**) reacts with acid chlorides and alkoxycarbonyl chlorides to give (**80**) and the mesoionic *N*-alkoxycarbonyl compound (**81**), respectively. Acylation of (**82**) gave the mesoionic *N*-acyl compound (**83**). The mesoionic azolides (**83**) transform to the thermodynamically more stable N^2-acyl analogs (**80**) ⟨83BCJ2969⟩. These compounds have found application as acylating agents in peptide syntheses ⟨83BCJ2974⟩.



(**78**)

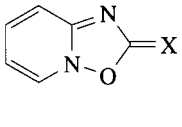


(**79**), R^1=H
(**80**), R^1=COR^2
(**82**), R^1=$SiMe_3$

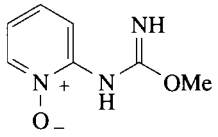


(**81**), R^1=OR^2
(**83**), R^1=Me, Bn, Ph

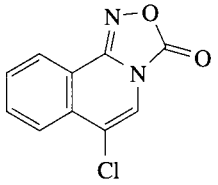
All of these systems are generally stable to oxidation. Compound (**84**) was oxidized with peracetic acid to give (**85**), whereas silver oxide and methanol gave the ring opened (**86**) ⟨75YZ87⟩. Oxidation of (**87**) with $KMnO_4$ in pyridine resulted in ring opening and the formation of (**88**) ⟨75CB3799⟩.



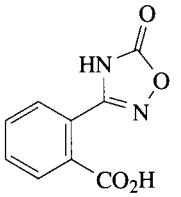
(**84**), X=NH
(**85**), X=O



(**86**)



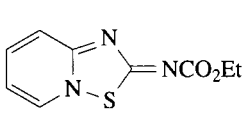
(**87**)



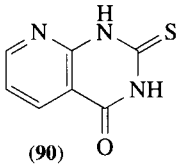
(**88**)

8.13.6.3 Nucleophilic Attack at Carbon

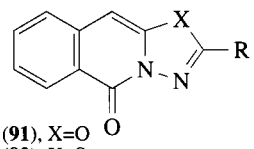
The majority of references under this heading deal with the hydrolytic ring opening of systems (**17**)–(**27**). Base cleavage of the S3—N4 bond in (**89**) yielded an intermediate ethoxycarbonylthiourea which cyclized to (**90**) ⟨87H(26)689⟩. Treatment with aqueous sodium carbonate, however, gave 2-cyanaminopyridine and *N*-(pyridyl-2′)thiourea ⟨77JHC621⟩. Base hydrolysis of (**91**) and (**92**) gave the corresponding oxadiazole (**93**) and thiadiazole (**94**), respectively ⟨75BCJ2915⟩. In a rare example of ring cleavage using hydride ion, treatment of (**95**) with excess sodium hydride gave the triazole (**96**). The corresponding NH compound did not undergo this cleavage since this proton is available for ionization and thus stabilizes the molecule ⟨90JOC5117⟩.



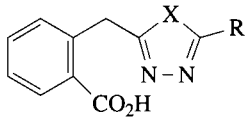
(**89**)



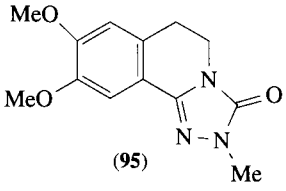
(**90**)



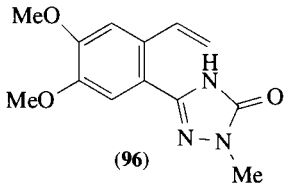
(**91**), X=O
(**92**), X=S



(**93**), X=O
(**94**), X=S



(**95**)



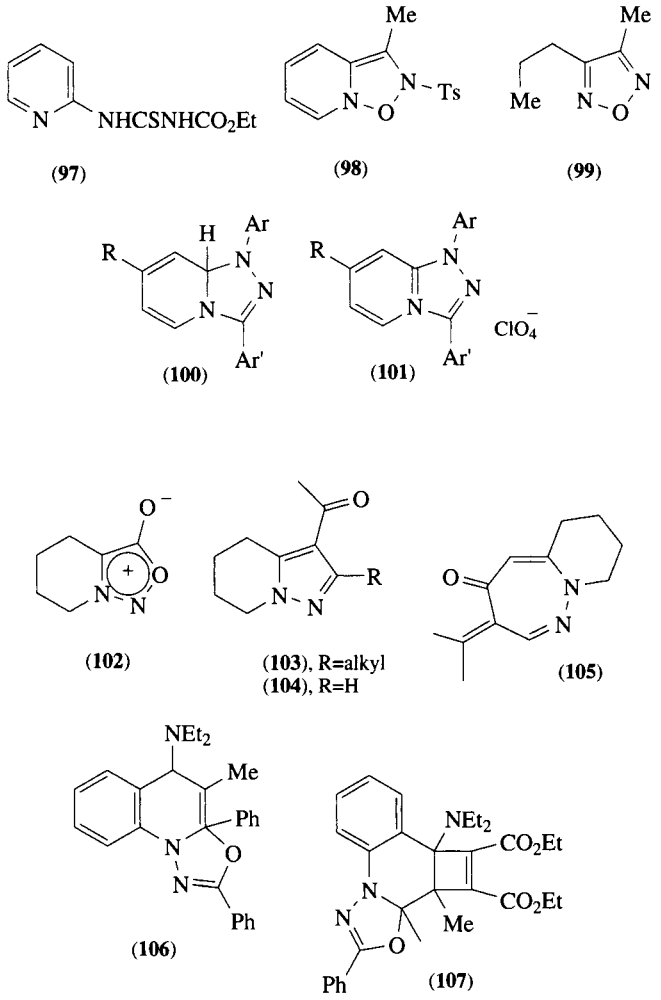
(**96**)

8.13.6.4 Reactions at Surfaces

Reduction of (**89**) with palladium or platinum catalysis gave the thiourea (**97**) ⟨75OPP55, 77JHC621⟩. Reduction of (**98**) with Pd/C in THF gave the corresponding tetrahydro derivative and (**99**) ⟨83CPB2269⟩. Anodic oxidation of the 4,8-dihydro analog (**100**) in the presence of Et_4NClO_4 in acetonitrile gave the salt (**101**) ⟨88ZC187⟩.

8.13.6.5 Reactions with Cyclic Transition States

Cycloaddition of β-alkyl or β-arylenones to the bicyclic sydnone (**102**) gave the tetrahydropyrazolo[1,5-*a*]pyridine (**103**) with small amounts of the ketone (**104**). The unusual hydrocarbon elimination is thought to involve the loss of R as a radical ⟨89TL4625⟩. 1,3-Dipolar cycloaddition of (**102**) with isopropylidenecyclobutenone in refluxing toluene gave the dihydro diazepin-5-one (**105**) ⟨87CB275⟩. [2 + 2] Cycloaddition of diethylalkynedicarboxylate with (**106**) gives (**107**) ⟨79CB3623⟩.

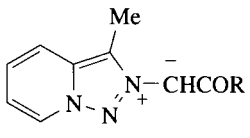


8.13.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

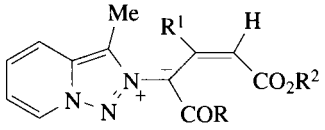
Reactivity of substituents of systems (**28**)–(**30**) have been covered up to 1983 in previous reviews ⟨83AHC(34)80, 84CHEC-I(5)847⟩.

2-Acylmethyltriazolopyridinium salts readily form ylides (**108**) with potassium carbonate in acetonitrile. These ylides react with alkynic esters to give further novel ylides (**109**) (1 : 1 adduct) and (**110**) (1 : 2 adduct) ⟨91T5277⟩. Under the same conditions but changing to a nonpolar solvent, such as toluene, the ylide (**108**) reacts with DMAD in a $[8\pi + 2\pi]$ cycloaddition to yield an intermediate diazacyclazine, which provides a 1,3-dipole for reaction with a further molecule of DMAD to give (**111**) ⟨91TL4977⟩. The use of methyl propiolate instead of DMAD provides a further change in reaction course. The ylides (**108**) now react in toluene to give excellent yields of 1,2,3-trisubstituted indolizines (**112**) ⟨92H(33)203⟩. The ylides (**108**) react with alkenes in toluene and potassium carbonate/triethylamine to provide three main products (**113**), (**114**), and (**115**) in 74, 3, and 11% yields, respectively. A further product (**116**) was isolated in a number of experiments ⟨93H(35)851⟩. These ylides also undergo reactions with electrophiles. Protonation of the ylides (**117**) gave (**118**) as the major product and (**119**) as the minor product. Alkylation of the ylides was not achieved ⟨92H(34)1005⟩.

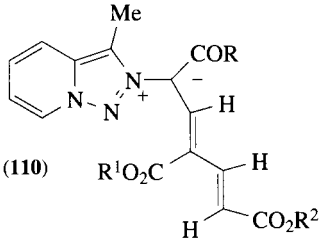
Treatment of the mesoionic compound (**120**) with the iminophosphorane ($ArN{=}PPh_3$) in refluxing toluene gave (**121**). This is a general method for the substitution of a methyl group by an aryl group ⟨88CB1495⟩. The anions (**122**) from the corresponding amines are ambident, acylating on nitrogen to give (**123**), but alkylating on nitrogen (**124**) or on C-6 (**125**). C-Alkylation precedes any ring opening and the balance of nitrogen vs. carbon alkylation is substantially as predicted by the hardness and softness of the electrophile ⟨93T703⟩.



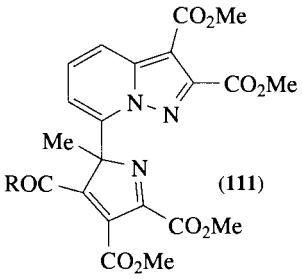
(108)



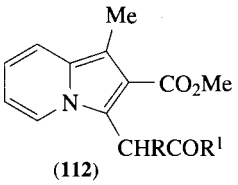
(109)



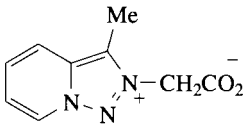
(110)



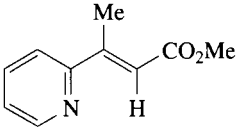
(111)



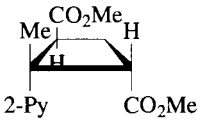
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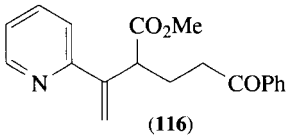
(113)



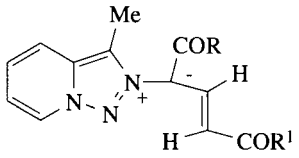
(114)



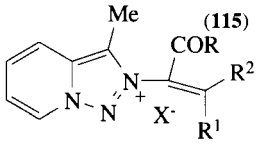
(115)



(116)

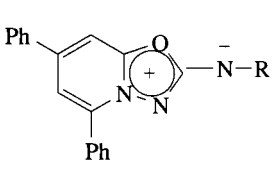


(117)

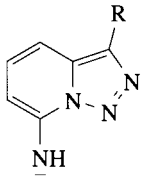


(115)

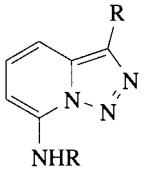
(118), R^1=CH_2COR_3, R^2=H
(119), R^1=H, R^2=CH_2COR^3



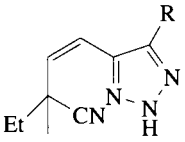
(120), R=Me
(121), R=Ph



(122)



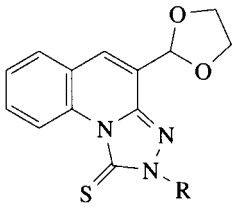
(123), R=COPh
(124), R=Me



(125)

8.13.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Such reports are extremely rare in the literature. Condensation of (**126**) with formaldehyde yielded (**127**) ⟨91AP(324)249⟩.



(126), R=H
(127), R=CH_2OH

8.13.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

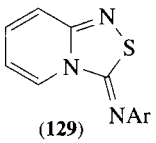
8.13.9.1 [1,2,4]Thiadiazolo[4,3-*a*]pyridine (17)

8.13.9.1.1 Closure of the thiadiazole ring

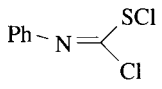
Condensation of 2-trichloromethylthioaminopyridine (**128**) with primary aromatic amines ($ArNH_2$) provides the most direct route to this ring system (**129**) ⟨70JOC1965⟩. In a similar fashion, the sulfenyl chloride (**130**) condensed with 2-aminopyridine to give (**129**; Ar = 2-pyridyl) ⟨86S1027⟩. Condensation of the sulfenamide (**131**), with 2-amino-5-methyl pyridine, in the presence of base gave (**129**; R = 2-amino-5-methylpyridyl) ⟨75JOC2600⟩. Condensation of 3-substituted-5-phenyl-1,2-dithiolylium salts (**132**) in ethanol, with 2-aminopyridine derivatives, gave (**133**) and (**134**) ⟨82JCS(P1)499⟩.



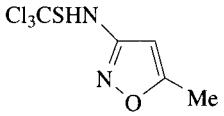
(**128**)



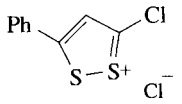
(**129**)



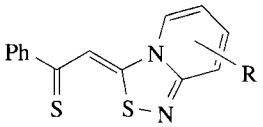
(**130**)



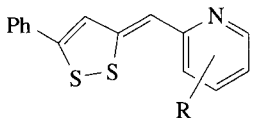
(**131**)



(**132**)



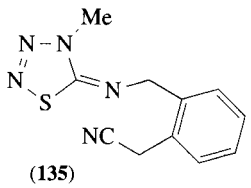
(**133**)



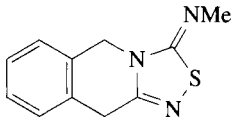
(**134**)

8.13.9.1.2 Closure of the pyridine ring

The masked 1,3-dipole, thiatriazole (**135**), undergoes intramolecular cycloaddition with subsequent elimination of molecular nitrogen, smoothly in ethanol at 75 °C to give (**136**). These reactions were studied in detail with isothiocyanates, isocyanates, ketenes, and electrophilic nitriles ⟨92T7505⟩.



(**135**)



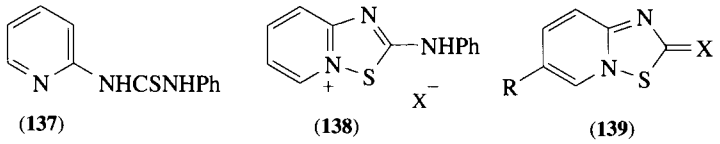
(**136**)

8.13.9.2 [1,2,4]Thiadiazolo[2,3-*a*]pyridine (18)

8.13.9.2.1 Closure of the thiadiazole ring

Oxidative cyclization of pyridyl thiourea derivatives is one of the most common methods for the synthesis of this ring system. Treatment of (**137**) with bromine or sulfuryl chloride in an inert solvent gave the salt (**138**). Similar products were obtained by sulfuryl chloride oxidation of the corresponding thioamides ⟨72AJC993⟩ and bromine in acetic acid oxidation of carboethoxythiourea derivatives ⟨75OPP55⟩. Conversion of *N*-(2-pyridyl)thiourea to the corresponding *N*,*N*-dimethylaminomethylene derivative, followed by oxidation with bromine in chloroform gave (**139**; R = H,

X = NCHO) ⟨78H(11)313⟩. Reaction of 2-amino-5-chloropyridine with chlorothioformyl chloride (ClSCOCl) gave (**139**; R = Cl, X = O) ⟨73JOC1575⟩.

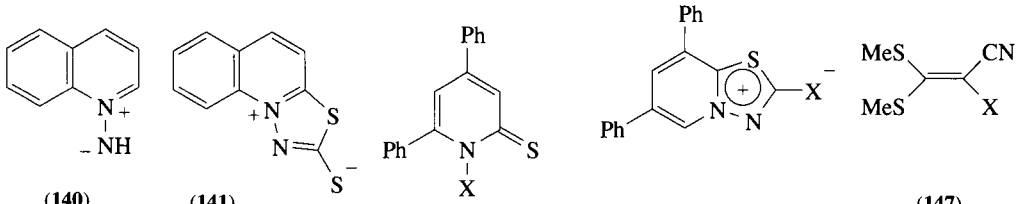


(**137**) (**138**) (**139**)

8.13.9.3 [1,3,4]Thiadiazolo[3,2-*a*]pyridine (20)

8.13.9.3.1 Closure of the thiadiazole ring

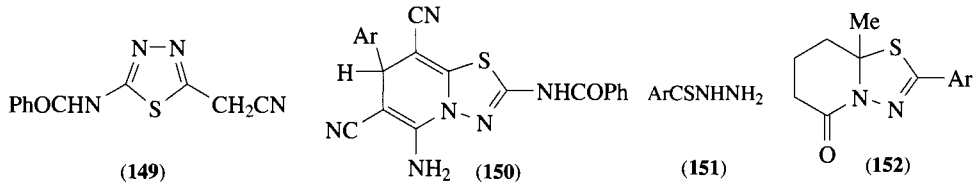
1,3-Dipolar cycloaddition of the azomethine imine (**140**) with carbon disulfide gave the mesoionic sydnone (**141**) ⟨77LA506⟩. The *N*,*N*′-disubstituted ureas (**142**) were cyclized, thermally, to give (**143**) ⟨82JCS(P1)351⟩. Alternatively, reaction of the iminophosphorane (**144**) with isocyanates or isothiocyanates gave the mesoionic 2-amidines (**145**). Reaction of the thione (**146**) with (**147**) in the presence of potassium *t*-butoxide in acetonitrile gave the 2-methylides (**148**) ⟨87SC1929⟩.



(**140**) (**141**) (**142**), X=NHCONHR (**143**), X=O (**147**)
(**144**), X=N=PPh$_3$ (**145**), X=NR
(**146**), X=NH$_2$ (**148**), X=C(X)R

8.13.9.3.2 Closure of the pyridine ring

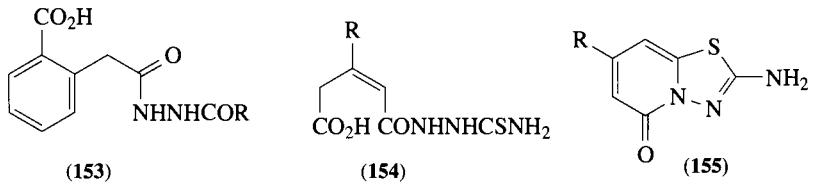
Michael addition of (**149**) to the activated double bond of an arylidenemalonitrile gave (**150**) ⟨88PHA533, 90JCR(S)148⟩. When 5-oxohexanoic acid was treated with (**151**) in ethanol at room temperature the expected thiadiazole was not formed, but instead spontaneous cyclization occurred to yield (**152**) ⟨86JCS(P1)1499, 89H(29)133⟩.



(**149**) (**150**) (**151**) (**152**)

8.13.9.3.3 Closure of both rings

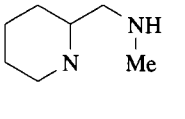
Treatment of the acylhydrazine (**153**) with P_2S_5 in pyridine yielded (**92**) ⟨75BCJ2915⟩. Alternatively, acylthiosemicarbazide (**154**) was cyclized using orthophosphoric acid at 140°C to yield (**155**) ⟨85IJC(B)330⟩.



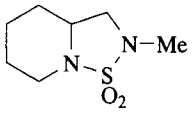
(**153**) (**154**) (**155**)

8.13.9.4 [1,2,5]Thiadiazolo[2,3-*a*]pyridine (22)

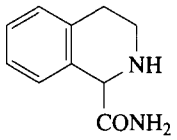
Reaction of the methylamine compound (**156**) with sulfuryl chloride at −70 °C gave (**157**) ⟨62AP(295)621⟩. Similarly, treatment of (**158**) with sulfur monochloride in DMF at 60 °C gave (**159**) ⟨81JCS(P1)1033⟩. In an intramolecular α-sulfamidoalkylation, dissolution of (**160**) in TFA yielded (**161**) ⟨90JOC6098⟩.



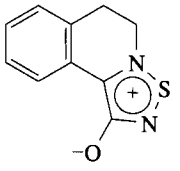
(**156**)



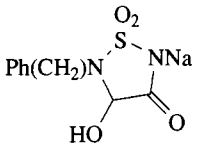
(**157**)



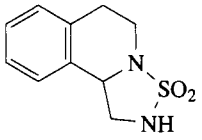
(**158**)



(**159**)



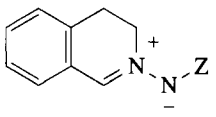
(**160**)



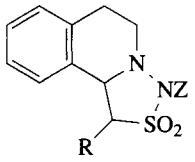
(**161**)

8.13.9.5 [1,2,3]Thiadiazolo[3,4-*a*]pyridine (24)

1,3-Dipolar cycloaddition of the azomethine imine (**162**) and an alkanesulfonyl chloride in excess trialkylamine and hydrocarbon solvent gave the first example (**163**) of this rare ring system ⟨75JOC2260⟩.



(**162**)



(**163**), R=alkyl

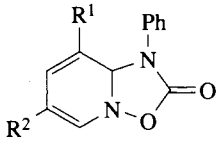
8.13.9.6 [1,2,4]Thiadiazolo[4,5-*a*]pyridine (26)

There are no reported syntheses of this ring system in the primary literature.

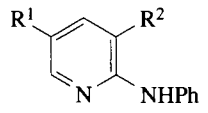
8.13.9.7 [1,2,4]Oxadiazolo[2,3-*a*]pyridine (19)

The only reported syntheses of this ring system involve closure of the oxadiazole ring. The earliest synthesis involved the thermal elimination of ethanol from the urethane-*N*-oxide (**63**) to yield the mesoionic (**60**) ⟨56JCS2063, 57JCS4385⟩. 1,3-Dipolar cycloaddition of 3-methyl-pyridine-1-oxide and phenylisocyanate in DMF at 110 °C yields the primary adducts (**164**) and (**165**) in 34% and 24% yields, respectively. At 150 °C, CO_2 is eliminated and only (**166**) and (**167**) are isolated ⟨74CPB1611, 74OPP243, 76CPB533⟩. However, it was subsequently reported that the primary adducts are unstable and rearrange by 1,5-sigmatropic shifts to give (**166**) and (**167**) ⟨76JHC171, 80H(14)19⟩. A similar cycloaddition occurred with the nitrone (**168**) and nitriles (RCN) to yield (**169**) under conditions of high temperatures or high pressures ⟨88T6491⟩. Phenyl isocyanate has also been employed as a dipolarophile in this reaction ⟨84JOC3127⟩. 2-Amino-quinoline-*N*-oxide reacted with cyanogen bro-

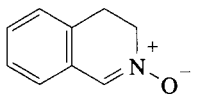
mide in ethanol to give (**170**) ⟨75YZ87⟩, whereas 2-amino-pyridine *N*-oxide reacted with phosgene to give (**61**) ⟨58HCA548⟩.



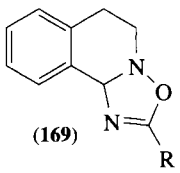
(**164**), R^1=Me, R^2=H
(**165**), R^1=H, R^2=Me



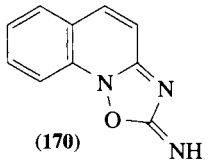
(**166**), R^1=Me, R^2=H
(**167**), R^1=H, R^2=Me



(**168**)



(**169**)

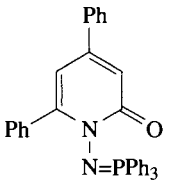


(**170**)

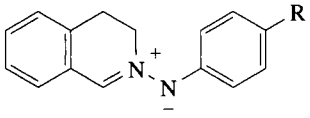
8.13.9.8 [1,3,4]Oxadiazolo[3,2-*a*]pyridine (21)

8.13.9.8.1 Closure of the oxadiazole ring

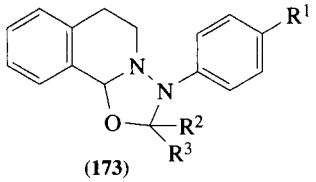
Condensation of 1-amino-2-pyridone with phosgene provided the first synthesis of this new mesoionic ring system (**60**) ⟨58HCA548, 76CB723⟩. Similarly, ring closure can be achieved using polyphosphoric acid at elevated temperatures ⟨75BCJ2915⟩ or thiophosgene in the presence of base ⟨70TL5087, 77CJC3736⟩. Elimination of methanol at 270 °C from pyridone (**69**; R = $NHCO_2Me$) gave (**68**) ⟨74CC621, 75CJC1973⟩. Condensation of the iminophosphorane (**171**) with the hydroximoyl chlorides (ArC(Cl)=NOH) gave (**121**) ⟨88CB1495⟩. 1,3-Dipolar cycloaddition of the azomethine imine (**172**) with carbonyl compounds gave the thermally unstable (**173**) ⟨62AG(E)267⟩.



(**171**)



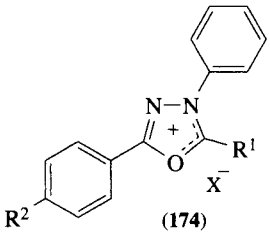
(**172**)



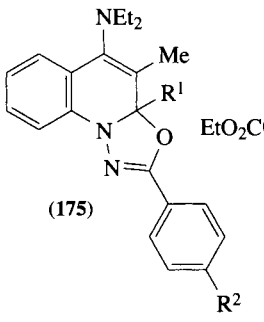
(**173**)

8.13.9.8.2 Closure of the pyridine ring

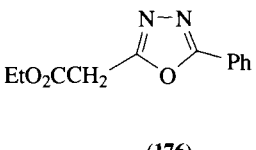
The oxadiazolium salt (**174**) reacted with $CH_3C{\equiv}CNEt_2$ in a [4 + 2] cycloaddition to give (**175**) ⟨79CB3623⟩. Condensation of the oxadiazole (**176**) with benzylidenemalonitrile gave (**177**) ⟨88LA909, 90JCR(S)148⟩.



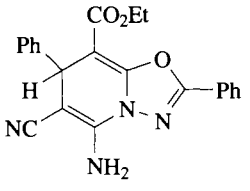
(**174**)



(**175**)



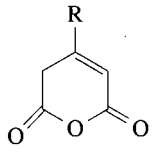
(**176**)



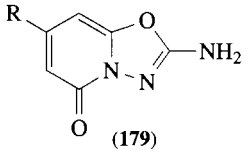
(**177**)

8.13.9.8.3 Closure of both rings

Reaction of the cyclic anhydride (**178**) with thiosemicarbazide and sodium acetate in DMF resulted in the loss of hydrogen sulfide and the formation of (**179**) ⟨85IJC(B)330⟩.



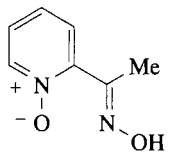
(**178**)



(**179**)

8.13.9.9 [1,2,5]Oxadiazolo[2,3-*a*]pyridine (23)

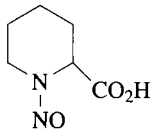
The *E*-oxime (**180**) reacts with *p*-toluenesulfonylchloride to give (**98**) as the sole product. Neighboring group participation is thought to occur since the corresponding *Z*-oxime only gives the tosylate of the oxime group ⟨83CPB2269, 86CPB564, 86CPB4984⟩.



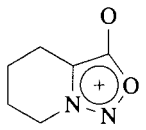
(**180**)

8.13.9.10 [1,2,3]Oxadiazolo[3,4-*a*]pyridine (25)

Treatment of the *N*-nitroso compound (**181**) with acetic anhydride gave the mesoionic compound (**182**) (the corresponding *N*-nitroso dihydro quinoline behaved similarly) ⟨61JCS3303⟩.



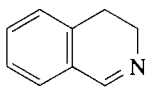
(**181**)



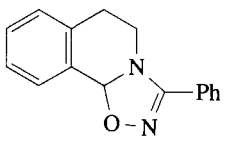
(**182**)

8.13.9.11 [1,2,4]Oxadiazolo[4,5-*a*]pyridine (27)

1,3-Dipolar cycloaddition of the azomethine (**183**) with benzonitrile *N*-oxide in benzene and base gave (**184**) ⟨72CB2825⟩. Both quinoline and isoquinoline have been shown to undergo a similar condensation ⟨88T4917⟩.



(**183**)

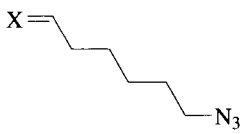


(**184**)

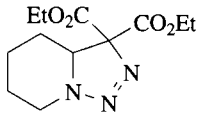
8.13.9.12 [1,2,3]Triazolo[1,5-*a*]pyridine (28)

In summary, the known preparative methods for the synthesis of [1,2,3]triazolo[1,5-*a*]pyridines prior to 1983 have been extensively reviewed in a number of different reviews ⟨61CHE749, 83AHC(34)80, 84CHEC-I(5)847⟩. These reviews reveal that the most straightforward methods involves an oxidation of the hydrazone of a pyridine-2-carbaldehyde or ketone, treatment of a tosylhydrazone with a base, cyclization of *N*-aminopyridinium oxime mesylates, pyrolysis of pyridyldiazoalkanes, and diazo group (tosyl azide as source of the diazo group) transfer to an active methylene group (e.g., 2-methylpyridines) under basic conditions.

Since 1983 there have not been many new synthetic methods reported for this ring system. A rare example in which both rings are formed simultaneously involves an intramolecular 1,3-dipolar cycloaddition of the ylide (**186**) formed from the corresponding azido compound (**185**) and diethyloxomalonate, to give (**187**) in 50% yield ⟨92JCR(S)52⟩.



(**185**; X = $C(CO_2Et)_2$)
(**186**; X = PPh_3)



(**187**)

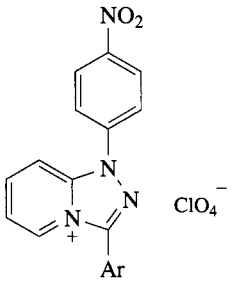
8.13.9.13 [1,2,4]Triazolo[4,3-*a*]pyridine (29)

Due to the interesting pharmacological properties observed with this ring system (see Section 8.13.11), it has been the subject of many literature citations, primarily for new synthetic methods. In summary, the most important methods for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines prior to 1983 ⟨61CHE749, 83AHC(34)80, 84CHEC-I(5)847⟩ involved the oxidative cyclization of hydrazones (usually derived from 2-pyridylhydrazine), cyclization of hydrazides under a variety of conditions, or reaction of 2-pyridylhydrazines with a single carbon fragment (e.g., formic acid or ethyl orthoformate) to produce 3-unsubstituted products. A range of other acids, esters, or anhydrides give 3-substituted products. The other major approach is from pyridines or 2-halogenopyridines, with the addition of a three-atom fragment to form the triazole ring. The corresponding benzo derivatives, [1,2,4]triazolo[4,3-*a*]quinolines and [1,2,4]triazolo[4,3-*a*]isoquinolines are prepared by similar methods, i.e., ring closure of 2-hydrazinoquinoline and 1-hydrazinoisoquinoline with carboxylic acids or by the oxidative cyclization of quinol-2-yl hydrazones of aromatic and heterocyclic aldehydes.

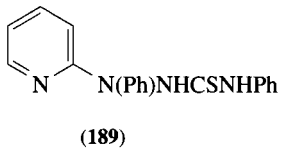
Since 1983, a variety of new synthetic methods have appeared utilizing closure of the triazole ring. Anodic oxidation of aldehyde hydrazones in the presence of pyridine gives the triazolopyridinium salts (**188**) ⟨81H(16)699, 88JOC5081⟩. The thiosemicarbazides (**189**) were cyclized to the betaines (**190**) using DCC in dichloromethane ⟨93JCS(P1)705⟩ or bromine in acetic acid ⟨88M83⟩. Treatment of the α,β-unsaturated ketone (**191**) with hydrazine hydrate gives (**192**) ⟨90MI 813-01⟩. The glyphosate thionoester (**193**) undergoes selective nucleophilic addition of 2-pyridylhydrazine at the activated thiono ester to yield (**194**), while retaining the reactive diphenyl phosphonate moiety ⟨92HAC279⟩. 2-Methoxypyridine reacted as an inverse demand dienophile with the tetrazine (**195**) to give (**196**) in 11% yield ⟨93AP(326)427⟩. 1,3-Dipolar cycloaddition of the triazolium dicyanomethylide (**197**) and alkynic dipolarophiles, such as DMAD, in DMF at 0°C gave (**198**) in 56% yield. Compounds of type (**30**) can also be synthesized using this methodology ⟨83JCS(P1)1317⟩. Similar azomethine ylides, such as (**199**), also undergo 1,3-dipolar cycloadditions to the N—N bond of diazonium salts to yield the salts (**200**) ⟨84TL65⟩. 1,3-Dipolar cycloaddition of the C,N-diphenylnitrilimine (**201**) with cyclic amines (such as (**202**)) in dichloromethane, gave (**203**) in 60% yield ⟨85AP(318)556⟩. In a rare example of the simultaneous formation of both rings, *N'*-acylacetamidrazones (**204**) react with ethyl ethoxymethylene cyanoacetate (EMCA) in DMSO to give (**205**) ⟨91JHC797⟩.

8.13.9.14 [1,2,4]Triazolo[1,5-*a*]pyridine (30)

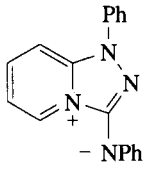
In summary, the known preparative methods for the synthesis of [1,2,4]triazolo[1,5-*a*]pyridines prior to 1983 have been extensively reviewed in a number of different reviews ⟨61CHE749, 83AHC(34)80,



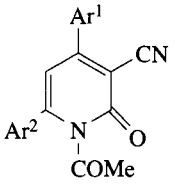
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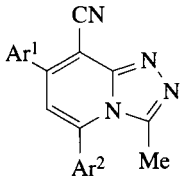
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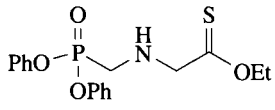
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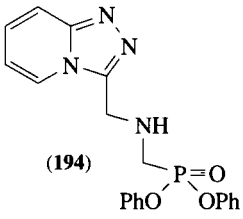
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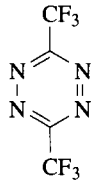
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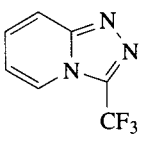
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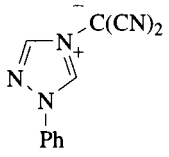
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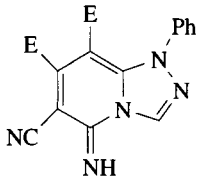
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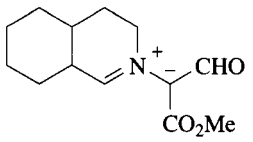
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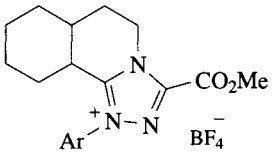
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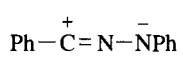
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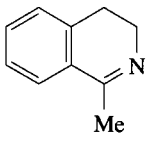
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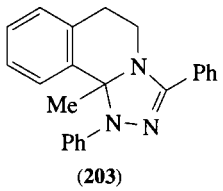
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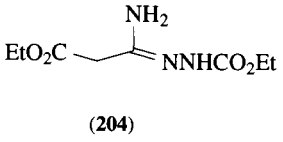
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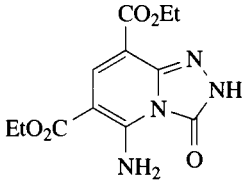
(202)



(203)



(204)



(205)

84CHEC-I(5)847〉. The most common methods are the oxidative cyclization of pyridylamidines or pyridylamidoximes, treatment of *N*-aminopyridinium salts with mesitylsulfonylhydroxylamine (MSH) and subsequent thermal cyclization to the 1-aminotriazolopyridinium salts, treatment of *N*-aminopyridinium salts with *N*-ethoxycarbonylacetimidate to give ylides which cyclize on heating, and the reaction between 1,2-diaminopyridinium salts and carboxylic acids (or their chlorides).

A variety of new synthetic methods have appeared utilizing closure of the triazole ring. Treatment of the formamidines (**206**) with HSA in methanol/pyridine gave (**207**) in 26–87% yields. The corresponding isoquinolines also undergo this reaction 〈81JOC3123〉. The *N*-cyanopiperidin-2-imine (**208**) also reacts with HSA to give (**209**) 〈91LA975〉. Condensation of ethyl carboethoxyformimidate with the imine (**210**) in refluxing methanol gave (**211**) 〈86T2625〉. The 2-aza-3-methylthiopropenium salts (**212**) reacted with 1,4- and 1,5-binucleophiles, such as (**213**), in methanol and acetic acid to give (**214**) 〈91JPR(333)149〉. Initial 1,3-dipolar cycloaddition of the pyridine-*N*-imide (**215**) to one nitrile triple bond of (**216**) gave an intermediate which underwent a 1,5-hydrogen shift and a 1,3

hydrogen shift to give (**217**). In addition to this product, the interesting dipolar compound (**218**) was also formed and provided the first example of an intramolecular charge transfer complex between a pyridinium cation and a carbanion ⟨84TL4429⟩. Pyridone (**219**) reacts with aromatic and heterocyclic nitriles under basic conditions to give (**220**) ⟨82S974⟩. Acid-catalyzed reaction of the thione (**221**) with aromatic or aliphatic nitriles gave the thione derivatives (**222**) ⟨88H(27)733⟩. Alternatively, the thione (**223**) reacted with diaryl carbodiimides in refluxing toluene to give (**224**) ⟨86H(24)3363⟩. Pyridones (**225**) also react with amides ($RCONH_2$), with Lewis acid catalysis, to give compounds of type (**226**) ⟨86S860⟩. Treatment of 2-nitrosopyridine with aromatic nitrile oxides in methylene chloride, in the presence of triethylamine, gave the di-*N*-oxides (**227**). Highly substituted aromatic nitrile oxides gave the 3-oxides only, which were easily deoxygenated to the parent by treatment with phosphorus oxychloride ⟨93JHC287⟩. The [1,2,4] triazolium salts (**228**) undergo [4 + 2] cycloaddition with the electron rich (**229**) to give (**230**) ⟨83CB186⟩. Condensation of the salt (**231**) with aryl isothiocyanates in DMF under basic conditions gave (**232**). If the reaction was performed in acetonitrile, the thiadiazolopyridine (**233**) was formed, but this was easily converted to (**232**) by treatment with TEA in DMF ⟨84JCS(P1)1891⟩. The short lived 1-aza-2-azoniallene salts (**234**) have been shown to react with a variety of multiple bonds (e.g., Bu^tCN) to give compounds such as (**235**) ⟨93T9973⟩.

There have been isolated examples in the literature where the formation of the six-membered ring is the final step. Dieckmann-type condensation of triazole (**236**) with sodium ethoxide gave (**237**) ⟨85S423⟩. There are also examples in which both rings are formed simultaneously. Intramolecular capture of the nitrile imine moiety by the unsaturated nitrile moiety in (**238**) gave a mixture of (**239**) and (**240**) ⟨83JCS(P1)539⟩. Reaction of 5-halovalerophenones (**241**) with semicarbazides (**242**) in isopropanol gave (**243**) in 67% yield ⟨88JHC1471⟩.

8.13.10 RING SYNTHESES BY TRANSFORMATION OF ANOTHER RING

8.13.10.1 [1,3,4]Thiadiazolo[3,2-*a*]pyridine (20)

Cycloaddition of the thiocarbonyl ylide dipole (**244**) with a variety of electron deficient dipolarophiles such as $R^1CH{=}CHR^2$ and $R^1C{\equiv}CR^2$) gave (**245**) ⟨79JOC3808⟩.

8.13.10.2 [1,2,3]Triazolo[1,5-*a*]pyridine (28) and [1,2,4]Triazolo[4,3-*a*]pyridine (29)

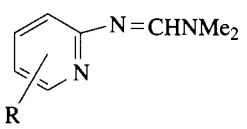
There have been no new syntheses of these ring systems by ring transformations since 1983 ⟨83AHC(34)80, 84CHEC-I(5)847⟩.

8.13.10.3 [1,2,4]Triazolo[1,5-*a*]pyridine (30)

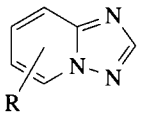
Since 1983, the following new methods have been reported; condensation of the 2-functionalized pyrylium salts (**246**) with amidrazones (**247**) in acetonitrile gave the salts (**248**) ⟨83JCS(P1)1395⟩. Heating the tetrazole (**249**) or the corresponding oxadiazole in polyphosphoric acid led to the elimination of nitrogen or carbon dioxide, respectively, to yield the aminotriazolopyridine (**250**) ⟨83M789⟩. Likewise pyrolysis of tetrazole (**251**) in tetralin gave (**252**), presumably via a nitrene intermediate ⟨83IJC(B)117⟩. Intramolecular Diels–Alder reaction of heterodienophiles to the oxazole (**253**) gave (**254**) ⟨91JOC3419⟩. The base catalyzed rearrangement of 3-(*N*-heteroarylamine-1,2,5-oxadiazoles (**255**) gave the *Z*-oxime (**256**). The *Z*-isomers rearrange to the *E*-isomers on workup or during purification. Similar transformations occur for the quinoline substituted oxadiazoles ⟨93H(36)1577⟩.

8.13.11 IMPORTANT COMPOUNDS AND APPLICATIONS

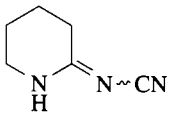
By far the most important compound covered by this chapter is trazodone (**257**) (Desyrel in the USA), a 1,2,4-triazolo [4,3-*a*] pyridin3(2*H*)-one marketed in a number of countries around the world as a treatment for depression. Trazodone blocks the re-uptake of 5-HT into serotoninergic neurons and is also a potent central antagonist of 5-HT ⟨81LS2449⟩. Compound (**258**), a closely



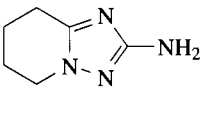
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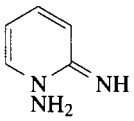
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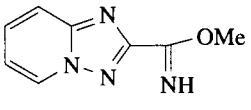
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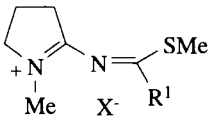
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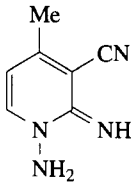
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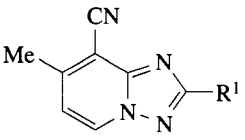
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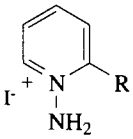
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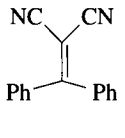
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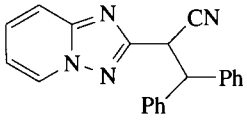
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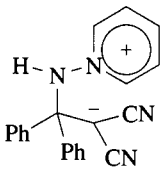
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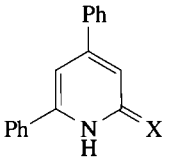
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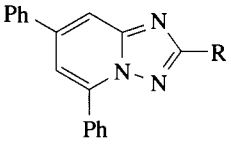
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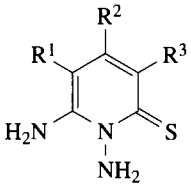
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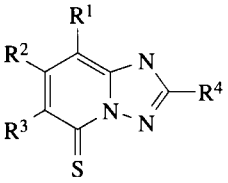
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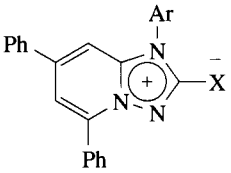
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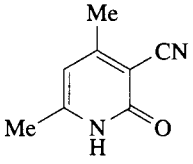
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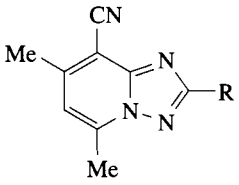
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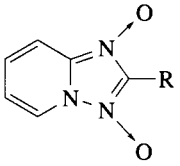
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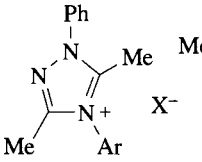
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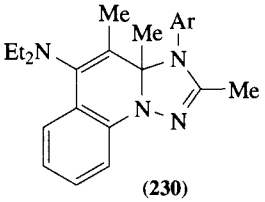
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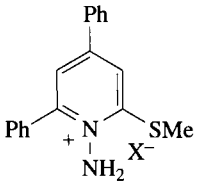
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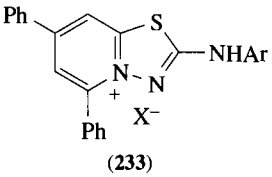
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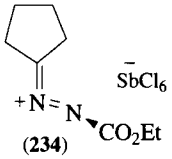
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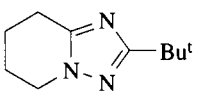
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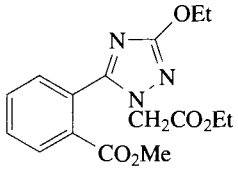
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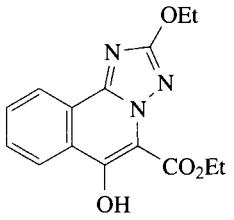
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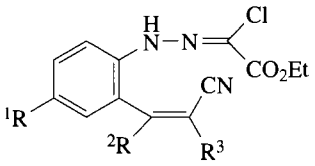
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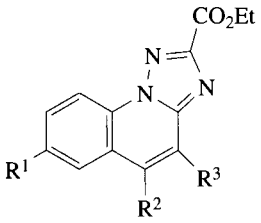
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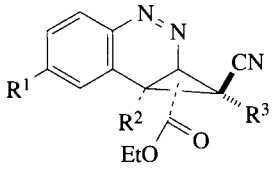
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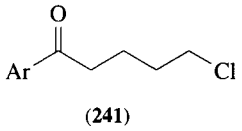
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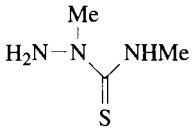
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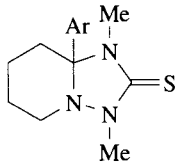
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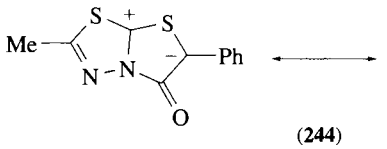
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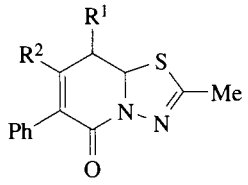
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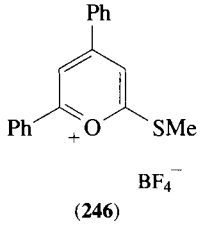


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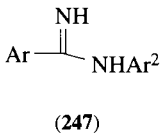


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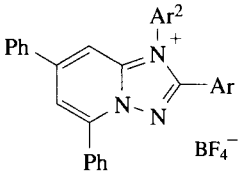
related trazodone analog, has been shown to possess 5-HT_2 antagonist activity, however, it is a weak inhibitor of central 5-HT_2 and is hepatotoxic ⟨92JMC189⟩. Other close congeners of trazodone have been shown to be potent and selective inhibitors of synaptosomal uptake of 5-HT ⟨92JPS99⟩. Compound (**259**) has been shown to have antiaggregant activity through phosphodiesterase inhibition ⟨91EJM189⟩.



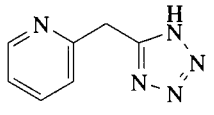
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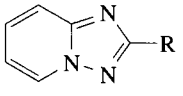
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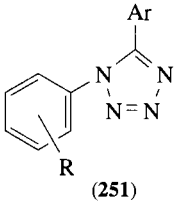
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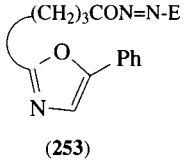
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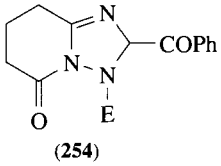
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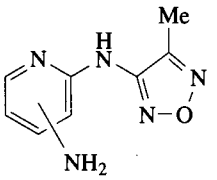
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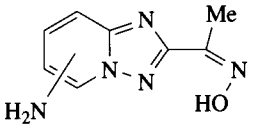
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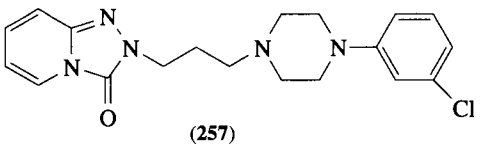
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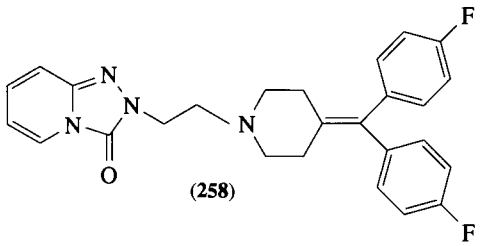
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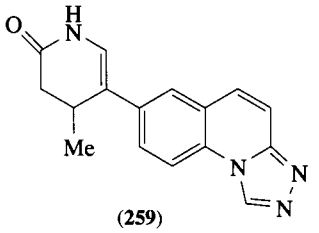
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8.14
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 0 : 2

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Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA

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8.14.1 INTRODUCTION

This chapter reviews those systems composed of a bicyclic system containing fused five- and six-membered rings with one ring junction nitrogen atom and two extra heteroatoms in the six-membered ring. The heteroatoms are primarily nitrogen, oxygen, and sulfur. However, a limited number of boron- and phosphorus-containing systems have been described. The total number of different ring systems falling within the scope of this definition, which have been reported in the literature, is 22, so clearly a comprehensive treatment of each system is impossible within the confines of this chapter. Based on an analysis of those ring systems attracting the greatest attention in the literature, this chapter will focus on all the regioisomeric pyrrolotriazines (**1–6**), both fully conjugated and nonconjugated, and related benzo derivatives. The other systems known, which fall within the scope of this chapter, are noted and all of the limited number of references are provided with pertinent comment when necessary. These systems include 1*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborine (**7**) ⟨90USP4943635⟩, 1*H*-pyrrolo[1,2-*c*][1,3,2]oxazaphosphorine (**8**) ⟨78JOC4996⟩, 1*H*-pyrrolo[1,2-*c*]-[1,2,3]oxathiazine (**9**) ⟨90TA885⟩, 4*H*-pyrrolo[1,2-*b*][1,5,2]dithiazine (**10**) ⟨89AP17⟩, 4*H*-pyrrolo[2,1-*d*][1,3,5]dithiazine (**11**) ⟨91MI 814-01⟩ (x-ray and spectral study), 1*H*-pyrrolo[1,2-*c*][1,2,4]dithiazine (**12**) ⟨89JCS(C)970⟩, 1*H*-pyrrolo[2,1-*c*][1,2,4]thiadiazine (**13**) ⟨72BSF985⟩, 1*H*-pyrrolo[1,2-*b*][1,2,4]-benzothiadiazine (**14**) ⟨66JHC1, 86JCS(P1)805⟩, 9*a*,10-dihydro[1,3,5]thiadiazino[3,2-*a*]indole (**15**) ⟨88JCS(P1)451⟩, 1*H*-pyrrolo[1,2-*b*][1,2,4]oxadiazine (**16**) ⟨79JOC4543⟩, 1*H*-pyrrolo[1,2-*d*][1,2,4]-oxadiazine (**17**) ⟨84JHC455⟩, 2*H*-pyrrolo[2,1-*d*][1,2,5]oxadiazine (**18**) ⟨88TL4415⟩, 4*H*-pyrrolo[1,2-*c*][1,3,5]oxadiazine (**19**) ⟨67JOC1346⟩, 2*H*-[1,3,5]oxadiazino[3,2-*a*]isoindole (**20**) ⟨92JHC369⟩, 2*H*-pyrrolo[2,1-*b*][1,3,4]oxadiazine (**21**) ⟨91CPB836⟩ (x-ray analysis), and 4*H*-pyrrolo[1,2-*c*][1,2,5]oxadiazine (**22**) ⟨73CB1172⟩.

The pyrrolotriazines (**1–6**) have been covered partially in various book chapters ⟨78CHE143, 78CHE848⟩.

By far the greatest number of literature citations are devoted to the pyrrolotriazines (**1–6**). Compounds of this type are the only representatives in this section which can form electronically neutral fully delocalized 10π-electron systems. Most of the parent systems are known, but surprisingly, these have received scant attention in the literature, the greatest number of citations being devoted to the nonconjugated systems. There has been little systematic study of spectral properties, x-ray structure, and molecular dimensions determination, and the use of theoretical methods to predict reactivity at ring atoms. Thus, owing to the sparsity of information, little space is devoted here to these subjects unless some feature warrants special note.

8.14.2 THEORETICAL METHODS

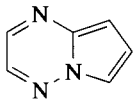
There have been no systematic studies, using molecular orbital calculations, on any members of this series. The only exception is an early study on the sites of electrophilic attack of pyrrolo[1,2-*c*][1,2,4]benzotriazine (**23**) ⟨71JCS(C)2018⟩. Hückel MO calculations were carried out on this molecule using the Coulomb and resonance integrals for heteroatoms. Electron density data showed the following order of decreasing activity towards electrophiles, for compound (**23**): $3 > 2 > 9 > 1$. Localization energies give an entirely different sequence: $1 > 2 > 3 > 9$. The predictions of the localization energy index are usually valid since, in general, the transition state in electrophilic substitution is more likely to resemble the Wheland intermediate than the unperturbed molecule.

8.14.3 EXPERIMENTAL STRUCTURAL METHODS

8.14.3.1 NMR Studies

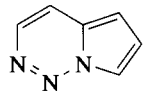
8.14.3.1.1 Proton NMR spectra

A detailed assignment and analysis of the ^{1}H NMR spectra of compound (**23**) has been reported ⟨76AJC827⟩.



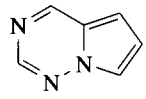
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Pyrrolo[1,2-*b*][1,2,4]triazine



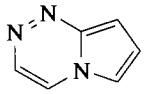
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Pyrrolo[1,2-*c*][1,2,3]triazine



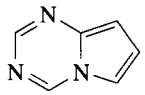
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Pyrrolo[2,1-*f*][1,2,4]triazine



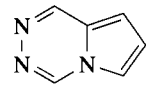
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Pyrrolo[1,2-*c*][1,2,4]triazine



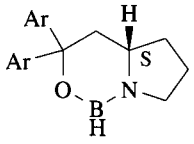
(5)

Pyrrolo[1,2-*a*][1,3,5]triazine

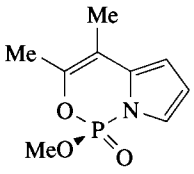


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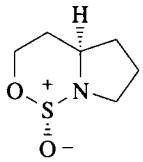
Pyrrolo[1,2-*d*][1,,2,4]triazine



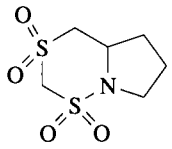
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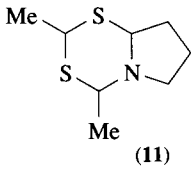
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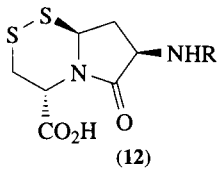
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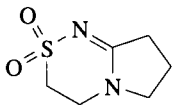
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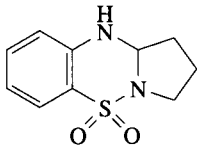
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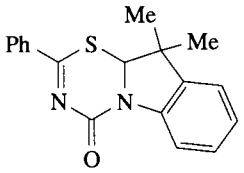
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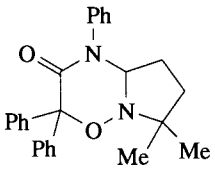
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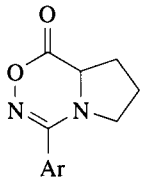
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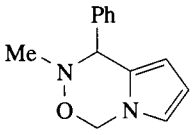
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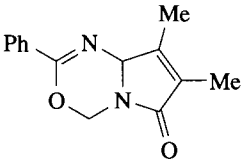
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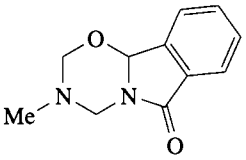
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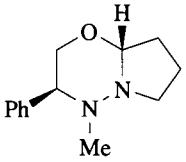
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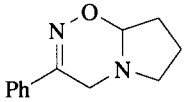
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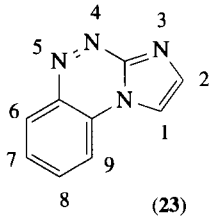
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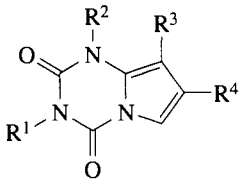
(23)

8.14.3.1.2 Carbon-13 and nitrogen-15 NMR spectra

Compound (**23**) was also included in a ^{13}C and ^{15}N NMR study on tricyclic analogues of indolizine. From the data presented, this compound is undoubtedly aromatic ⟨80AJC499⟩.

8.14.3.2 Mass Spectrometry Studies

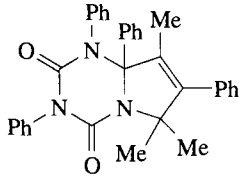
The use of mass spectrometry in this series of compounds has been mainly confined to molecular ion determination and structure determination. The only systematic study has been on compounds (**24**)–(**27**) ⟨75OMS(10)432⟩. Under electron impact, these compounds are generally stable and exhibit intense molecular ions. The diones (**24**)–(**26**) initially eject neutral isocyanate, a mode of fragmentation which is of major importance for cyclic systems containing the NHCONHCO system. The $(M—RNCO)^{+\cdot}$ fragments derived from (**24**)–(**26**) further cleave by loss of CO_2 and HCN either synchronously or simultaneously, both pathways being confirmed by metastable transitions. In contrast, those compounds containing a 7-ethoxycarbonyl function initially fragment by breakdown of the ester function. From compound (**27**), there is a simultaneous loss of C_2H_4 and CO_2 from the molecular ion.



(**24**) R^1 = Me, R^2 = H, R^3 = CN, R^4 = Ph
(**25**) R^1 = Et, R^2 = H, R^3 = CN, R^4 = Ph
(**26**) R^1 = Ph, R^2 = H, R^3 = CN, R^4 = Ph
(**27**) $R^1 = R^2 = R^3$ = H, $R^4 = CO_2Et$

8.14.3.3 X-ray Studies

No systematic study of any of the individual systems falling within this chapter has been made. The nucleophilic addition of a 2*H*-pyrrole to phenyl isocyanate has been shown to yield a 2 : 1 molar adduct whose structure has been confirmed by x-ray crystallography as (**28**) ⟨89MI 814-01⟩.



(**28**)

8.14.4 THERMODYNAMIC ASPECTS

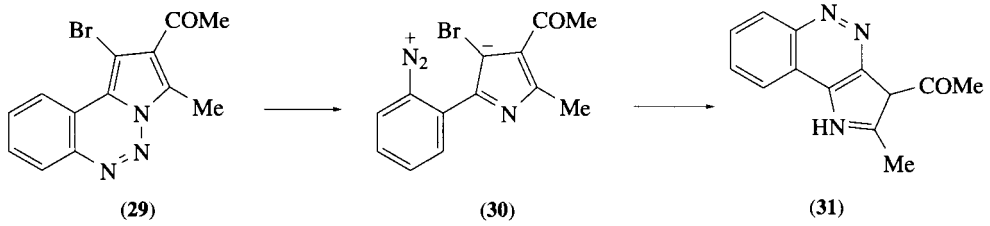
There has been no systematic study on the thermodynamic aspects of these systems.

8.14.5 REACTIVITY OF FULLY CONJUGATED RINGS

There have been few systematic studies on the reactivity of the pyrrolotriazines. The chemistry of the fully conjugated systems can best be understood by assuming that the system consists of a five-membered π-excessive heterocyclic ring that is fused to a six-membered π-deficient ring. Thus, electrophilic reagents are expected to attack the pyrrole carbons and nucleophilic reagents are expected to attack the six-membered ring. In general, the reactivity of the fully conjugated systems is similar to that found for indolizine.

8.14.5.1 Thermal and Photochemical Reactions

Treatment of the benzotriazine (**29**) with hydroxide ion in refluxing dimethylsulfoxide gave the pyrrolo[3,2-*c*]cinnoline derivative (**31**) (Scheme 1). The reaction can be envisaged as occurring by heterolytic cleavage of the N(1)—N(2) bond of (**29**) to yield the zwitterion (**30**), followed by electrophilic attack of the diazonium group on the negatively charged carbon atom and subsequent base-assisted elimination of bromonium ion. This azadehalogenation represented the first example of the Japp–Klingemann reaction in which the extrusion of positive halogen ion was verified ⟨90JHC983⟩.

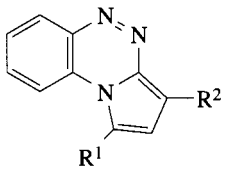


(**29**) (**30**) (**31**)

Scheme 1

8.14.5.2 Electrophilic Attack at Carbon

There have been no studies on electrophilic attack at nitrogen by proton acids, alkylating (or acylating) agents, halogen, peracids, Lewis acids, or aminating agents. There have been a few studies on the electrophilic substitution reactions at carbon, and they have confirmed the earlier assumptions on the sites of electrophilic attack. For the pyrrolo[1,2-*c*][1,2,4]triazine system, the experimentally determined sites of substitution were found to be identical to those predicted by molecular orbital theory (see Section 8.14.2). For example, (**32**) was converted to the 3-nitro derivative (**33**) by KNO_3/H_2SO_4, and sulfonation was shown to occur at the 3-position (**34**). Bromination (NBS/H_2SO_4) gave mainly the 1-bromo derivative (**35**) which rearranged to the 3-bromo derivative (**36**) on acid treatment; this is in contrast to the results of iodination with bispyridineiodonium nitrate, which gave the 1-iodo derivative (**37**) which, upon acid treatment, regenerated the parent base (**32**) ⟨71JCS(C)2018⟩.

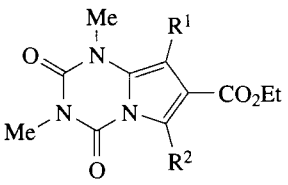


(**32**) $R^1 = R^2 = H$
(**33**) $R^1 = H$, $R^2 = NO_2$
(**34**) $R^1 = H$, $R^2 = SO_3H$
(**35**) $R^1 = Br$, $R^2 = H$
(**36**) $R^1 = H$, $R^2 = Br$
(**37**) $R^1 = I$, $R^2 = H$

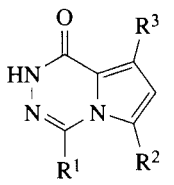
Treatment of the dimethyl derivative (**38**) with NBS gave a mixture of the 8-bromo (**39**) and 6,8-dibromo derivatives (**40**) ⟨74JCS(P1)1781⟩. Similarly, treatment of (**41**) with bromine in chloroform gave the monobromo derivative (**42**); however, nitration with nitric acid in sulfuric acid gave the dinitro derivative (**43**) ⟨73TL3239⟩. In a closely related study, nitration of (**44**) with the same nitrating agents was reported to give a mixture of (**45**) and (**46**). Treatment with one, two, or three equivalents of bromine in chloroform gave the monobromo (**47**), dibromo (**48**), and tribromo derivatives (**49**) ⟨80JHC631⟩.

8.14.5.3 Nucleophilic Attack at Carbon

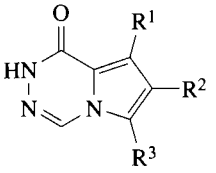
As expected, these ring systems undergo nucleophilic substitution reactions in the six-membered triazine ring. The chloro derivatives (**50**) readily undergo nucleophilic substitution reactions with sodium methoxide or ethoxide to yield the alkoxy derivatives (**51**) ⟨73TL3235⟩.



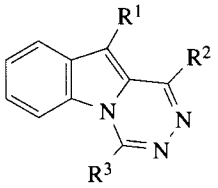
(**38**) $R^1 = R^2 = H$
(**39**) $R^1 = Br$, $R^2 = H$
(**40**) $R^1 = R^2 = Br$



(**41**) $R^1 = R^2 = H$
(**42**) $R^1 = Br$, $R^2 = H$
(**43**) $R^1 = R^2 = NO_2$



(**44**) $R^1 = R^2 = R^3 = H$
(**45**) $R^1 = NO_2$, $R^2 = R^3 = H$
(**46**) $R^1 = R^2 = H$, $R^3 = NO_2$
(**47**) $R^1 = R^2 = H$, $R^3 = Br$,
(**48**) $R^1 = R^3 = Br$, $R^2 = H$
(**49**) $R^1 = R^2 = R^3 = Br$



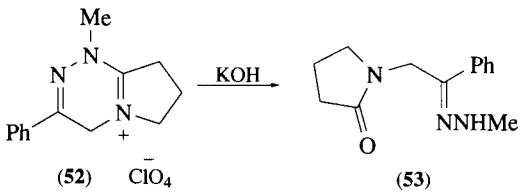
(**50**) $R^3 = Cl$
(**51**) $R^3 = OMe$ or OEt

8.14.6 REACTIVITY OF NONCONJUGATED RINGS

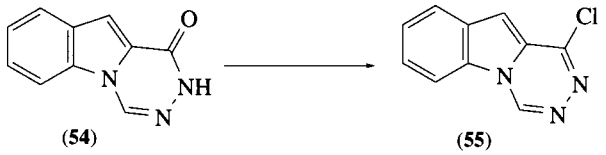
The majority of references dealing with nonconjugated systems primarily deal with those systems which contain oxo groups (either one or two) in the six-membered ring and thus can be considered to be in equilibrium with the corresponding hydroxy compound. However, the literature suggests that this equilibrium predominately favors the uncharged canonical oxo form. However, in those systems containing two oxo groups, the situation may be a little more complicated, since by analogy with the pyridazinediones where both oxygens are α to nitrogen, one might expect both to exist in the carbonyl form, in fact one exists in the hydroxyl form. Most of the systems covered behave as cyclic amides and are thus weakly basic. Strong nucleophiles of the type that attack amides generally do react with these systems; however, it is likely that the nucleophilic attack is preceded by electrophilic attack at the carbonyl oxygen.

8.14.6.1 Nucleophilic Attack at Carbon

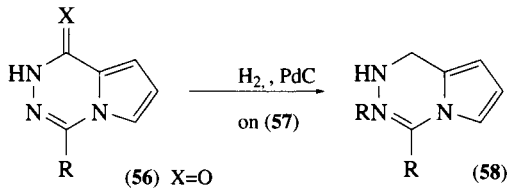
The majority of references deal with nucleophilic attack at the carbon atom of the carbonyl group to give substitution rather than ring opening. The only studies showing ring opening involve hydrolysis. Thus, hydrolysis of (**52**) with potassium hydroxide gives the lactam (**53**) (Equation (1)) ⟨87AP(320)258⟩. Treatment of (**54**) with $POCl_3$ gave the fully aromatic chloro derivative (**55**) (Equation (2)) ⟨80JHC77⟩, and treatment of (**56**) with phosphorus pentasulfide in pyridine gave the thione (**57**), which was catalytically hydrogenated to give (**58**) (Equation (3)) ⟨73TL3239, 79JHC1193⟩. Compound (**59**) was desulfurized with Raney nickel to give (**60**); catalytic hydrogenation of (**59**) gave (**61**) which was readily oxidized to (**60**) ⟨73TL3235⟩.



(**52**) ClO_4^- (**53**) (1)

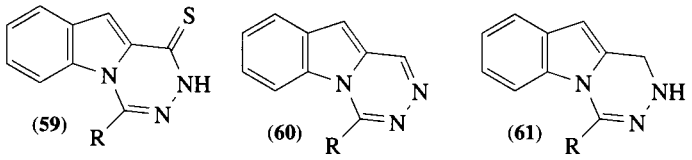


(54) (55) (2)



(56) X=O
(57) X=S

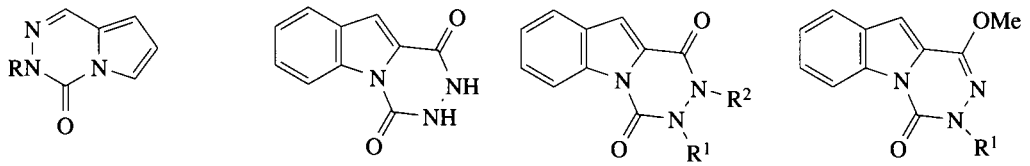
(58) (3)



(59) (60) (61)

8.14.6.2 Electrophilic Attack at Oxygen and Nitrogen

In systems with only one oxo moiety, electrophilic attack occurs at the nitrogen atom of the cyclic amide. Thus, (**62**) was methylated, using dimethyl sulfate, to yield the *N*-methyl analogue (**63**) ⟨72CR(C)1703⟩. However, systems closely related to the pyridazinones give mixtures of both *O*- and *N*-alkylated products. Thus, methylation of (**64**) with dimethyl sulfate gave a 9 : 1 mixture of (**65**) and (**66**). Methylation with diazomethane, however, in addition to (**65**) and (**66**), also gave (**67**) and (**68**) ⟨75CR(C)521⟩.



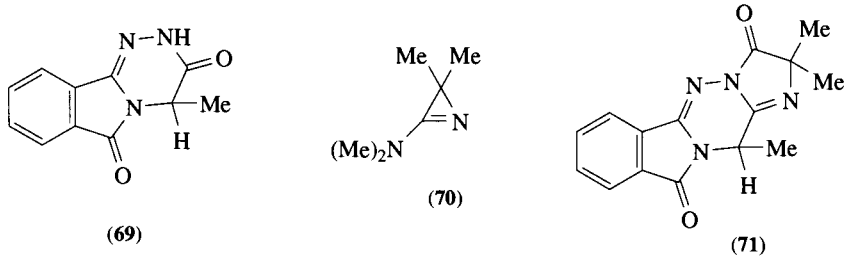
(**62**) R = H
(**63**) R = Me

(**64**)

(**65**) R^1 = Me, R^2 = H
(**67**) R^1 = R^2 = Me

(**66**) R^1 = Me
(**68**) R^1 = H

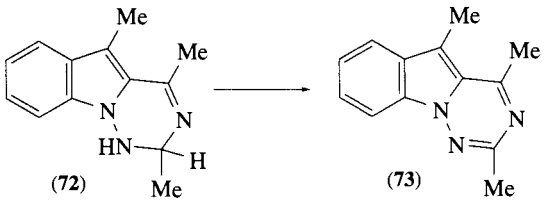
Compound (**69**) reacts with the 2*H*-azirine (**70**) to form the tetracyclic ring system (**71**), whose structure was confirmed by x-ray crystallography ⟨80HCA1797⟩.



(**69**) (**70**) (**71**)

8.14.6.3 Other Reactions

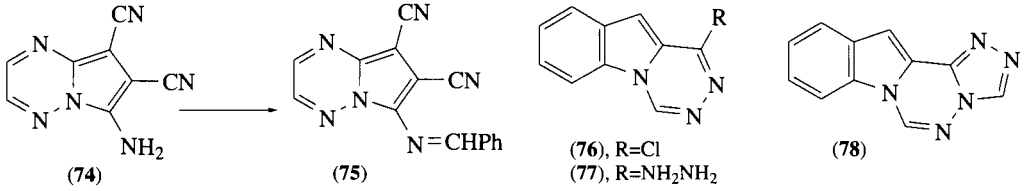
Compound (**72**) was readily oxidized either on exposure to air or by the action of chloranil to give the fully conjugated (**73**) (Equation (4)) ⟨75CPB2891⟩.



(4)

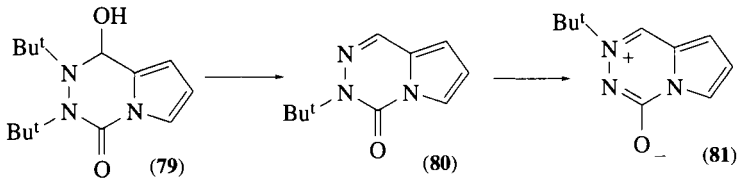
8.14.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Reaction of benzaldehyde with (**74**) gave the anil (**75**) ⟨62JOC2470⟩. The presence of the extra nitrogen atoms in the six-membered ring facilitates nucleophilic substitution with displacement of halogen. Thus, treatment of (**76**) with hydrazine gives the hydrazino derivative (**77**), which was subsequently condensed with formic acid to give the tetracyclic derivative (**78**) ⟨80JHC77⟩.



8.14.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Compound (**79**) was easily de-*t*-butylated by Lewis acid-catalyzed thermolysis to yield (**80**) and an isomeric betaine (**81**) (Equation (5)) ⟨93JOC6620⟩.

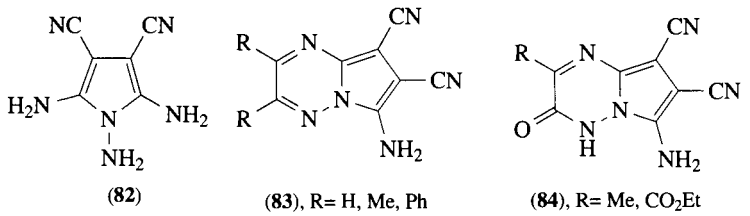


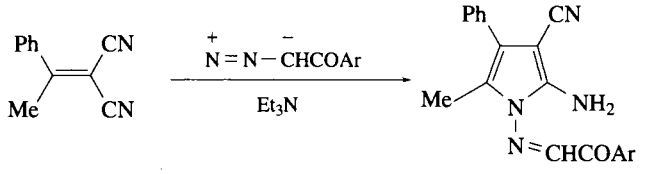
(5)

8.14.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

8.14.9.1 Pyrrolo[1,2-*b*][1,2,4]triazine (1)

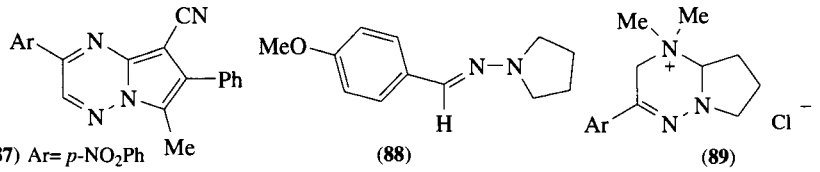
This synthesis is by closure of the triazine ring. Treatment of the diamino pyrrole (**82**) with glyoxal or 1,2-diketones gave the pyrrolotriazines (**83**) ⟨62JOC2470⟩. Treatment with ethyl pyruvate or diethyl oxomalonate gave the oxo derivatives (**84**). The reaction of alkylidenemalononitriles (**85**) with diazoketones under basic conditions gave the 1,4-cycloaddition product (**86**) (Equation (6)) which cyclized under basic conditions to yield (**87**) ⟨69JPR388⟩. Hydrazones (**88**) have also been shown to react with the Vilsmeier reagent to yield the pyrrolotriazinium salt (**89**) ⟨90CB2039⟩.





(6)

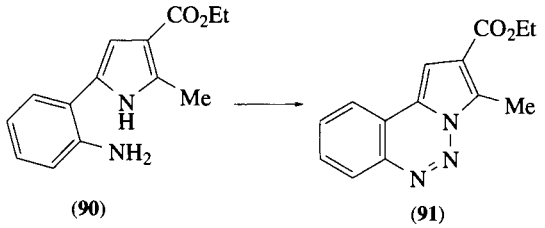
(85) (86)



(87) Ar= *p*-NO_2Ph (88) (89)

8.14.9.2 Pyrrolo[1,2-*c*][1,2,3]triazine (2)

This system is the most poorly studied of all the pyrrolotriazines and synthetic methods only exist for the synthesis of the benzo derivative (**91**) by diazotization of the aminophenyl pyrrole (**90**) (Equation (7)) ⟨71MI 814-01⟩.

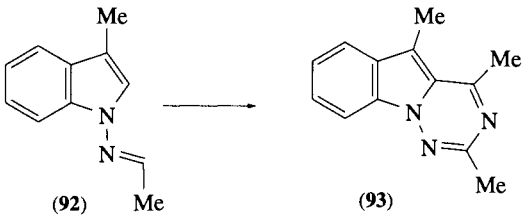


(7)

(90) (91)

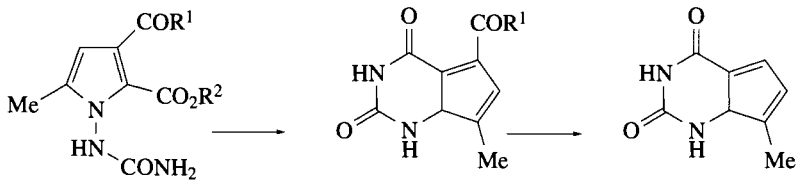
8.14.9.3 Pyrrolo[2,1-*f*][1,2,4]triazine (3)

The first method is by closure of the triazine ring. Intermolecular acid catalyzed Diels–Alder cyclization of (**92**) gave (**93**) (Equation (8)) ⟨75CPB2891⟩. 1-Ureidopyrroles (**94**) cyclized under basic conditions to give the dioxo compounds (**95**) (Scheme 2), which were readily decarboxylated at 280°C to the dione (**96**) ⟨79JHC833⟩.



(8)

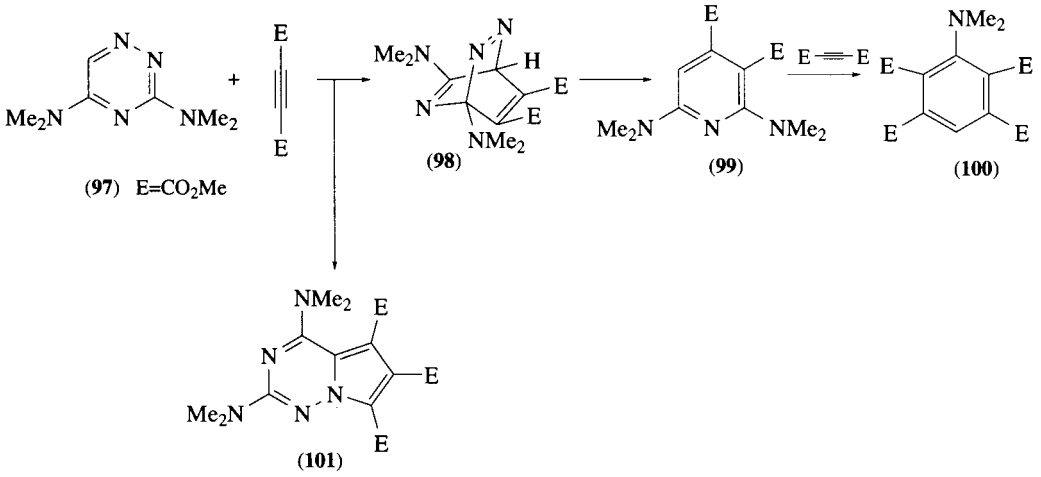
(92) (93)



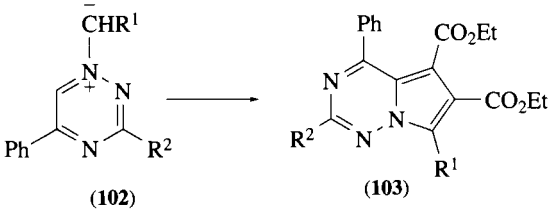
(94) (95) (96)

Scheme 2

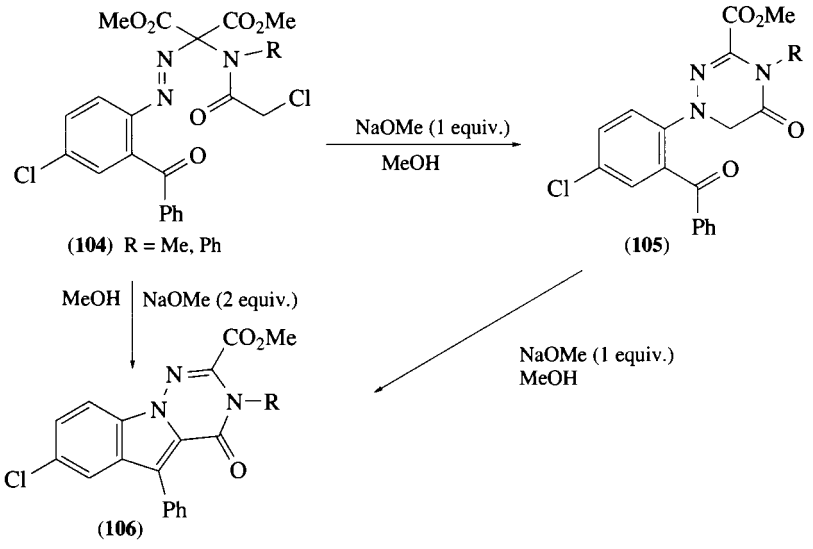
The second method is by closure of the pyrrole ring. A [4 + 2] cycloaddition between 1,2,4-triazine (**97**) and DMAD in chloroform (Scheme 3) gave three products identified as (**99**), (**100**), and (**101**) in 4.7%, 7.4%, and 22% yields, respectively. The formation of (**99**) and (**100**) can be rationalized by elimination of nitrogen from adduct (**98**) ⟨77LA1413⟩. The azomethine ylide (**102**) reacted (Equation (9)) with diethyl acetylenedicarboxylate to give the pyrrolotriazines (**103**) in good yields (Scheme 4) ⟨92MI 814-01⟩. Treatment of the azomalonates (**104**) with one equivalent of base gave the intermediate triazinones (**105**); further aldol-type condensation occurred upon treatment with another equivalent of base to yield (**106**), which may also be obtained by treatment of (**104**) with two equivalents of base (Scheme 4) ⟨90HCA1700⟩.



Scheme 3



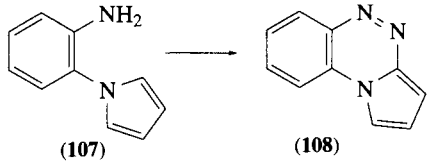
(9)



Scheme 4

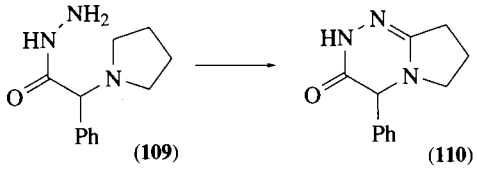
8.14.9.4 Pyrrolo[1,2-*c*][1,2,4]triazine (4)

Cyclization of *N*-(2-aminophenyl)pyrrole (**107**) with nitrous acid gave the benzo derivative (**108**) (Equation (10)) ⟨71JCS(C)2018⟩. Dehydrogenation of the hydrazide (**109**) with EDTA–Hg(II) gave (**110**) (Equation (11)) ⟨77AP(310)588⟩. Under similar conditions, the hydrazone (**111**) cyclized to give the dihydrotriazine (**112**), and the methylhydrazone (**113**) cyclized under acidic conditions ($HClO_4$) to give (**114**) ⟨87AP(320)198, 87AP(320)258⟩. Cyclization of the isoindole (**115**) with hydrazine hydrate gave (**116**) ⟨80HCA1797⟩. Improved yields were obtained from the lactam-*N*-acetic ester (**117**) via sulfurization with phosphorus pentasulfide and reaction of the resultant thiolactam (**118**) with hydrazine hydrate to give (**119**) ⟨82S853⟩.



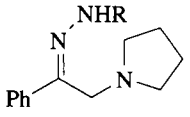
(10)

(107) (108)

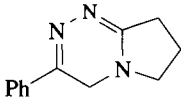


(11)

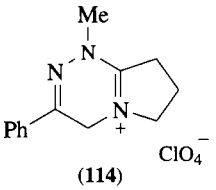
(109) (110)



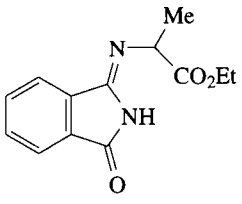
(111), R=H
(113), R=Me



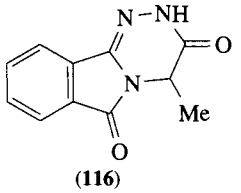
(112)



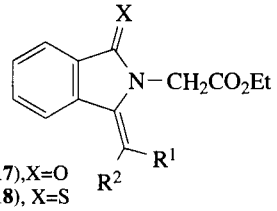
(114)



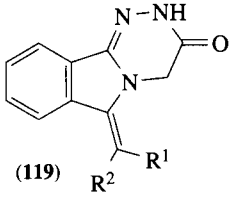
(115)



(116)

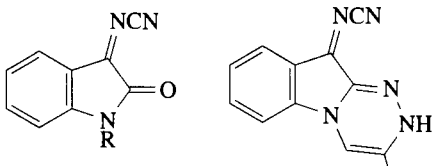


(117),X=O
(118), X=S



(119)

Reaction of the indole derivative (**120**) with phenacyl bromide in DMF gave the corresponding *N*-alkyl derivative (**121**), which was cyclized with hydrazine to give (**122**) ⟨91JIC621⟩.



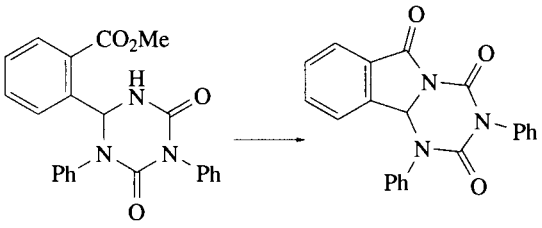
(120), R=H
(121), R=CH_2COPh

(122)

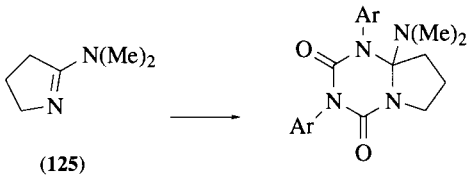
8.14.9.5 Pyrrolo[1,2-*a*][1,3,5]triazine (5)

The first method is by closure of the pyrrole ring. Thermolysis of the methyl ester (**123**) in benzonitrile gave (**124**) (Equation (12)) ⟨67CB1107⟩. Addition of aromatic isocyanates to the amidine

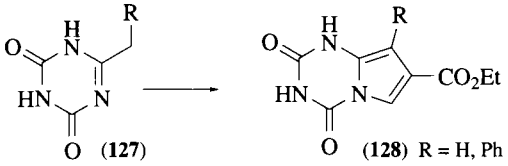
(**125**) gave the diones (**126**) (Equation (13)) ⟨68CB3002⟩. In a variation of the Tschitschibabin indolizine synthesis, treatment of ethyl bromopyruvate with the diones (**127**) in refluxing acetone gave the diones (**128**) (Equation (14)) ⟨74JCS(P1)1781⟩.



(**123**) (**124**) (12)

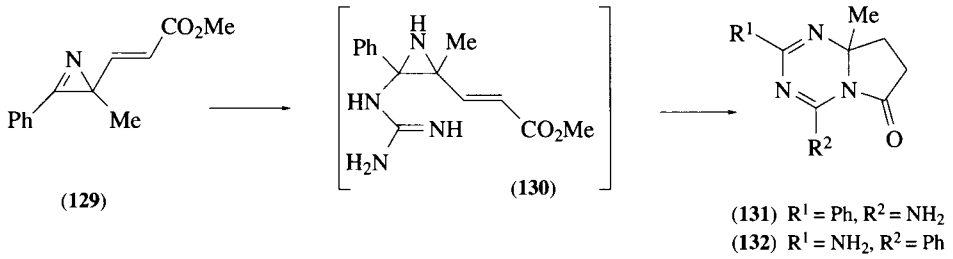


(**125**) (**126**) (13)



(**127**) (**128**) R = H, Ph (14)

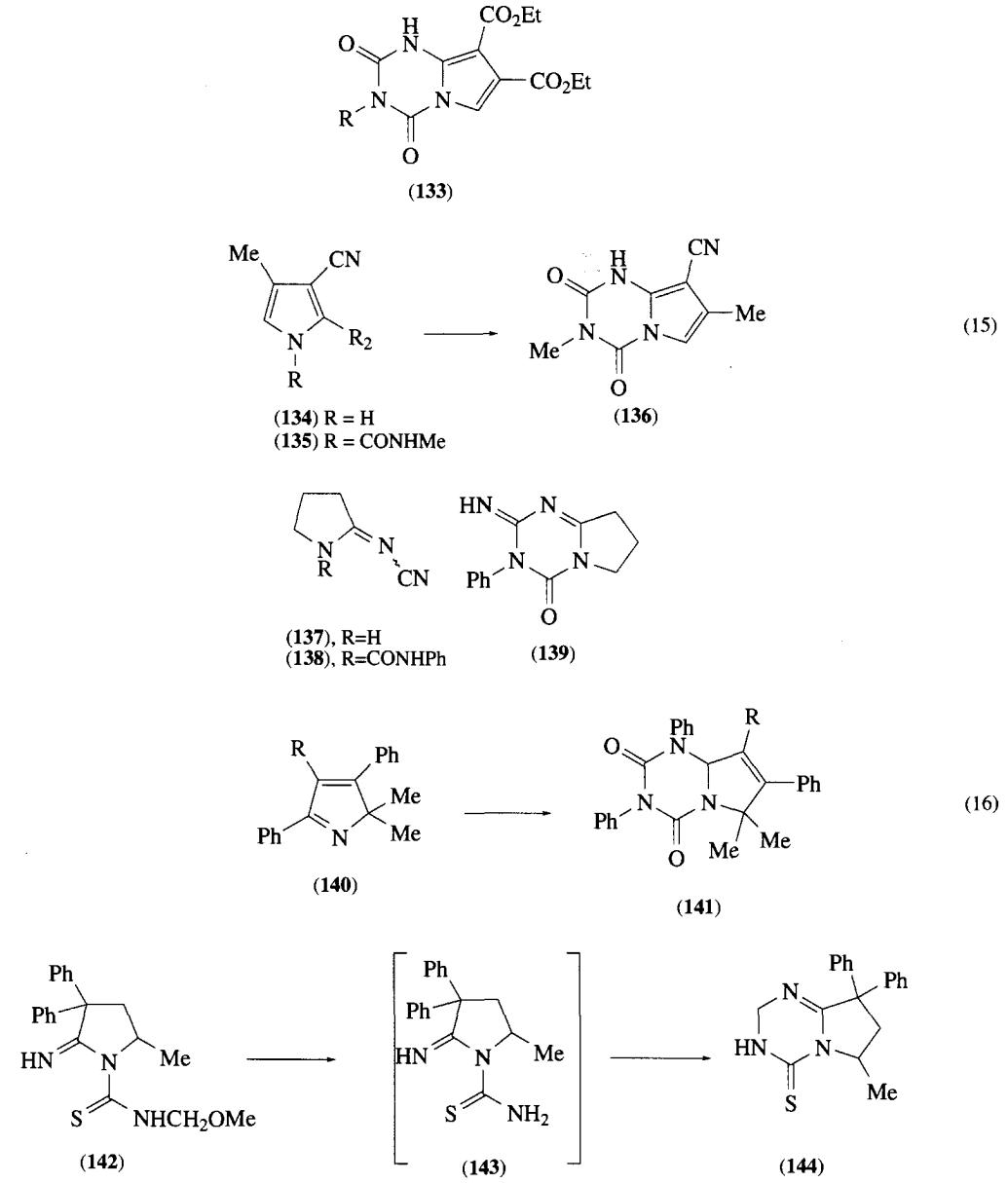
The reaction of the simple 1-azirine (**129**) with guanidine displayed a remarkable solvent effect (Scheme 5). In methanol, only complex mixtures were obtained but in dimethylsulfoxide the selective formation of (**131**) or (**132**) was observed. The proposed mechanism involves the formation of several different tautomers resulting from C—C bond cleavage in the aziridine intermediate (**130**). It was not possible spectroscopically to distinguish between (**131**) and (**132**) ⟨91JOC7⟩.



(**129**) (**130**) (**131**) R^1 = Ph, R^2 = NH_2 (**132**) R^1 = NH_2, R^2 = Ph

Scheme 5

The second method is closure of the triazine ring. Modification of the normally unreactive 2-aminopyrroles, by the incorporation of electron-withdrawing groups (e.g., esters) at positions 3 and 4, allowed condensation with alkyl or aryl isocyanates in refluxing pyridine to give dioxo compounds such as (**133**) ⟨74JCS(P1)1786⟩. Addition of methyl isocyanate to the aminopyrrole (**134**) in a molecular ratio of 3 : 1 gave the adduct (**135**), which was then cyclized in base to give (**136**) (Equation (15)) ⟨76CB2983⟩. Condensation of (**137**) with phenyl isocyanate in benzene gave the amide (**138**), which on heating with triethylamine (TEA) in toluene gave (**139**) ⟨91LA975⟩. The nucleophilic addition of 2*H*-pyrroles (**140**) to phenyl isocyanate gave a 2 : 1 molar adduct identified by x-ray crystallography as (**141**) (Equation (16)) ⟨89MI 814-01⟩. Acid hydrolysis of (**142**) gave (**144**) as one component of a number of stable end products of the reaction. The imine (**143**) was formed as an intermediate or an end product according to the conditions of the hydrolysis (Scheme 6) ⟨75M491⟩.

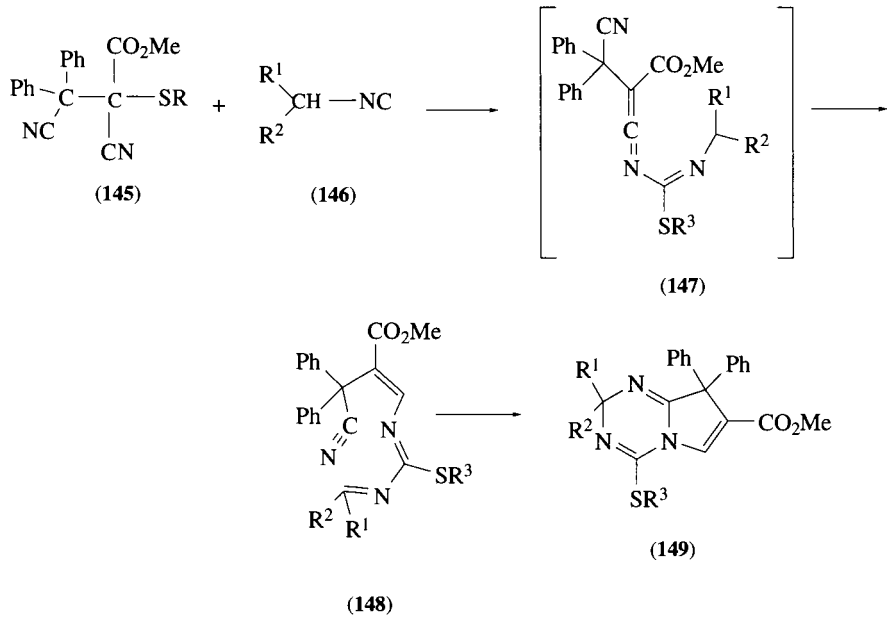


Scheme 6

The third method involves formation of both rings simultaneously. The ketene *N*-imidoylimines (**147**) were shown to be transitory intermediates formed by the reaction of isocyanides (**145**) with sulfides (**146**) (Scheme 7). When the nitrogen atom of the imidoyl group bears a primary or secondary substituent, the imines (**147**) were converted to the diazatrienes (**148**) by a very fast 1,5 migration of the hydrogen atom of the imidoyl group. This then underwent a [4 + 2] cycloaddition to form the dihydrotriazines (**149**) ⟨85JOC771⟩.

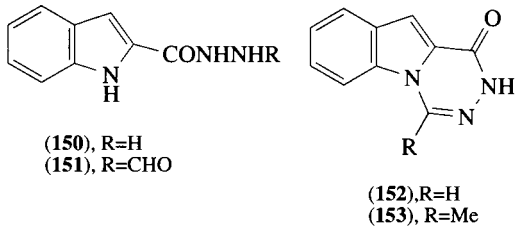
8.14.9.6 Pyrrolo[1,2-*d*][1,2,4]triazine (6)

Treatment of 2-indole carboxylic acid hydrazide (**150**) with triethylorthoformate in DMF or thermal cyclodehydration of (**151**) gave (**152**; R = H) ⟨80JHC77⟩. Reaction with triethyl *ortho*-acetate gave the corresponding methyl analogue (**153**) ⟨89JPS780⟩. The parent heterocycle (**155**) was first prepared by base-catalyzed cyclodehydration of the formyl hydrazone (**154**) (Equation (17)) ⟨73JCS(C)35⟩. Acid-catalyzed cyclization of hydrazones (**156**) yielded the triazinones (**157**); the formylhydrazone (**156**; R = CHO) yielded (**157**; R = H) (Scheme 8).



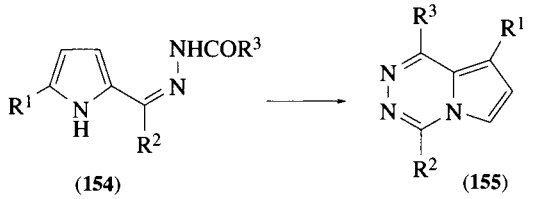
(145) (146) (147) (148) (149)

Scheme 7



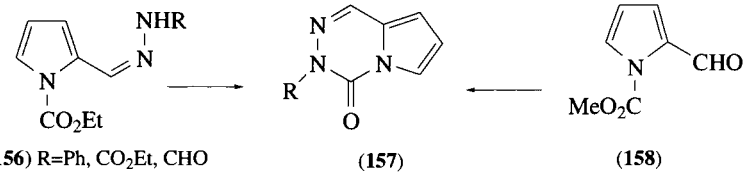
(150), R=H
(151), R=CHO

(152),R=H
(153), R=Me



(154) (155)

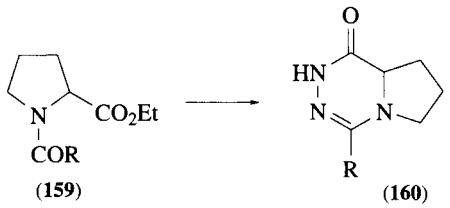
(17)



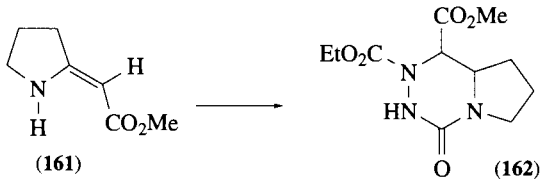
(156) R=Ph, CO_2Et, CHO (157) (158)

Scheme 8

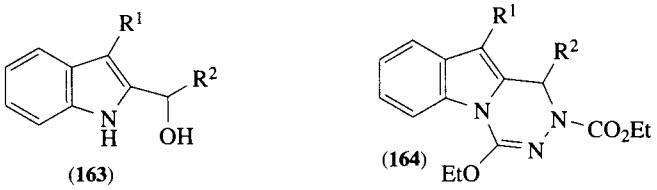
Treatment of the pyrrole (**158**) with hydrazines gave (**157**) ⟨72CR(C)1703⟩. Reaction of the tetrahydropyrrole (**159**) with hydrazine in ethanol gave the triazine (**160**) (Equation (18)) ⟨83T3419⟩. Reaction of (**161**) with *n*-butyl lithium and dead gave (**162**) in excellent yields (Equation (19)) ⟨88AP(321)491⟩. Using the Mitsunobo reagent (dead, Ph_3P), alcohol (**163**) was cyclized to the triazinoindole (**164**) ⟨84AG(E)518⟩. The 2-formyl- (**165**) and 2-cyanopyrrole (**166**) possess an endocyclic nucleophilic nitrogen atom and an electrophilic group, and are usually poor nucleophiles, even in their anionic forms, but it has been shown that the highly reactive diaziridinone (**167**) reacts with both of these compounds. Thus, reaction of (**167**) and deprotonated (**165**) gave (**168**) in good yields. Under similar conditions, (**166**) gave an acyclic 1 : 1 adduct (**169**) which was cyclized under acid catalysis to (**170**) and a de-*t*-butylated compound (Equation (20)) ⟨93JOC6620⟩.



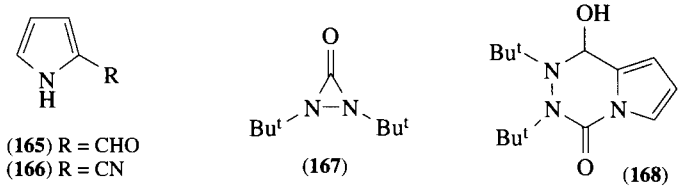
(159) (160) (18)



(161) (162) (19)

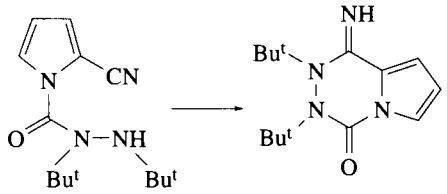


(163) (164)



(165) R = CHO
(166) R = CN

(167) (168)

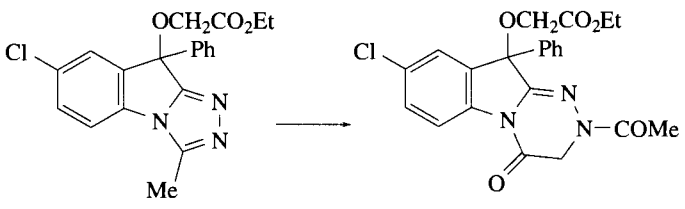


(169) (170) (20)

8.14.10 RING SYNTHESES BY TRANSFORMATION OF ANOTHER RING

8.14.10.1 Pyrrolo[1,2-*c*][1,2,4]triazine (4)

The only reported synthesis of this ring system by transformation of another ring system involved treatment of the triazoloindoline (**171**) with ethyl bromoacetate and alkaline workup to give the lactam (**172**) (Equation (21)) ⟨75JHC717⟩.

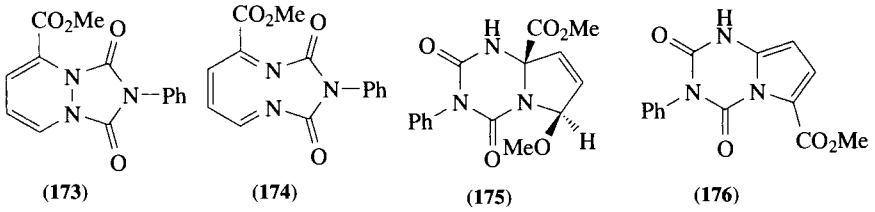


(171) (172) (21)

8.14.10.2 Pyrrolo[1,2-*a*][1,3,5]triazine (5)

The cleavage of the N—N bond in bicyclic systems containing bridgehead hydrazine presents a facile route to medium-size heterocycles containing two or more heteroatoms.

Photolysis of (**173**) gave (**174**) by electrocyclic ring opening, followed by transannular addition of methanol to give (**175**). Addition–elimination of methanol to (**174**) gave (**176**) ⟨84JOC587⟩.

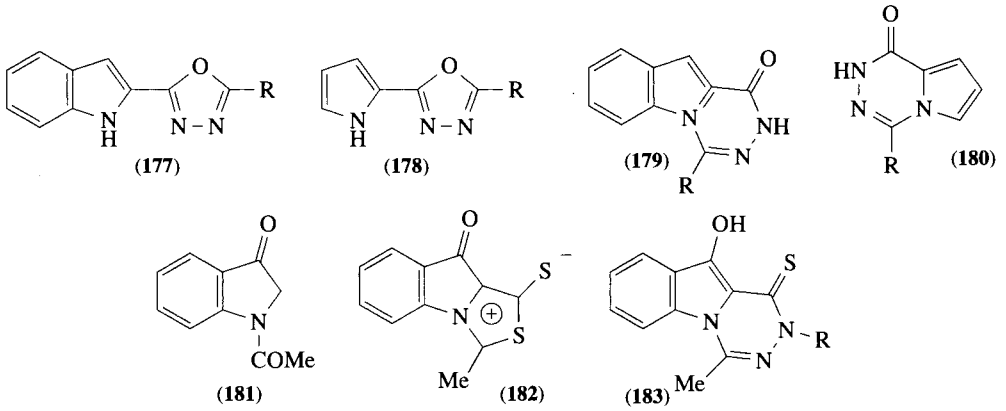


(**173**) (**174**) (**175**) (**176**)

8.14.10.3 Pyrrolo[1,2-*d*][1,2,4]triazine (6)

One of the most common methods for the synthesis of this ring system involves the base-catalyzed ring opening of an oxadiazoyl indole (**177**) or pyrrolyloxadiazole (**178**) to yield either a triazinoindole (**179**) or a pyrrolotriazine (**180**) ⟨73TL3235, 73TL3239⟩.

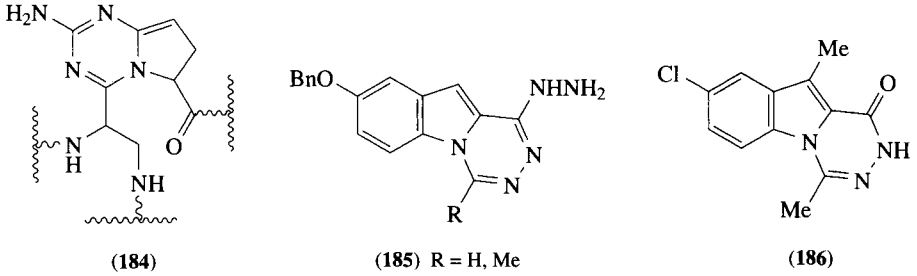
Treatment of (**181**) with carbon disulfide in the presence of sodium hydride gave the mesoionic compound (**182**) which upon reaction with hydrazine gave (**183**) ⟨75YZ980⟩.



(**177**) (**178**) (**179**) (**180**) (**181**) (**182**) (**183**)

8.14.11 IMPORTANT COMPOUNDS AND APPLICATIONS

The *Streptomyces* antibiotic, viomycin, has been shown to be tuberculostatic. Degradation studies have suggested that the structure of the compound contains the fragment best represented by (**184**) ⟨65TL585⟩. A series of 1-hydrazinotriazinoindoles (e.g., (**185**)) were shown to be potent anti-hypertensive agents, which although not as effective as hydralazine, were considerably less toxic ⟨83MI 814-01⟩. Compound (**186**) was shown to be a potent antimicrobial agent with good activity against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* ⟨89JPS780⟩.



(**184**) (**185**) R = H, Me (**186**)

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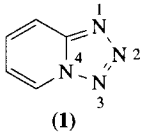
8.15
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 3 : 0

Dr GYÖRGY HAJÓS
Hungarian Academy of Sciences, Budapest, Hungary

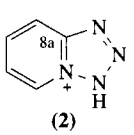
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8.15.1 INTRODUCTION

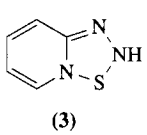
This chapter reviews those 5-6 fused systems having three extra heteroatoms either in the five- or the six-membered ring. Very few such systems exist. Most data is available on tetrazolo[1,5-*a*]pyridine (**1**), its protonated (or quaternized) cation (**2**) and the benzologues of these. A concise survey on spectral properties, reactivity, and synthesis can be found in the first edition ⟨84CHEC-I(5)847⟩, respectively. Thiatriazolopyridines (derivatives of (**3**)) have also been synthesized, but since the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(5)847⟩ further reports about them can be found in the literature. Only one bicyclic ring system having the three heteroatoms in the six-membered ring is known; pyrrolo[1,2-*b*][1,2,4,5]tetrazine (**4**) which also will be discussed here.



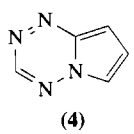
(**1**)



(**2**)



(**3**)



(**4**)

8.15.2 THEORETICAL METHODS

Molecular orbital analysis of tetrazolo[1,5-*a*]pyridine (**1**) using the CNDO/2 method has been carried out ⟨88JOC973⟩ and the coefficients of the ring nitrogen atoms of the HOMO (π-type) and "n-HOMO" (the highest σ-type MO) have been compared (Table 1).

Table 1 Coefficients of the HOMO (π-type) and 'n-HOMO' (the highest σ-type HOMO) of nitrogen atoms of tetrazolo[1,5-*a*]pyridine (**1**).

	N-1	*N-2*	*N-3*
c^2_{HOMO}	0.28	0.00	0.27
$c^2_{n\text{-}HOMO}$	0.07	0.06	0.01

The two sets of values differed to a considerable extent; that of the n-HOMO proved to be in good correlation with the experimental findings in alkylation reactions.

Molecular orbital calculations for tetrazolo[1,5-*a*]pyridinium cation (**2**) showed that the highest coefficient (c_{LUMO}) values can be found, except the bridgehead N-4, for C-5 and C-8a atoms which satisfactorily explained the observed selective nucleophilic attacks at these centers ⟨86T5415⟩.

8.15.3 EXPERIMENTAL STRUCTURAL METHODS

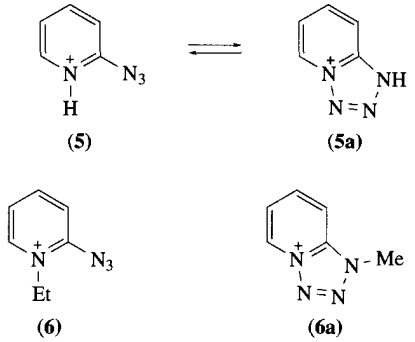
8.15.3.1 NMR Studies

The ^{1}H NMR spectrum of (**1**) has been described ⟨84CHEC-I(5)847⟩. Several studies on ^{13}C NMR investigation of (**1**) have appeared (Table 2) ⟨80AJC499, 80AJC1275, 87JHC805⟩. The comparison of the ^{13}C NMR shifts and the calculated (INDO) electron charge distribution for (**1**) showed a satisfactory correlation ⟨80JST(64)15⟩.

Table 2 Carbon-13 NMR shifts of carbon atoms of tetrazolo[1,5-*a*]-pyridine (**1**).

	C-5	*C-6*	*C-7*	*C-8*	*C-8a*
^{13}C shift	126.5	117.4	133.2	115.2	148.2

A ^{13}C NMR study on (**1**) under strongly protonating conditions ⟨86AQ(C)61⟩ has also been carried out to determine the position of the equilibrium between the protonated azide (**5**) and the protonated tetrazolopyridinium salt (**5a**). Comparison of the ^{13}C NMR values of (**1**) in trifluoroacetic acid (i.e., those of (**5**) or (**5a**)) with those of 2-azido-1-ethylpyridinium salt (**6**) and 1-methyltetrazolo[1,5-*a*]pyridinium salt (**6a**) revealed unambiguously that the bicyclic cation (**5a**) is present under these conditions.



(5) (5a) (1)

(6) (6a)

The ^{14}N NMR spectrum of (**1**) measured in an earlier study ⟨79JMR(36)227⟩ showed that the ring junction nitrogen atom has the sharpest signal, whereas the "pyridine-type" nitrogen atoms are

broadened due to the significant quadrupolar relaxation and therefore, these could only be assigned by the help of assumptions of field gradient calculations.

The ^{15}N NMR investigation of (**1**) in different solvents has been published and the observed and calculated nitrogen shielding values have been compared ⟨80AJC499, 84OMR(22)209⟩. Generally a sequence of nitrogen shielding of N-4 > N-1 > N-3 > N-2 has been observed. The most reliable assignment was made by combination of ^{14}N and ^{15}N NMR results (Table 3) ⟨89MI 815-01⟩.

Table 3 Nitrogen-15 NMR shifts of nitrogen atoms of tetrazolo[1,5-*a*]-pyridine (**1**).

^{15}N shift solvent	*N-1*	*N-2*	*N-3*	*N-4*
Acetone + $Cr(acac)_3$	+70.0	−17.1	+34.4	+131.9
Me_2SO	+67.8	−18.3	+31.8	+128.3

Me $^{15}NO_2$ was used as external standard.

8.15.3.2 Photoelectron Spectroscopic Investigations

Photoelectron spectroscopy was applied to study the azide–tetrazole equilibrium of (**1**). The observed bands were correlated with calculated (MNDO) ionization potentials ⟨81MI 815-01, 82MI 815-01, 90ZN(B)59⟩. Measurements carried out at different temperatures revealed that the equilibrium is clearly shifted to the azide with higher temperatures.

8.15.3.3 X-ray Analyses

The low temperature x-ray determination of 3-phenyltetrazolo[1,5-*a*]pyridinium tetrafluoroborate ((**21**), Ar = phenyl, A = BF_4) has been published ⟨79AX(B)2145⟩ which showed that the ring system is almost planar, and has a medium aromaticity.

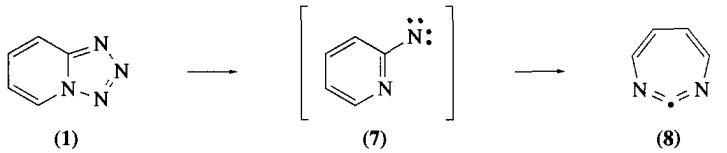
8.15.4 THERMODYNAMIC ASPECTS

On the basis of the photoelectron spectroscopic results (see Section 8.15.3.2; ⟨81MI 815-01⟩) thermodynamic properties for the azido–tetrazole equilibrium of (**1**) in vapor phase have also been investigated. Equilibrium constants have been determined, and the following parameters have been found: $\Delta G^\circ_{391} = 0.4$ kcal mole^{-1}, $\Delta H^\circ = 1.8$ kcal mole^{-1}, $\Delta S^\circ = 3.5$ cal K^{-1}mol^{-1}.

8.15.5 REACTIVITY OF THE RINGS

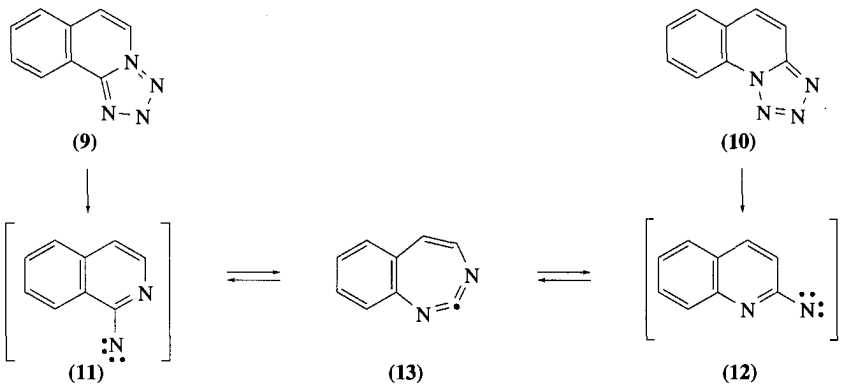
Flash vacuum pyrolysis of tetrazolo[1,5-*a*]pyridine (**1**) and its benzologues (**9**), (**10**), and (**14**) have been investigated in detail ⟨80JA6159, 82BSB997, 86AG(E)480, 92JCS(P1)1062⟩. In all cases, nitrenes were formed first (e.g., tetrazolo[1,5-*a*]pyridine (**1**) afforded nitrene (**7**)) which rapidly underwent subsequent simultaneous reactions, affording cyclic carbodiimides. Thus, the carbodiimide (**8**) was isolated from the reaction of (**1**) (Scheme 1). Tetrazolo[5,1-*a*]isoquinoline (**9**) and tetrazolo[1,5-*a*]quinoline (**10**) gave the same bicyclic carbodiimide (**13**), whereas the linearly fused tetrazolo[1,5-*b*]isoquinoline (**14**) led to the nitrene (**15**) which gave the carbodiimide (**16**) (Schemes 2 and 3).

Studies on photolysis and thermolysis of mono and bis trifluoromethyl derivatives of (**1**) resulted in formation of the correspondingly substituted derivatives of (**8**) as the only products.



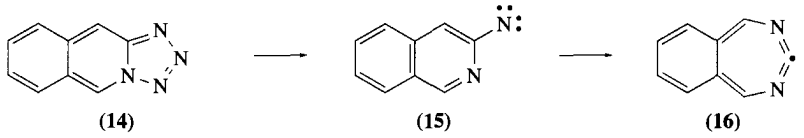
(1) (7) (8)

Scheme 1



(9) (10) (11) (13) (12)

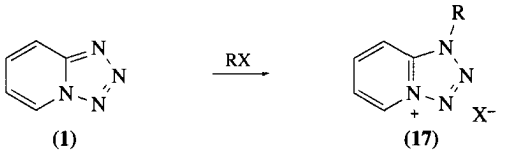
Scheme 2



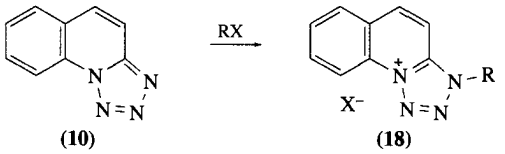
(14) (15) (16)

Scheme 3

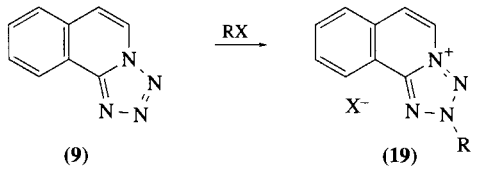
Previously only a few publications have appeared on the alkylation of tetrazolo[1,5-*a*]pyridine (**1**) ⟨75JCS(P1)1232⟩ and tetrazolo[1,5-*a*]quinoline (**10**) ⟨63BEP630906⟩, and formation of the alkyl salts (**17**; R = Me) and (**18**; R = Et), respectively, have been reported. A more detailed study ⟨88JOC973⟩ on the alkylation of the bicycle (**1**) and its tricyclic benzologues ((**10**), (**9**), and (**14**)) revealed that, in all cases, both nitrogen atoms, N-1 and N-2, undergo alkylation, but not even traces of N-3-alkylated product could be detected. In accord with the earlier findings with tetrazoles (**1**) and (**10**), alkylated salts (**17**; R = Me or R = Et) and (**18**; R = CH_3 or C_2H_5) were found as main products with alkylating agents of different kinds. The 1-alkyl salt (**20**) was found also to be formed from the linearly fused tetrazolo[1,5-*b*]isoquinoline (**14**; R = Me or Et), whereas the angularly fused isomer (**9**), obviously for steric reasons, afforded mainly 2-substituted salts (**19**) (Equations (2)–(5)). The fact of the steric hindrance was convincingly shown by the finding that the percentage of this isomer produced was even higher when an ethyl group was introduced instead of methyl.



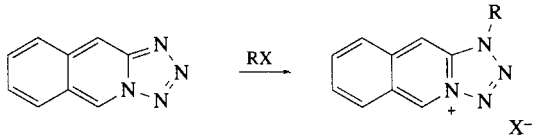
(1) (17) (2)



(10) (18) (3)



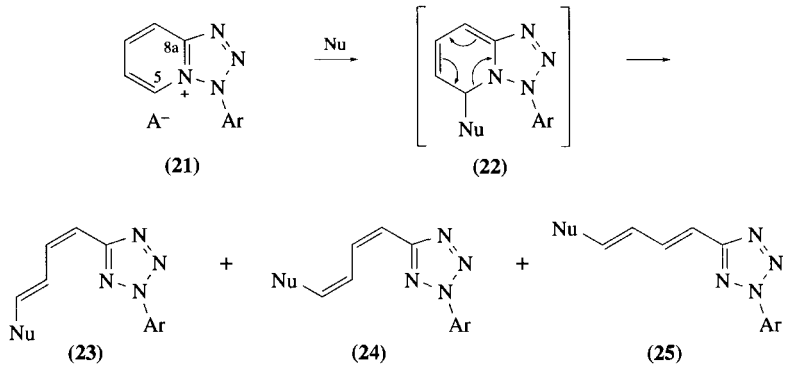
(9) (19) (4)



(14) (20) (5)

The bicyclic and tricyclic tetrazoles ((**1**), (**9**), and (**10**)) could also be arylated ⟨85M1227⟩ directly by diphenyliodonium tetrafluoroborate with a similar regioselectivity as was shown in the alkylation reactions. Thus, 1-phenyltetrazolo[1,5-*a*]pyridinium fluoroborate (**17**; R = Ph, X = BF_4) and 2-phenyltetrazolo[5,1-*a*]isoquinolinium fluoroborate (**19**; R = Ph, X = BF_4) were prepared.

Investigations of reactions of 3-aryl-tetrazolopyridinium salts (**21**) with nucleophiles ⟨80TL663, 86T4827, 88M1113, 92T8451⟩ showed that the reagents attack the heteroaromatic cation at positions 5 or 8a depending on the nature of the reagent. Certain nucleophiles (e.g., secondary amines, cyanide ion, borohydride ion) form a pseudo base-like intermediate (**22**), which rapidly undergoes a retro-electrocyclization with opening of the pyridine moiety to give tetrazolylbutadienes. These products can be obtained as *cis–trans* (**23**), *cis–cis* (**24**), or full *trans* isomers (**25**) (Scheme 4).



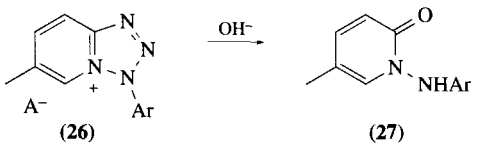
(21) (22)

(23) (24) (25)

Scheme 4

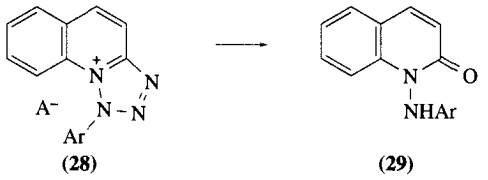
The *trans–trans* products (**25**) are mostly formed in reactions of (**21**) with secondary amines, where the isomerization of the presumably primarily formed (**23**) and/or (**24**) to (**25**) is promoted by the protic conditions. Under aprotic conditions, on the other hand (e.g., in reactions of (**21**) with alcoholates or the sodium salts of secondary amines) different mixtures of the *cis–trans* (**23**) and *cis–cis* (**24**) products were obtained, the ratio of which was rationalized by supposing a nitrogen inversion in the intermediate (**22**). It was concluded ⟨92TL8451⟩ that the smaller the size and the higher the electron-withdrawing property of the nucleophile, the higher the ratio of the *cis–cis* isomer (**24**). Thus, the (**24**) : (**23**) ratio was found 92 : 8 for cyanide ion, 40 : 60 for ethoxide ion, and 80 : 20 for trifluoroethoxide ion (Ar = *p*-chlorophenyl).

In many cases the reaction of the tetrazolopyridinium salt (**21**) with nucleophiles is not regiospecific and takes place at C-5 and C-8a simultaneously. When the reagent attacks the tetrazolium salt (**21**) at position 8a, nitrogen elimination occurs ⟨86T4827⟩. This was observed as the only reaction when 7-methyltetrazolo[1,5-*a*]pyridinium salt (**26**) was treated with tetramethylammonium hydroxide, and the *N*-anilino-2-pyridone (**27**) was isolated in good yield (Equation (6)).

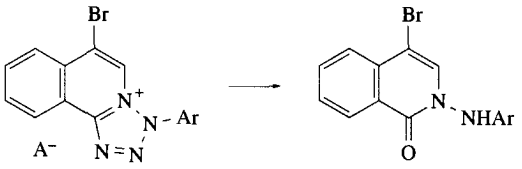


(26) (27) (6)

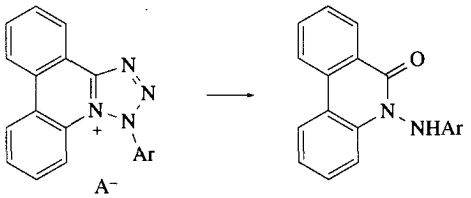
Similar reactions were found with the angularly fused benzologues of the tetrazolopyridinium salt: 1-aryltetrazolo[1,5-*a*]quinolinium (**28**), 3-aryl-6-bromotetrazolo[5,1-*a*]isoquinolinium (**30**), and 3-aryltetrazolo[1,5-*f*]phenanthridinium salts (**32**). All these three fused tetrazolium salts underwent nitrogen elimination reactions with hydroxide anion and afforded analogous products: the salt (**28**) gave the *N*-anilinoquinolone (**29**), the salt (**30**) yielded the *N*-anilinoisoquinolone (**31**), and the tetracyclic tetrazolium salt (**32**) led to the *N*-anilinophenanthridone (**33**) (Equations (7), (8), and (9)).



(28) (29) (7)

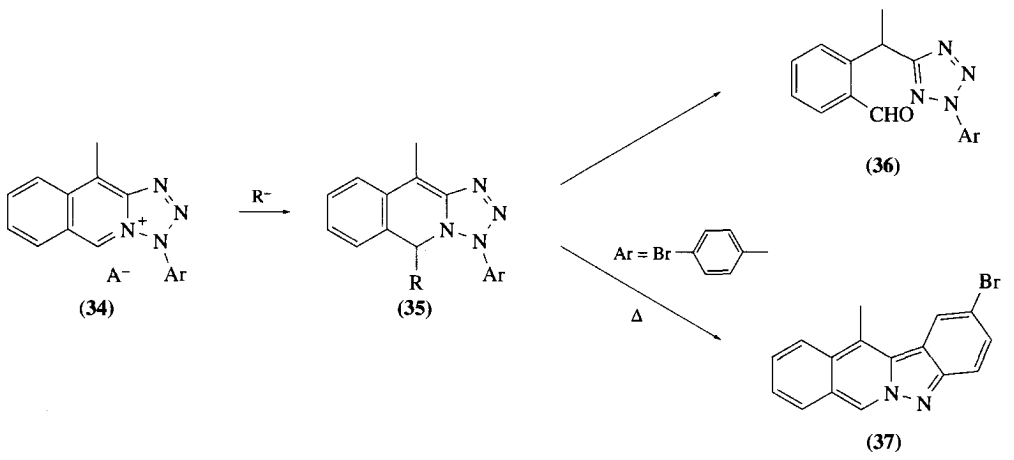


(30) (31) (8)



(32) (33) (9)

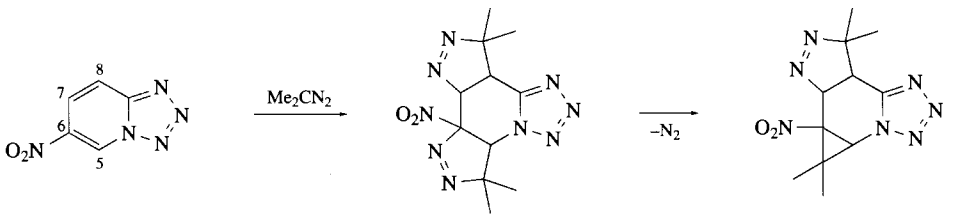
The linearly-fused tricyclic tetrazolium salt (**34**) showed different behavior ⟨86T5415⟩. This compound gave two products simultaneously; a tetrazolyltolualdehyde derivative (**36**), and a tetracyclic indazolo[2,3-*b*]isoquinoline (**37**) (Scheme 5). Investigation of the reaction mechanism revealed that both reaction paths proceed via the same intermediate (**35**) which could also be isolated with R = OEt or SEt groups. The regioselective reactions of the fused tetrazolium salts with different annelation was explained in terms of FMO theory (see Section 8.15.2).



(34) (35) (36) (37)

Scheme 5

A study of the ability of tetrazolo[1,5-*a*]pyridines to act as dipolarophiles in 1,3-dipolar cycloadditions showed that the presence of a nitro group in the pyridine moiety is necessary for transformations with diazopropane ⟨89H(28)259⟩. When 6-nitrotetrazolo[1,5-*a*]pyridine (**38**) was treated with this reagent, both double bonds C-5—C-6 and C-7—C-8 reacted and the bis-cycloadduct (**39**) was formed which easily underwent nitrogen elimination to give the product (**40**) (Scheme 6).

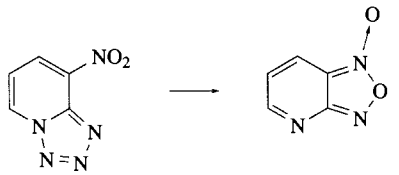


(38) (39) (40)

Scheme 6

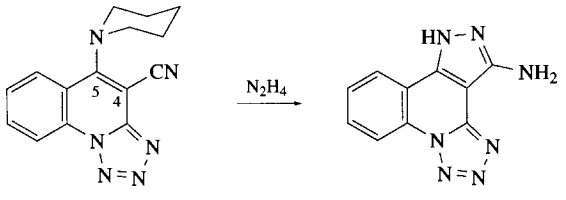
8.15.6 REACTIVITY OF SUBSTITUENTS

Although the ring transformation of 8-nitrotetrazolo[1,5-*a*]pyridine (**41**) to oxadiazolo[3,4-*b*]pyridine-1-oxide (**42**) has been known for a long time ⟨53JA5298⟩, the reinvestigation of this conversion ⟨80M407, 90JOC3755⟩ led to elaboration of a safe laboratory procedure for the synthesis of this fairly unstable product (**42**) (Equation (10)).

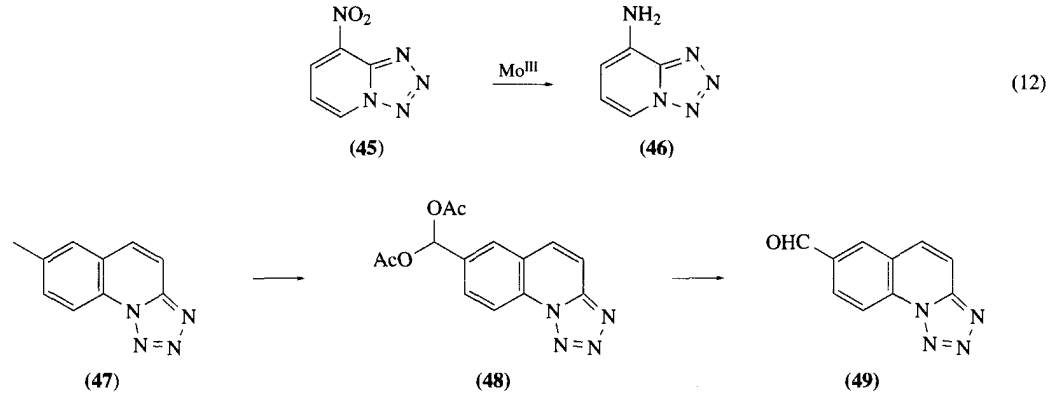


(41) (42) (10)

With some tetrazolo[1,5-*a*]quinoline derivatives, an additional ring closure to a fused pyrazole moiety was reported ⟨93BCJ2936⟩; the tetrazoloquinoline derivative (**43**) bearing a cyano and a morpholino group at neighbouring positions (at C-4 and C-5, respectively) was reacted with hydrazine to give the tetracyclic pyrazolo[4,3-*c*]quinoline heteroaromatic system (**44**) (Equation (11)). Additional, more routine, conversions of substituents of tetrazolo[1,5-*a*]pyridine and tetrazolo[1,5-*a*]quinoline have also been published. Thus, reduction of 8-nitrotetrazolo[1,5-*a*]pyridine (**45**) by molybdenum(III) reagent gave selectively 8-aminotetrazolo[1,5-*a*]pyridine (**46**) in high yield (Equation (12)) ⟨80S129⟩. Transformation of the 7-methyl group of tetrazolo[1,5-*a*]quinoline (**47**) to the 7-aldehyde (**49**) through the diacetyloxymethyl compound (**48**) has also been reported ⟨89H1085⟩ (Scheme 7).



(43) (44) (11)



(45) (46) (12)

(47) (48) (49)

Scheme 7

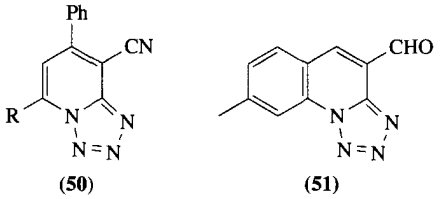
8.15.7 RING SYNTHESES

8.15.7.1 Synthesis of Tetrazolo[5,1-*a*]pyridines

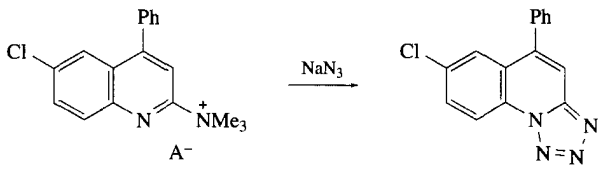
8.15.7.1.1 Synthesis of neutral unsaturated ring systems

As described in CHEC-I ⟨84CHEC(5)901⟩ the most general routes to the title ring systems involve two approaches; (i) nucleophilic substitution of 2-halopyridines (and benzologues) by azide to 2-azido derivatives followed by electrocyclization to tetrazole and (ii) transformation of 2-hydrazinopyridines (and benzologues) by nitrous acid through to the same azido compound.

These common procedures have also been applied in examples not reported in CHEC-I. Thus, 8-cyano-5-R-7-phenyltetrazolo[1,5-*a*]pyridines (**50**; R = Me and *p*-Me-C_6H_4) ⟨76KGS1085, 86MI 815-01⟩ and 4-formyl-8-methyltetrazolo[1,5-*a*]quinoline (**51**) ⟨81JCS(P1)2509⟩ have been synthesized by reacting the corresponding α-chloroazine with sodium azide. Analogous transformations of 1-chloroisoquinolines have also been reported ⟨93IJC(B)675⟩. The reaction of 6-chloro-4-phenyl-2-trimethylaminoquinolinium salt (**52**) with sodium azide ⟨86AP(319)338⟩ to give the tetrazoloquinoline derivative (**53**) represents in principle the same method (Equation (13)).



(50) (51)

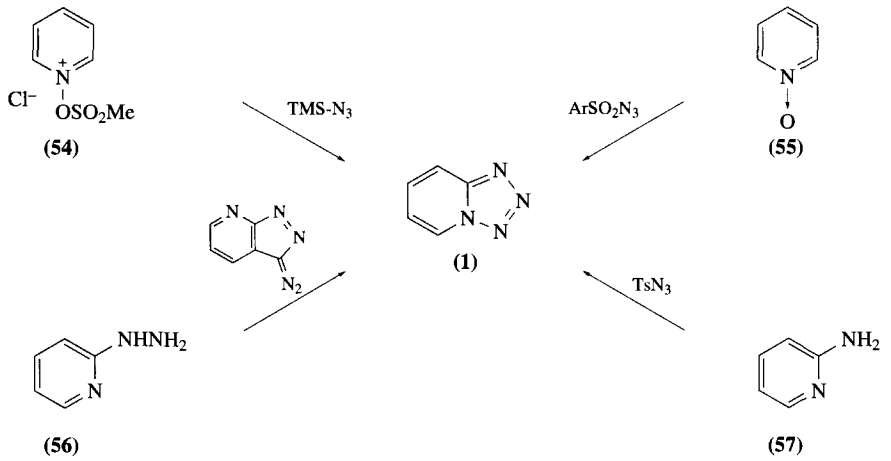


(52) (53) (13)

Some new approaches to tetrazolopyridine and its benzologues have also been reported. 1-Methylsulfonyloxypyridinium chloride (**54**) was found to react with trimethylsilylazide ⟨85BCJ2419⟩ and gave tetrazolopyridine (**1**) in 29% yield. The same reagent was successfully applied for the synthesis of tetrazolo[1,5-*a*]quinoline (**10**) from the analogous starting material, in 64% yield.

Pyridine-*N*-oxide (**55**) when reacted with sulfonylazides gave directly tetrazolopyridine (**1**) (yield: 40%) ⟨83CL1745⟩. Tetrazolo[1,5-*a*]quinoline (**10**) and tetrazolo[5,1-*a*]isoquinoline (**9**) were analogously synthesized in 70% to 75% yields.

Aza-transfer reactions were successfully applied to the synthesis of fused tetrazoles and represent a substantially new approach to this class of compounds. Thus, 2-hydrazinopyridine (**56**) was reacted with 3-diazopyrazolo[3,4-*b*]pyridine to give the tetrazole (**1**) ⟨78JHC1175⟩. The same product (**1**) was obtained from 2-aminopyridine (**57**) by reaction with tosylazide (Scheme 8) ⟨79JHC1567⟩.



Scheme 8

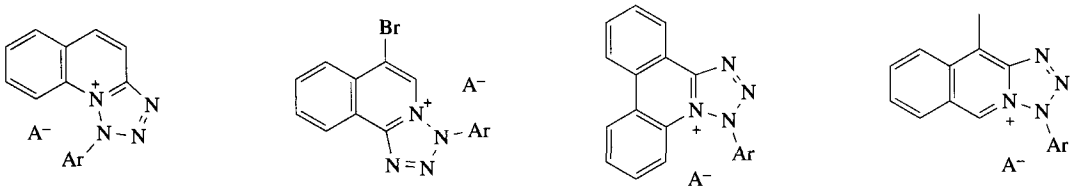
8.15.7.1.2 Synthesis of charged unsaturated ring systems

A simple ring closure to 3-aryltetrazolo[1,5-*a*]pyridinium salts (**21**) starting from α-pyridyltriazene (**58**) has been described ⟨65AG171⟩ and was later reinvestigated and extended for some benzologue cases (Equation (14)) ⟨86T4827, 86T5415⟩.



(58) (21) (14)

As a result, 1-aryltetrazoloquinolinium salts (**28**), 3-aryl-6-bromotetrazolo[5,1-*a*]isoquinolinium salts (**30**), 3-aryl-10-methyltetrazolo[1,5-*b*]isoquinolinium salts (**34**), and 3-aryltetrazolo[1,5-*f*]phenanthridinium salts (**32**) have been synthesized in good yields. These products with yields and m.p.s are summarized in Table 4.



(28) (30) (32) (34)

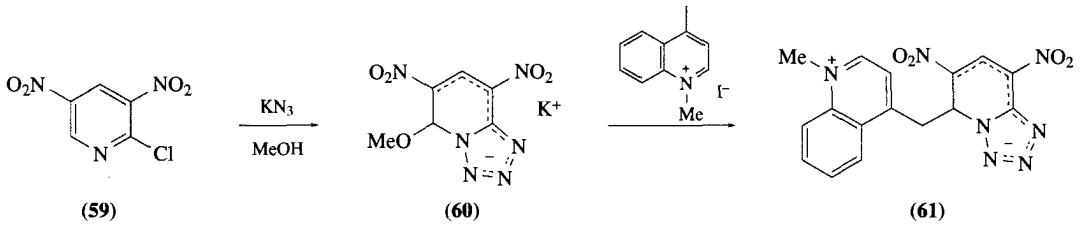
In the reaction of 2-chloro-3,5-dinitropyridine (**59**) with potassium azide in methanol ⟨92KGS1145⟩ formation of the tetrazolo[1,5-*a*]pyridine ring system was followed by addition of the methoxide ion to give the potassium salt (**60**) (Scheme 9).

Subsequent reaction of (**60**) with 1,4-dimethylquinolinium iodide resulted in formation of the zwitterion (**61**) ⟨92KGS1146⟩.

Table 4 Some experimental data (m.p. %) of fused tetrazolium salts obtained by ring closure of azinyltriazenes.

Ring system[a]	*Ar*	*R*	*A*−	*m.p.*	*%*
tetrazolo[1,5-*a*]Py	p-CH_3O-C_6H_4−	H	BF_4	179	89
(**21**)	p-Cl-C_6H_4−	H	BF_4	198	85
	p-Br-C_6H_4−	H	BF_4	207	84
	Ph−	7-Me	BF_4	198	78
	p-Br-C_6H_4−	7-Me	BF_4	228	92
	Ph−	H	BF_4	246	84
	p-Cl-C_6H_4−	5-Me	BF_4	204	61
	p-Cl-C_6H_4−	6-Me	BF_4	204	78
	p-Cl-C_6H_4−	8-Me	BF_4	208	76
tetrazolo[1,5-*a*]Q	Ph−	H	BF_4	209	82
(**28**)	p-Cl-C_6H_4−	H	BF_4	248	87
	p-Br-C_6H_4−	H	BF_4	208	79
	3,4-di-Cl-C_6H_3−	H	BF_4	258	74
tetrazolo[5,1-*a*]IQ	Ph−	6-Br	BF_4	292	53
(**30**)	p-Br-C_6H_4−	6-Br	BF_4	200	72
tetrazolo[1,5-*b*]IQ	p-Br-C_6H_4−	10-Me	BF_4	252	61
(**34**)	p-Cl-C_6H_4−	10-Me	BF_4	238	63
	p-F-C_6H_4−	10-Me	BF_4	233	60
	p-NO_2-C_6H_4−	10-Me	Br	228	55
	p-NO_2-C_6H_4−	5-Br-10-Me	Br	147	33
tetrazolo[1,5-*f*]Ph	p-Br-C_6H_4−	H	Br	240	66
(**32**)	p-F-C_6H_4−	H	BF_4	241	45

[a]Py = pyridine; Q = quinoline; IQ = isoquinoline; Ph = phenanthridine.

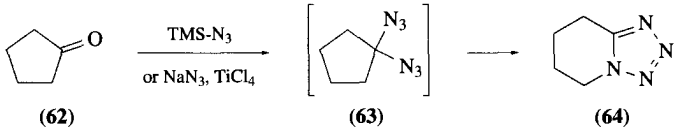


(**59**) (**60**) (**61**)

Scheme 9

8.15.7.1.3 Synthesis of partially saturated ring systems

Tetrahydrotetrazolo[1,5-*a*]pyridine (**64**) has been synthesized by reacting cyclopentanone (**62**) with trimethylsilylazide ⟨84CL455, 93S1218⟩. The reaction was thought to proceed through the geminal diazide (**63**) and therefore particular care should be taken with these transformations (Scheme 10). An analogous reaction by using hydrazoic acid–borontrifluoride has been reported starting from the benzologue system (**65**) to afford 4,5-dihydrotetrazolo[5,1-*a*]isoquinoline (**66**) (Equation (15)) ⟨92IJC(B)610⟩.



(**62**) (**63**) (**64**)

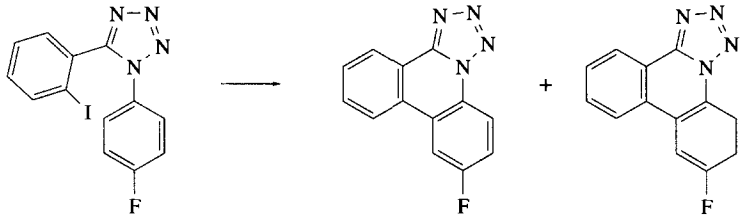
Scheme 10



(**65**) (**66**) (15)

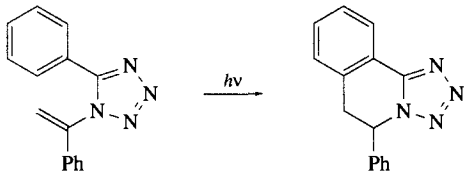
Investigation of the photolysis and electrochemical reduction of 1-(4-fluorophenyl)-5-(2-iodophenyl)tetrazole (**67**) showed formation of two products ⟨93JCS(P1)1557⟩. In the photolysis experi-

ments, 7-fluorotetrazolo[1,5-*f*]phenanthridine (**68**) was obtained in high yield, whereas electrolytic reduction of the same starting compound (**67**) afforded the partially reduced derivative (**69**) as the main product (Equation (16)).

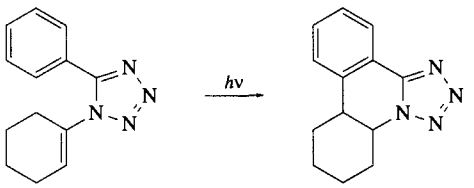


(67) (68) (69) (16)

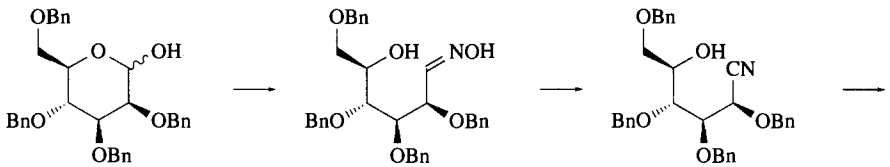
Partially saturated fused tetrazoles were also formed in photolytical transformations of some phenyl-alkenyltetrazoles ⟨82CC714, 84JCS(P1)1933, 87JCS(P1)1389⟩. The derivative (**70**) containing a phenylethenyl side chain at the position (N-1) adjacent to the phenyl substituent afforded the partially reduced phenyltetrazolo[5,1-*a*]isoquinoline (**71**) (Equation (17)). The related starting compound (**72**) having the unsaturated side chain closed into a ring (i.e., having a cycloalkenyl substituent) gave the analogous tetrazolo[1,5-*f*]phenanthridine (**73**) (Equation (18)). In another study a protected carbohydrate derivative, tetrabenzylmannose (**74**), was used as a starting material to fused saturated tetrazoles ⟨82JCS(P1)2139, 93CAR113⟩. The synthetic path starting from (**74**) led first to the ring opened oxime (**75**), which was first dehydrated to the cyano compound (**76**); an oxidation step led to the oxo derivative (**77**) which was reduced and subsequently tosylated to (**78**; R = Ts). This compound was reacted with sodium azide to give the optically active final product (**79**) (Scheme 11).



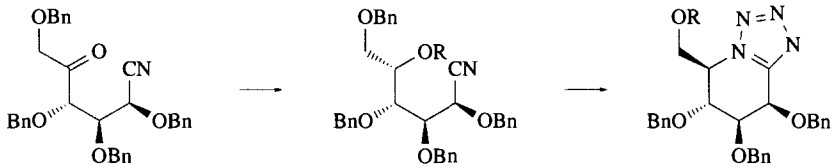
(70) (71) (17)



(72) (73) (18)



(74) (75) (76)

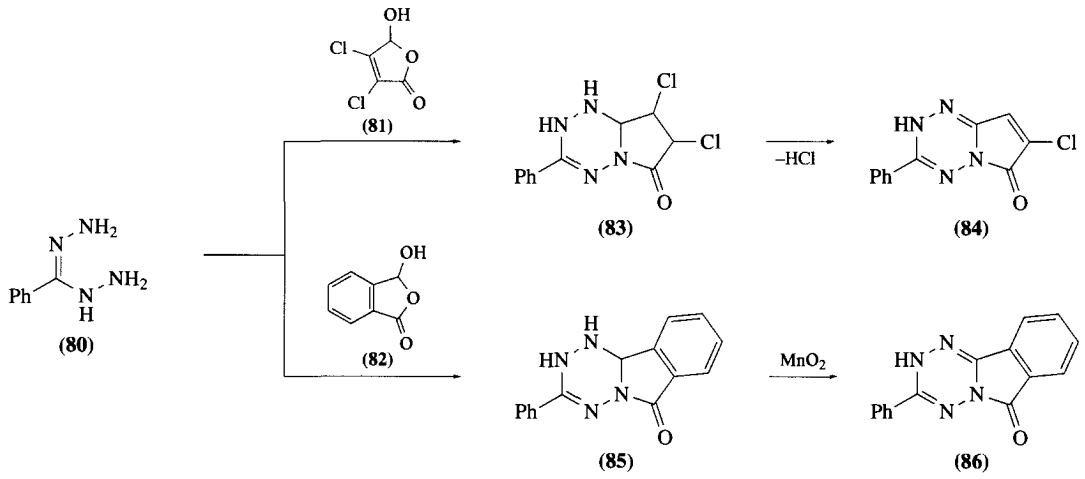


(77) (78) (79)

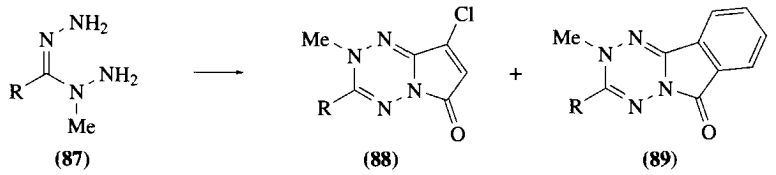
Scheme 11

8.15.7.2 Synthesis of Pyrrolo[1,2-*b*][1,2,4,5]tetrazines

Substituted hydrazidines (**80**) were found to react with cyclic lactones to give partially saturated derivatives of the title ring system and its benzologue ⟨92LA115⟩. Thus, the dichloro substituted lactone (**81**) afforded the product (**83**) which upon elimination of hydrogen chloride gave the monochloro compound (**84**). A similar reaction was reported when the bicyclic lactone (**82**) was used; (**85**) was formed as a primary product and was oxidized by manganese dioxide to give the indolo[2,1-*b*][1,2,4,5]tetrazine compound (**86**) (Scheme 12). Analogous products were formed in transformations of the *N*-methyl substituted starting compound (**87**); with the reagents (**81**) and (**82**) the *N*-methyl products (**88**) and (**89**), respectively, were obtained (Equation (19)).



Scheme 12

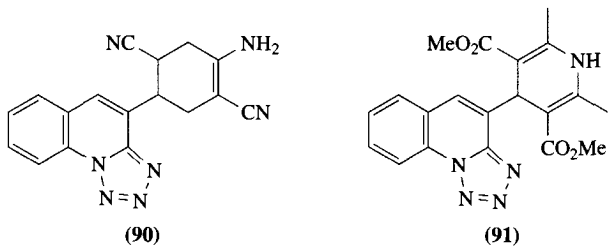


(19)

8.15.8 IMPORTANT COMPOUNDS AND APPLICATIONS

Among the fused tetrazoles, tetrazolo[1,5-*a*]quinoline derivatives were mostly found active in various biological applications.

Thus, some derivatives were found to have anxiolytic activity ⟨93YZ400⟩. A substituted tetrazoloquinoline compound (**90**) showed, furthermore, antileishmanial and contragestational effects ⟨89IJC(B)562⟩. This ring system was also built in as a side chain into 1,4-dihydropyridines ⟨89JMC2297⟩; the derivative (**91**) showed the pregnancy-interceptive property in mated hamsters.



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8.16
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 2 : 1

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8.16.1 INTRODUCTION

As many as 57 different ring systems are appropriate for inclusion in this chapter. On the basis of the six-membered ring component, the following classification can be made.

8.16.1.1 Fused Oxazines and Thiazines

Three fused oxazines and thiazines, [1,2,4]triazolo[3,4-*c*][1,4]oxazine (**3**) ⟨84CHEC-I(5)852⟩, [1,2,3]triazolo[5,1-*c*][1,4]oxazine (**4**) ⟨84CHEC-I(5)852⟩ and [1,2,4]triazolo[3,4-*b*][1,3]thiazine (**6**) ⟨84CHEC-I(5)852⟩, have already been mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). However, the additional seven ring systems (**1**), (**2**), (**5**), (**7**), (**8**), (**9**), (**10**), as well as the three tricyclic benzologs (**11**), (**12**), and (**13**) are discussed here for the first time.

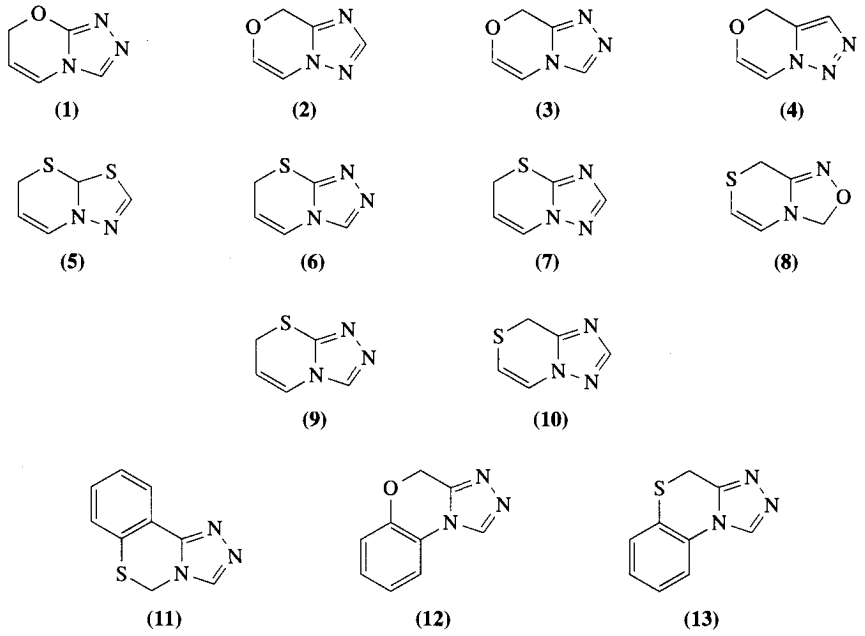


Figure 1 Fused oxazines and thiazines.

8.16.1.2 Fused Pyridazines and Pyrazines

Most of these ring systems (except (**23**)) have already been described in CHEC-I. These are as follows: [1,2,4]thiadiazolo[2,3-*b*]pyridazine (**14**) ⟨84CHEC-I(6)741⟩, [1,2,4]triazolo[4,3-*b*]pyridazine (**15**) ⟨84CHEC-I(5)868⟩, [1,2,4]triazolo[1,5-*b*]pyridazine (**16**) ⟨84CHEC-I(5)868⟩, [1,2,3]triazolo[1,5-*b*]pyridazine (**17**) ⟨84CHEC-I(5)852⟩, [1,2,4]thiadiazolo[4,3-*a*]pyrazine (**18**) ⟨84CHEC-I(6)742⟩, [1,2,4]thiadiazolo[2,3-*a*]pyrazine (**19**) ⟨84CHEC-I(6)741⟩, [1,2,4]triazolo[4,3-*a*]pyrazine (**20**) ⟨84CHEC-I(5)877⟩, [1,2,4]triazolo[1,5-*a*]pyrazine (**21**) ⟨84CHEC-I(5)877⟩, [1,2,3]triazolo[1,5-*a*]pyrazine (**22**) ⟨84CHEC-I(5)877⟩, as well as two benzologous tricycles: [1,2,4]triazolo[4,3-*a*]quinoxaline (**24**) ⟨84CHEC-I(5)878⟩ and [1,2,3]triazolo[1,5-*a*]quinoxaline (**25**) ⟨84CHEC-I(5)878⟩.

8.16.1.3 Oxa-, Thia-, and Selenadiazole-fused Pyrimidines

Some of these have been discussed earlier—[1,2,4]oxadiazolo[2,3-*a*]pyrimidine (**27**) ⟨84CHEC-I(6)713⟩, [1,2,5]oxadiazolo[2,3-*a*]pyrimidine (**28**) ⟨84CHEC-I(6)727⟩, [1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**30**) ⟨84CHEC-I(6)743⟩, [1,2,4]thiadiazolo[3,2-*a*]pyrimidine (**31**) ⟨84CHEC-I(6)741⟩, and [1,3,4]selenadiazolo[3,2-*a*]pyrimidine (**32**) ⟨84CHEC-I(5)142⟩—whereas the ring systems (**26**), (**29**), (**33**), (**34**), and (**35**) are first discussed in this edition.

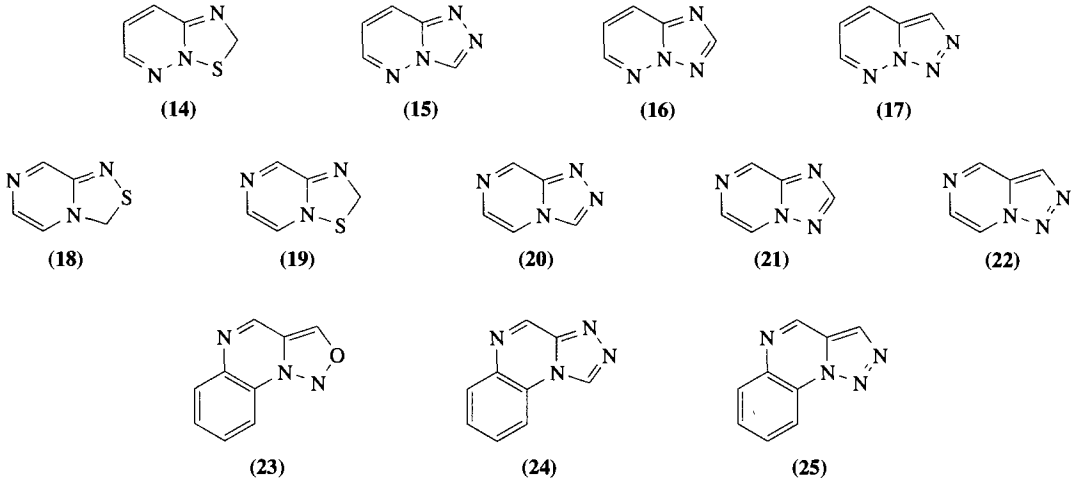


Figure 2 Fused pyridazines and pyrazines.

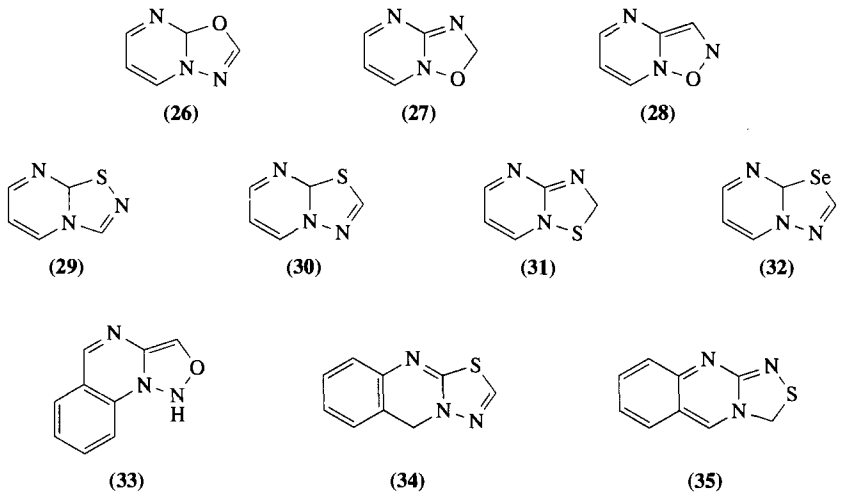


Figure 3 Oxa-, thia-, and selenadiazole-fused pyrimidines.

8.16.1.4 Triazoles Fused to the a-Site of Pyrimidine

With the exception of the tricyclic benzologue (**40**), all these have already been mentioned in the first edition. There are three bicyclic systems—[1,2,4]triazolo[4,3-*a*]pyrimidine (**36**) ⟨84CHEC-I(5)861⟩, [1,2,4]triazolo[1,5-*a*]pyrimidine (**37**) ⟨84CHEC-I(5)864⟩, [1,2,3]triazolo[1,5-*a*]pyrimidine (**38**) ⟨84CHEC-I(5)866⟩—and four differently annelated benzologues: [1,2,4]triazolo[4,3-*a*]quinazoline (**39**) ⟨84CHEC-I(5)893⟩, [1,2,4]triazolo[1,5-*a*]quinazoline (**41**) ⟨84CHEC-I(5)873⟩, [1,2,4]triazolo[5,1-*b*]quinazoline (**42**) ⟨84CHEC-I(5)874⟩ and [1,2,3]triazolo[1,5-*a*]quinazoline (**43**) ⟨84CHEC-I(5)876⟩.

8.16.1.5 Azoles Fused to the c-Site of Pyrimidine

Seven ring systems—(**44**), (**46**), (**47**), (**48**), (**52**), (**53**), (**54**)—are discussed in this edition. Some chemistry of the others can be found in CHEC-I: [1,2,4]oxadiazolo[2,3-*c*]pyrimidine (**45**) ⟨84CHEC-I(6)724⟩, [1,2,4]triazolo[4,3-*c*]pyrimidine (**49**) ⟨84CHEC-I(5)872⟩, [1,2,4]triazolo[1,5-*c*]pyrimidine (**50**) ⟨84CHEC-I(5)873⟩, [1,2,3]triazolo[1,5-*c*]pyrimidine (**51**) ⟨84CHEC-I(5)875⟩, and the tricycles [1,2,4]triazolo[4,3-*c*]quinazoline (**55**) ⟨84CHEC-I(5)873⟩, [1,2,4]triazolo[1,5-*c*]quinazoline (**56**) ⟨84CHEC-I(5)873⟩ and [1,2,4]oxadiazolo[2,3-*c*]quinazoline (**57**) ⟨84CHEC-I(6)714⟩.

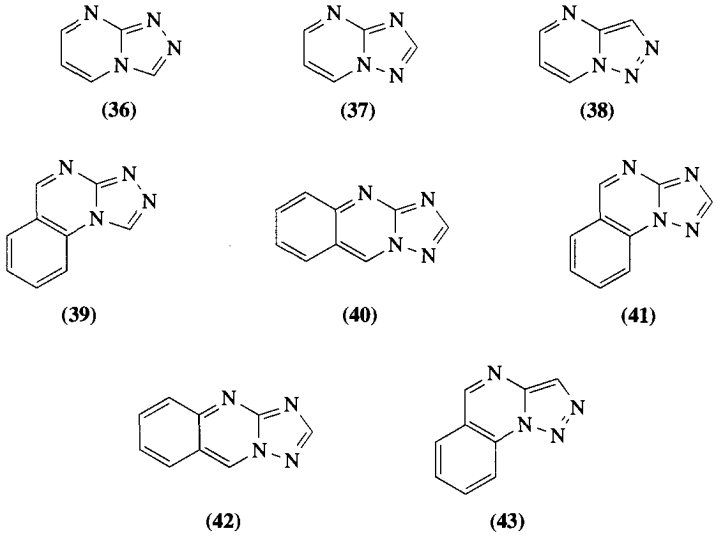


Figure 4 Triazoles fused to the a-site of pyrimidine.

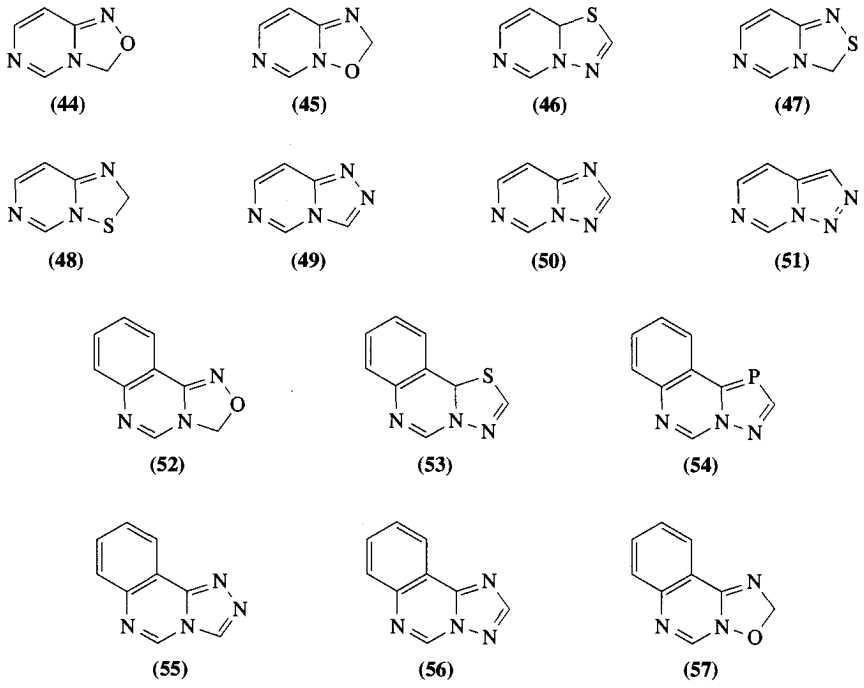


Figure 5 Azoles fused to the c-site of pyrimidine.

8.16.2 THEORETICAL METHODS

The aromaticity indexes of (**36**) and (**37**) were calculated ⟨87T4725⟩, and it was concluded that the major driving force of the Dimroth-rearrangement of (**36**) to (**37**) is the increased aromatic character of the latter.

Calculation of the electronic distribution of 6- and 7-phenyl derivatives of (**15**) showed that there is only a very slight difference between the two compounds, which cannot account for the essentially different biological behavior of the two compounds ⟨89MI 816-01⟩. Quantum chemical studies have also been reported on an ylide derivative of (**37**) (i.e. (**106**)), and the frontier orbital energies have been calculated by an *ab initio* (STO-3G) method ⟨87JCS(P1)2531⟩.

8.16.3 EXPERIMENTAL STRUCTURAL METHODS

8.16.3.1 Carbon-13 NMR Measurements

The most important ^{13}C NMR assignments of the derivatives discussed in this chapter (Figure 6) are compiled in Table 1.

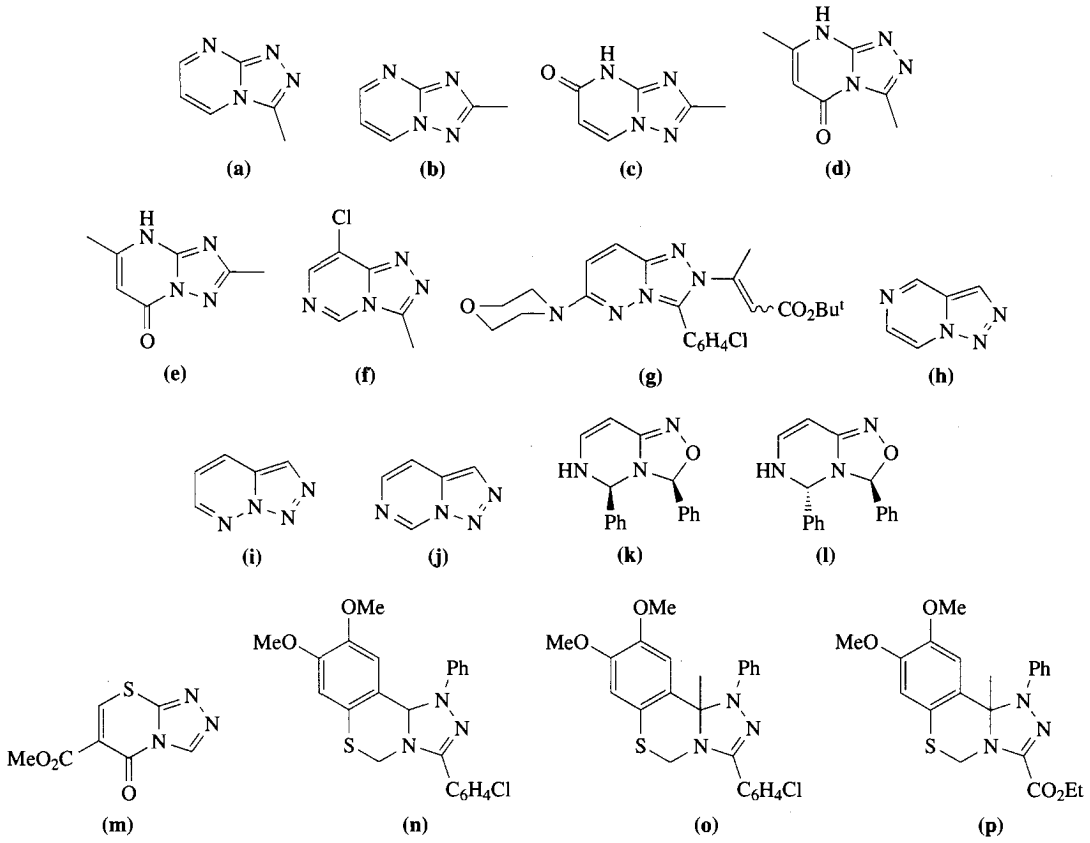


Figure 6 Derivatives for which ^{13}C NMR assignments are given in Table 1.

8.16.3.2 Nitrogen-15 NMR Investigations

In some cases (Figure 7), ^{15}N NMR studies on the derivatives appropriate to this chapter have been carried out. The results are summarized in Table 2.

8.16.3.3 UV Studies

While efforts to differentiate between isomers (**58**)–(**61**) by IR spectroscopy failed, UV proved to be the most powerful method for this purpose ⟨87T2497⟩. These four isomers possessed characteristic and different UV absorptions: (**58**) had two absorption maxima at 230 nm and 270 nm; in (**59**) these two bands shifted to 208 nm and 290 nm, respectively; compound (**60**) had, in turn, three peaks at 230 nm, 260 nm, and 310 nm, whereas (**61**) had a maximum only at 230 nm.

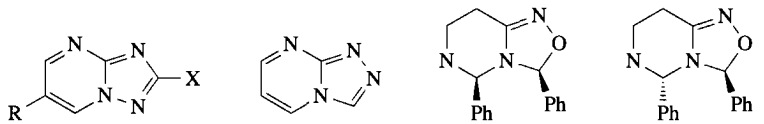
8.16.3.4 Mass Spectrometry

The electron impact mass spectra of (**62**) and (**63**) revealed that these compounds are fairly stable to EI, and ring contraction reactions are characteristic ⟨84OMS(19)433⟩. Furthermore, retro Diels–Alder reactions have been observed with the 7-oxo derivative (**62**), whereas this did not occur with

Table 1 Carbon-13 NMR shifts of selected compounds (Figure 6).

Compound[a]	*C-1*	*C-2*	*C-3*	*C-5*	*C-6*	*C-7*	*C-8*	*C-8a*	*C-9*	*C-10*	*C-10a*	*C-10b*	*C-2Me*	*C-3Me*	*C-7Me*	*Ref.*
(a)	–	–	142.1	131.9	108.5	152.3	–	154.0	–	–	–	–	–	9.8	–	89H(28)239
(b)	–	165.2	–	136.6	110.2	154.7	–	154.7	–	–	–	–	14.6	–	–	
(c)	–	–	150.2	160.2	96.2	143.3	–	157.5	–	–	–	–	–	13.3	–	
(d)	–	–	145.4	143.9	107.6	160.8	–	149.2	–	–	–	–	–	13.8	–	
(e)	–	155.2	–	150.8	98.1	160.6	–	151.0	–	–	–	–	14.2	–	18.6	
(f)	–	–	142.3	125.7	–	117.9	140.3	150.1	–	–	–	–	–	14.1	–	
(g)	–	–	–	–	145.9	(123.7	124.7)[b]	156.3	–	–	–	–	–	–	–	89T7921
(h)	127.5	–	–	118.4	131.9	–	145.7	129.6	–	–	–	–	–	–	–	82BSB153
(i)	126.6	–	–	–	146.9	118.7	128.4	127.8	–	–	–	–	–	–	–	
(j)	125.7	–	–	138.8	–	139.3	112.5	134.0	–	–	–	–	–	–	–	
(k)	–	–	97.55	79.05	–	42.75	23.73	155.1	–	–	–	–	–	–	–	91CB2065
(l)	–	–	93.47	71.09	–	40.35	22.62	151.85	–	–	–	–	–	–	–	
(m)	–	–	–	161.2	122.0	139.7	–	142.7	–	–	–	–	–	–	–	91JHC325
(n)	–	–	152.2	49.4	126.9	113.9	149.6	–	148.0	113.4	125.2	84.6	–	–	–	84OMR(22)720
(o)	–	–	150.3	49.9	127.9	114.0	149.2	–	147.2	113.4	126.2	85.4	–	–	–	
(p)	–	–	143.0	46.0	123.5	112.6	149.0	–	146.3	112.0	126.5	89.0	–	–	–	

[a] **(a)**–**(f)** in $CDCl_3$, 25°C. [b] Values in brackets: interchangable data. **(g)**–**(p)** in DMSO-d_6.



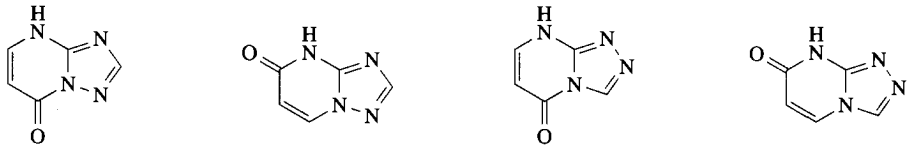
(a) (b) (c) (d)

Figure 7 Derivatives for which ^{15}N NMR studies have been carried out (see Table 2).

Table 2 ^{15}N NMR shifts of some derivatives (Figure 7).

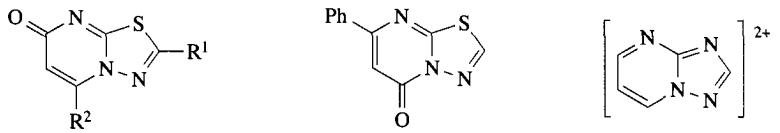
Compound		*N-1*	*N-2*	*N-3*	*N-4*	*N-6*	*N-8*	*Ref.*
(a) R = X = H		276.3	–	231.9	279.3	–	228.3	83S44
R = *n*-Bu	X = H	275.4	–	231.5	279.3	–	227.0	
R = $(CH_2)_3OH$	X = H	257.4	–	230.9	278.3	–	227.6	
R = H	$X = NH_2$	230.4	–	199.8	266.4	–	226.0	
R = *i*-Pr	$X = NH_2$	231.0	–	198.6	266.7	–	25.0	
(b)		84.3[a]	49.4[a]	–	196.9[a]	–	103.5[a]	89MI 816-03
(c)		299.6	–	–	117.7	55.1	–	91CB2065
(d)		297.8	–	–	106.5	51.5	–	

$CDCl_3$, 25 °C; ammonia as standard except[a]. [a]Nitromethane as standard.



(58) (59) (60) (61)

the 5-oxo isomer (**63**). This finding provided a sensitive diagnostic tool for differentiation between these isomers. Fragmentation of both metastable and collisionally activated dications (e.g., (**64**) and related cases) have been compared ⟨92OMS(27)89⟩.



(62) (63) (64)

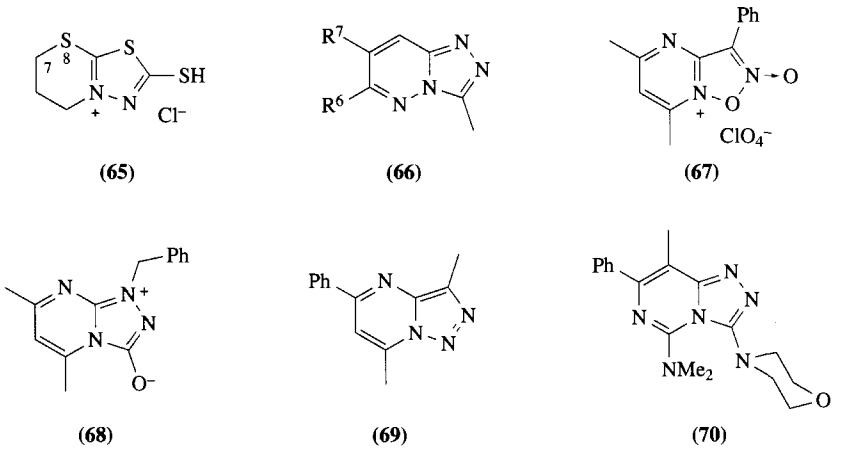
8.16.3.5 Magnetic Circular Dichroism

Magnetic circular dichroism of five isomeric ring systems—(**15**), (**20**), (**21**), (**36**) and (**37**)—have been studied ⟨85JOC302⟩. Based on these results, predictions could be made for the site of protonation of these ring systems. Thus, N(5) is favored for (**15**), whereas protonation at N(1) can be expected for most of the other ring systems.

8.16.3.6 X-ray Elucidations

Some detailed x-ray studies in this field have appeared; the structures investigated are summarized in Figure 8. In the partially reduced [1,3,4]thiadiazolo[2,3-*b*][1,3]thiazinium salt (**65**) the C(7)—S(8) bond proved to be longer (1.846 Å) than expected (1.82 Å) which might account for the enhanced chemical reactivity of this compound towards nucleophiles at this site ⟨89JOC2024⟩. Structure elucidation of the isomers (**66a**; R^6 = Ph, R^7 = H) and (**66b**; R^6 = H, R^7 = Ph) revealed that both compounds are planar and the phenyl group in each derivative is coplanar ⟨89MI 816-01⟩. X-ray analysis

of the salts (**67**) ⟨92KGS233⟩ and (**68**) ⟨88JCS(P1)351⟩ has also been carried out. In this latter case the contribution of the canonical form depicted in the structure (**68**) seemed of major importance. The structure of the [1,2,3]triazolo[1,5-*a*]pyrimidine derivative (**69**), which was obtained as a product of a fairly complicated rearrangement, was unambiguously clarified by x-ray ⟨90CPB2108⟩ (see Section 8.16.5.3.2.(i)). Analysis of 5-dimethylamin-8-methyl-3-morpholino-7-phenyl[1,2,4]triazolo[4,3-*c*]pyrimidine (**70**) ⟨90T3897⟩ showed that the pyrimidine ring significantly deviates from planarity (flat boat conformation), whereas the thiazole ring is planar.



(65) (66) (67)

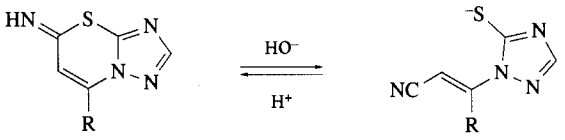
(68) (69) (70)

Figure 8 Structures elucidated by x-ray studies.

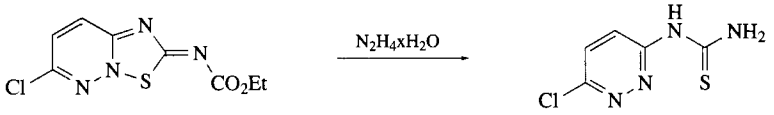
8.16.4 REACTIVITY

8.16.4.1 Ring-opening Reactions

The 7-imino[1,2,4]triazolo[3,2-*b*][1,3]triazine compounds (**71**) when deprotonated, were found to form a ring-chain equilibrium with (**72**) (Equation (1)) ⟨88KGS992⟩. Opening of the thiadiazole ring of (**73**) and formation of (**74**) was observed in the reaction with hydrazine hydrate (Equation (2)) ⟨87H(26)689⟩.



(71) (72) (1)

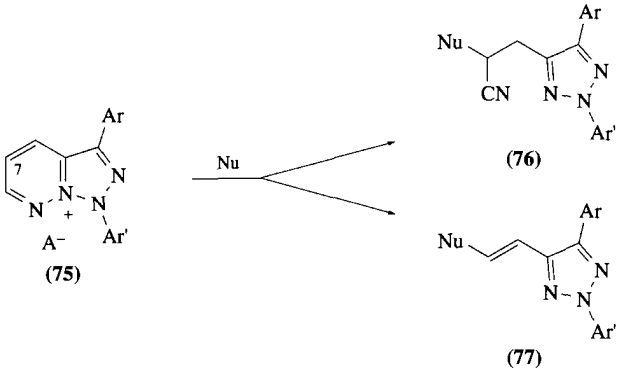


(73) (74) (2)

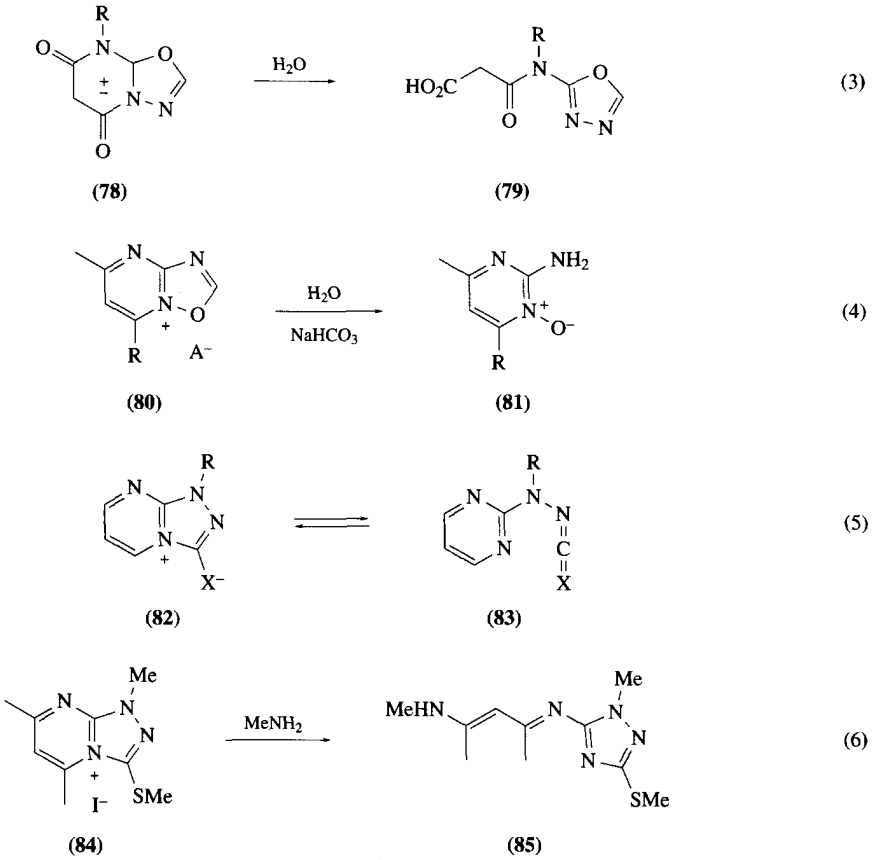
The v-triazolo[1,5-*b*]pyridazinium salt (**75**) reacted with nucleophiles selectively at position 7, and the cyanoethyl compound (**76**) or the fragmentation product (**77**) was obtained (Scheme 1) ⟨93JHC819⟩. The zwitterionic compound (**78**) underwent spontaneous ring opening on standing at room temperature ⟨87JHC1291⟩ to yield the aminooxadiazole derivative (**79**) (Equation (3)). Hydrolysis of a derivative of the isomeric ring system [1,3,4]oxadiazolo[3,2-*a*]pyrimidine (**80**) resulted, however, in opening of the five-membered ring and led to 2-amino-4-methylpyrimidine-1-oxide (**81**) (Equation (4)) ⟨86JHC1175⟩.

Six examples of ring opening of differently fused triazolopyrimidines have been reported up to 1995. Compound (**82**) was found to form an equilibrium with the valence bond tautomer (**83**)

(Equation (5)) ⟨88JCS(P1)351⟩. Ring opening of the S-alkylated derivative (**84**) of (**82**, X = S) with methylamine afforded the triazolylazabutadiene (**85**) (Equation (6)) ⟨88JCS(P1)351⟩.

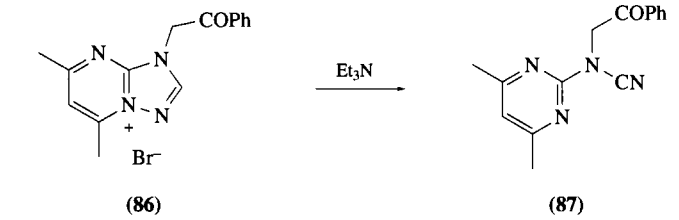


Scheme 1

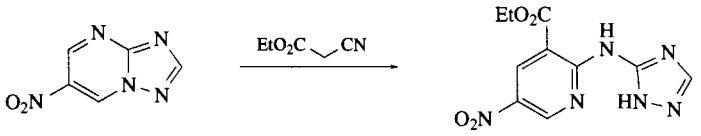


Ring opening of salt (**86**) to (**87**) in the presence of triethylamine (Equation (7)) was interpreted as occurring by formation of an ylide intermediate containing a carbanion in the side chain ⟨85TL1321⟩. A more complicated case was reported for the reaction of (**88**) with ethyl cyanoacetate (Equation (8)) ⟨92TL3695⟩: addition of the reagent and pyrimidine-to-pyridine rearrangement was followed by Dimroth rearrangement to yield the substituted aminotriazole compound (**89**). The opening of the v-triazole ring of (**90**), which is accompanied by nitrogen elimination, can be accomplished by iodine chloride in acceptable (48%) yield (Equation (9)) ⟨83JHC735⟩. Ring opening of (**92**) under acidic conditions to (**93**) is of special importance because of the absence of the expected Dimroth rearrangement (Equation (10)) ⟨89H(28)239⟩. Some ring-opening reactions have also been reported for benzologues. Thus, 2-methylthio-5-phenyl[1,3,4]thiazolo[3,2-*c*]quinazolinium iodide

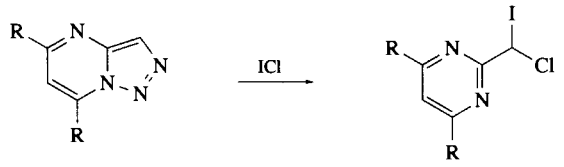
(**94**) reacts with reagents containing active methylene groups in the presence of potassium *t*-butoxide to give the exo-metheno quinazoline compounds (**95**) (Equation (11)) ⟨85JHC1189⟩. Treatment of (**96**) with potassium hydroxide followed by addition of acid results in opening of the pyrimidine ring to give (**97**) (Equation (12)) ⟨85JHC1189⟩.



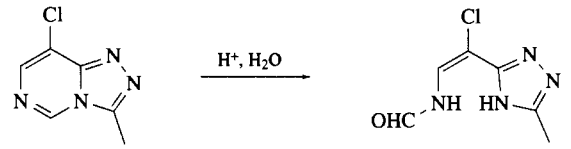
(86) (87) (7)



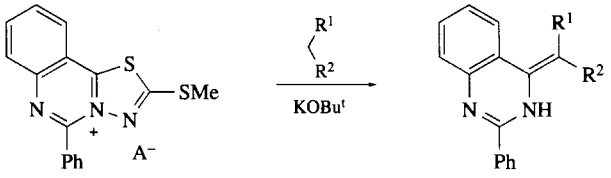
(88) (89) (8)



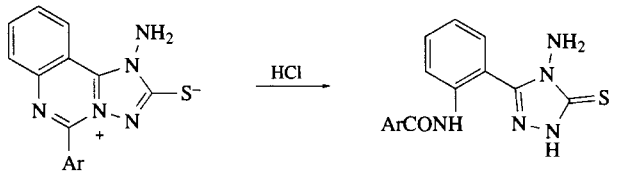
(90) (91) (9)



(92) (93) (10)



(94) (95) (11)

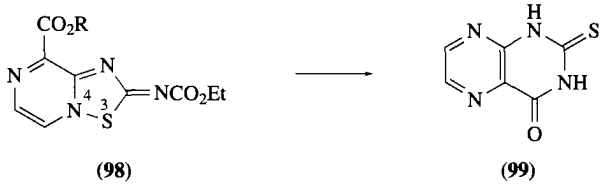


(96) (97) (12)

8.16.4.2 Ring Transformations

Six different ring transformation reactions in compounds appropriate to this chapter have been described. Formation of (**99**) from (**98**) (Equation (13)) is interpreted as resulting from cleavage of the S(3)—N(4) bond followed by cyclization of the intermediate ethoxycarbonylthiourea ⟨87H(26)689⟩.

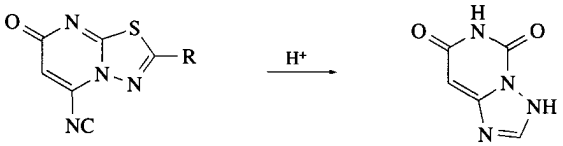
Reaction of the saturated [1,2,4]thiadiazolo[4,5-*a*]pyrimidine (**100**) with carbon disulfide gave the dithiazolopyrimidine derivative (**101**) (Equation (14)) ⟨87CE421⟩. The isocyanide compound (**102**) was found to give (**103**) under acidic conditions (Equation (15)) ⟨91JHC489⟩. The Dimroth rearrangement of (**104**) to the isomeric (**105**) (Equation (16)) was reported ⟨89H(28)239⟩. Compound (**106**) was found to react with 2 moles of acetylenic ester to give (**107**) (Equation (17)) ⟨87JCS(P1)2531⟩. In the course of reactions of (**94**) with nucleophiles (see Section 8.16.4.1) the reaction with malononitrile represents a special case and leads to the ring transformation product (**108**) (Equation (18)) ⟨85JHC1189⟩.



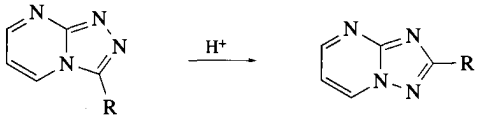
(98) (99) (13)



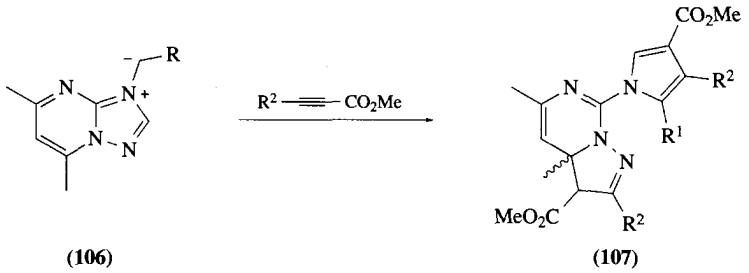
(100) (101) (14)



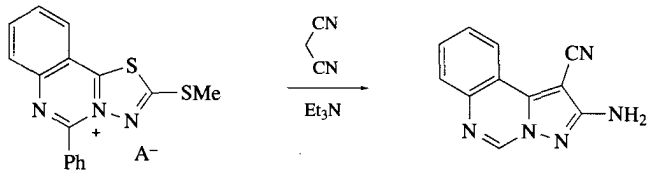
(102) (103) (15)



(104) (105) (16)



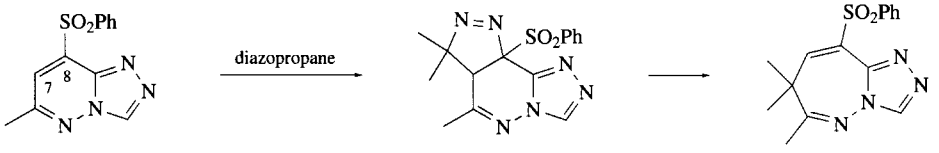
(106) (107) (17)



(94) (108) (18)

8.16.4.3 Formation of Further Condensed Rings

Several reports on closures to additional rings fused to the parent system have been described. The double bond C(7)=C(8) of (**109**) underwent cycloaddition with diazoalkanes ⟨89JHC445⟩, and the product (**110**) was found to rearrange to (**111**) containing a seven-membered ring (Scheme 2) ⟨89H(28)259⟩. Similar cycloaddition with a different regioselectivity was found in the reaction of (**112**) which yielded (**113**) (Equation (19)) ⟨90JHC2145, 86MI816-01⟩. Ring fusions were also reported for the following cases: (**114**) reacted with ethyl isothiocyanate to give the *peri* fused tricycle (**115**) (Equation (20)) ⟨87CE421⟩; the diamino derivative (**116**) was transformed to the tricyclic compound (**117**) (Equation (21)) ⟨92CPB357⟩; and reaction of 6-nitro-[1,2,4]triazolo[1,5-*a*]pyrimidine (**118**) with malononitrile or ethyl cyanoacetate was found to lead, through ring opening and Dimroth rearrangement of the intermediate, to (**119**) (Equation (22)) ⟨90S713⟩.

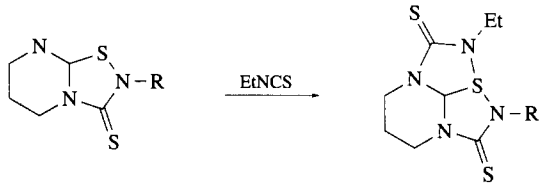


(**109**) (**110**) (**111**)

Scheme 2



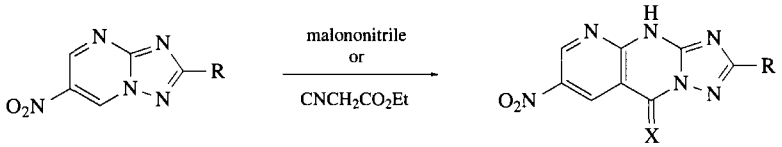
(**112**) (**113**) (19)



(**114**) (**115**) (20)



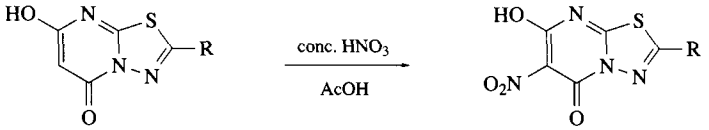
(**116**) (**117**) (21)



(**118**) (**119**) X = NH or O (22)

8.16.4.4 Electrophilic Reaction

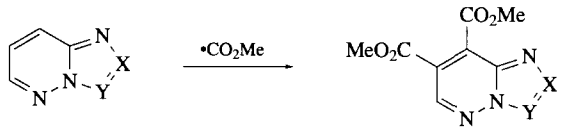
Nitration of (**120**) was found to take place at position 6 to give (**121**) (Equation (23)) ⟨92CPB357⟩.



(120) (121) (23)

8.16.4.5 Radical Substitutions

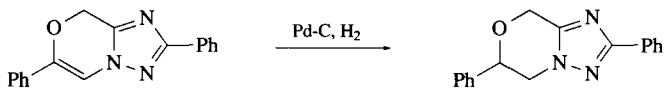
Radical methoxycarbonylation of ring systems (**15**) and (**16**)—i.e., (**122**; X = N, Y = CH) and (**122**; X = CH, Y = N), respectively—have been reported to furnish 8- and/or 7-substituted compounds, e.g., (**123**) (Equation (24)), depending on the substituents and reaction conditions ⟨89JHC1751⟩.



(122) (123) (24)

8.16.4.6 Reductions

Catalytic hydrogenation of the [1,2,4]triazolo[3,2-*c*][1,4]thiazine compound (**124**) gave the reduced compound (**125**) (Equation (25)) ⟨88H(28)2297⟩.



(124) (125) (25)

8.16.4.7 Alkylation Reactions

The starting compounds for alkylation reactions of derivatives belonging to this chapter are shown in Figure 9. The site of the attack is shown by arrows: the [1,2,4]triazolo[3,4-*b*][1,3]oxazine compound (**a**), the [3,4-*c*] fused isomer (**b**), and its thio analog (**c**) reacted at N(2) ⟨92JMC189⟩; alkylation of (**d**) ⟨89JOC2024⟩, (**e**) ⟨83JHC735⟩, and (**f**) ⟨84S881⟩ gave S-alkyl products, whereas the isomeric (**g**) and (**h**) reacted at different nitrogen atoms ⟨86JHC833⟩.

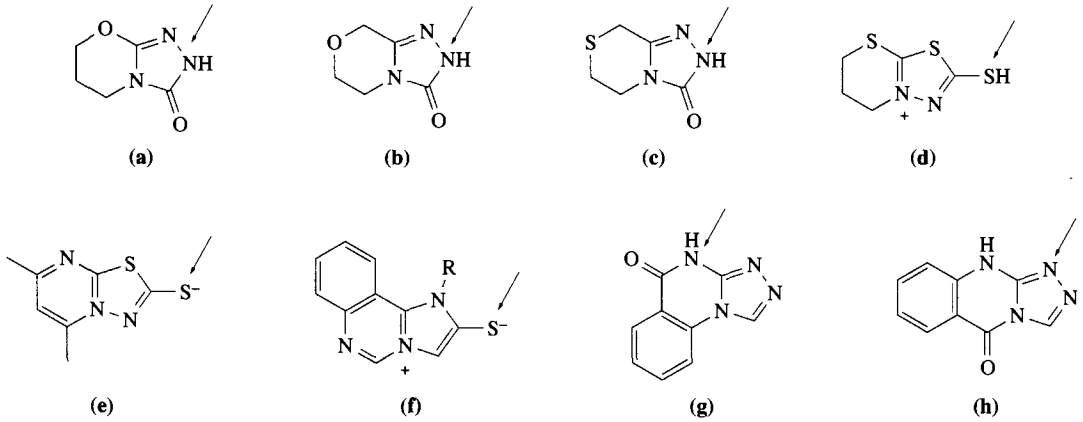


Figure 9 Starting compounds for alkylation reactions.

8.16.4.8 Transformations of Substituents of the Various Ring Systems

Some routine transformations of substituents of the ring systems have been reported: nucleophilic exchange of chlorine atom by alkoxy and amino substituents of ring system (**15**) ⟨81JHC893⟩; several transformations (formation of a chloro compound from a hydroxy derivative, nucleophilic substitutions of the chloro substituent, reduction of nitro group) of derivatives of (**30**) ⟨92CPB357⟩.

8.16.5 RING SYNTHESES CLASSIFIED BY RING SYSTEMS

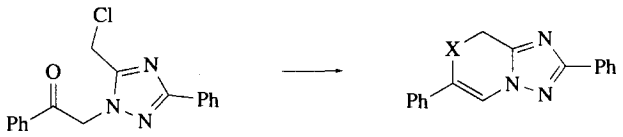
8.16.5.1 Synthesis of Fused Oxazines and Thiazines

8.16.5.1.1 Bicyclic systems

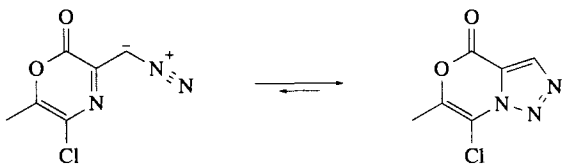
Ring closures to reduced derivatives of the ring systems [1,2,4]triazolo[3,4-*b*][1,3]oxazine (**1**) (i.e., (**127**; X = CH, Y = O)), [1,2,4]triazolo[3,4-*c*][1,3]oxazine (**3**) (i.e., (**127**; X = O, Y = CH)) and [1,2,4]triazolo[3,4-*c*][1,3]thiazine (**9**) (i.e., (**127**; X = S, Y = CH) have been carried out by reaction of (**126**) with carbethoxyhydrazine (Equation (26)) ⟨92JMC189⟩. Treatment of (**128**) with sodium hydride resulted in formation of 7,8-dihydro-[1,2,4]triazolo[3,2-*c*][1,4]oxazine (**129**, X = O) (Equation (27)), and the reaction of (**128**) with Lawesson-reagent followed by ring closure proved to be suitable for the synthesis of 7,8-dihydro-[1,2,4]triazolo[3,2-*c*][1,4]thiazine (**129**, X = S) ⟨88H(27)2297⟩. The fused system (**131**) was found to be the major component in the equilibrium with (**130**) (Equation (28)) ⟨92TL2713⟩. Alkylating ring closure of mercaptothiadiazole (**132**) with dibromopropane offered a simple route to [1,3,4]thiadiazolo[2,3-*b*][1,3]thiazines (**133**) (Equation (29)) ⟨87JOC405, 89JOC2024⟩. Reaction of triazolethiones (**134**; X = N, Y = C—Me) and (**134**; X = C—Ar, Y = N) with DMAD afforded the fused thiazinones (**135**) with corresponding substitution (Equation (30)) (⟨91JHC325⟩ and ⟨91H(32)231⟩, respectively). In the course of investigations of reactivity of small rings ⟨87KGS271, 89ZOR1533, 90ZOR1761⟩, compound (**136**) was found to be a suitable starting compound for ring closure to the partially reduced [1,2,4]triazolo[3,2-*b*][1,3]thiazine derivative (**137**) (Equation (31)). Ring transformation of (**138**) under acidic conditions gave the [1,2,4]oxadiazolo[3,4-*c*][1,4]thiazinone (**139**) (Equation (32)) ⟨92CC1394⟩.



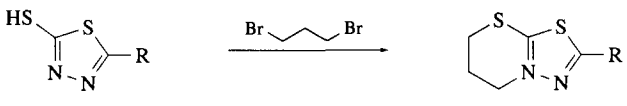
(126) (127) (26)



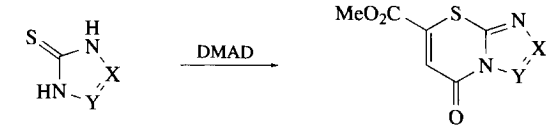
(128) (129) (27)



(130) (131) (28)



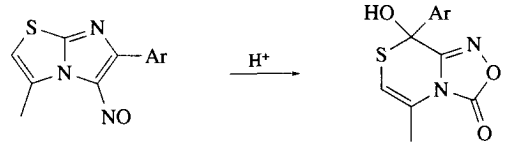
(132) (133) (29)



(134) (135) (30)



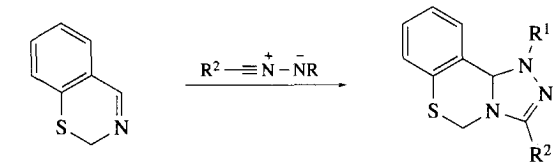
(136) (137) (31)



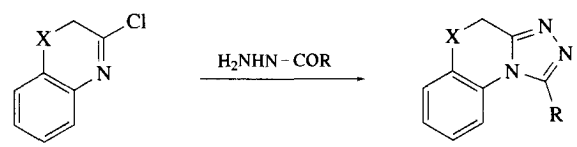
(138) (139) (32)

8.16.5.1.2 Benzologues

Ring closures of three benzologues of the above ring systems have been reported: cycloaddition of (**140**) with nitrilimines resulted in the formation of the new ring system 5H-[1,2,4]triazolo[4,3-*c*][1,3]benzothiazine (**141**) (Equation (33)) ⟨84H(22)537⟩. Reaction of 3-chloro-2H-[1,4]benzothiazine (**142**, X = S) and 3-chloro-2-oxo-2H-[1,4]benzoxazine (**142**, X = O) with acylhydrazines afforded the corresponding tricyclic compounds, the [1,2,4]triazolo[3,4-*c*][1,4]benzothiazine (ring system (**13**)) (**143**, X = S) and [1,2,4]triazolo[3,4-*c*][1,4]benzoxazine (ring system (**12**)) (**143**, X = O) derivatives (Equation (34)) ⟨85H(23)871⟩. The same ring closure principle has also been applied to other derivatives of (**13**) ⟨87FES43⟩.



(140) (141) (33)



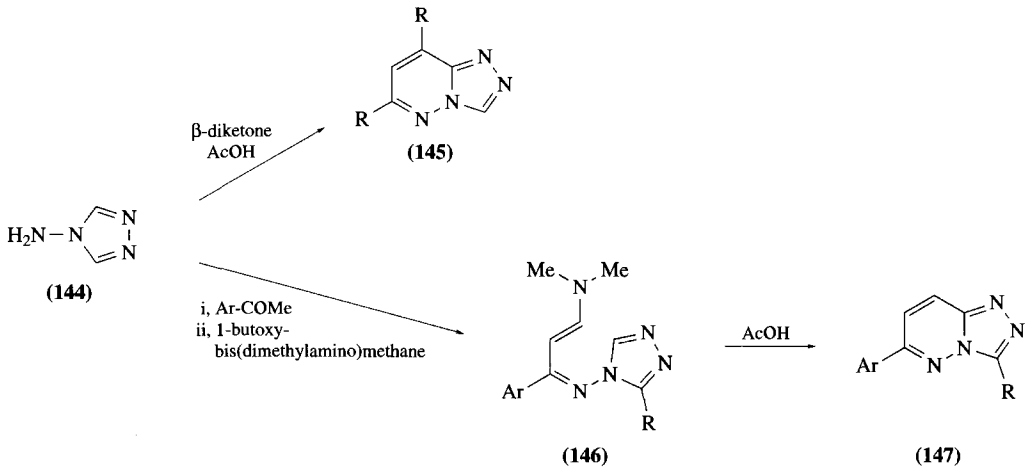
(142) (143) (34)

8.16.5.2 Synthesis of Fused Pyridazines and Pyrazines

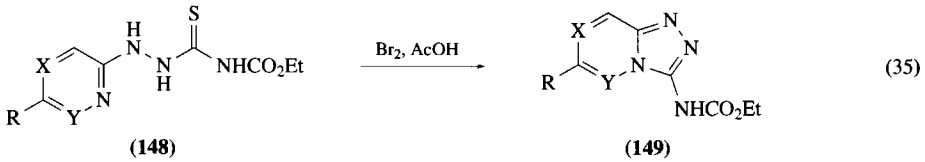
8.16.5.2.1 Bicyclic systems

The approaches described for the [1,2,4]triazolo[4,3-*b*]pyridazine ring system (**15**) follow two major strategies: (a) ring closure of the six-membered ring and (b) closure of the five-membered ring. Route (a) was realized in reactions of 4-amino[1,2,4]triazoles (**144**) with β-diketones ⟨83JHC735⟩ to give (**145**), or with acetophenones followed by treatment with 1-butoxy-bis(dimethylamino)methane to give the intermediate (**146**) which was cyclized to (**147**) (Scheme 3) ⟨88JHC827⟩.

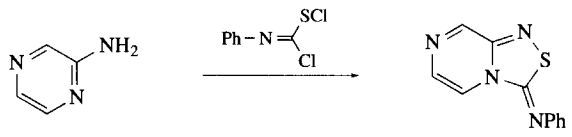
Oxidation of (**148**; X = CH, Y = N) with bromine to the cyclized compound (**149**; X = CH, Y = N), in turn, proceeds according to route (b) (Equation (35)) ⟨88M83⟩. The same ring closure method (formation of (**149**) from (**148**)) was also accomplished for the X = N, Y = CH case, to result in [1,2,4]triazolo[4,3-*a*]pyrazines (**149**; X = N, Y = CH). Ring closure to the imino derivative (**151**) starting from (**150**) (Equation (36)) has been described ⟨86S1027⟩. Procedures to the neutral (**153**) ⟨82BSB153, 83MI 816-01⟩ and positively charged (**154**) ⟨93JHC819⟩ can be accomplished by the oxidation reagents lead tetraacetate or NBS, respectively (Scheme 4). Compound (**155**) was found to undergo rearrangement under relatively mild conditions and gave the 3-amino-[1,2,4]triazolo[4,3-*a*]pyrazine-8(7*H*)thione (**156**) (Equation (37)) ⟨85H(23)913⟩. For the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyrazine (**159**) the transformations of (**157**) and (**158**) with DMF/DMA and PPA, respectively (Scheme 5), provided suitable approaches ⟨83M789⟩, while the 2-hydroxy derivative (**161**) was obtained by the ring closure of the azabutadiene (**160**) (Equation (38)) ⟨87HCA187⟩. A novel route to the reduced [1,2,3]triazolo[1,5-*a*]pyridazine (**163**) is represented by the intramolecular dipolar cyclization of (**162**) (Equation (39)) ⟨90H(30)817⟩.



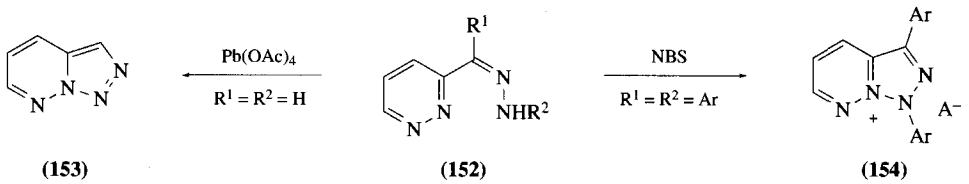
Scheme 3



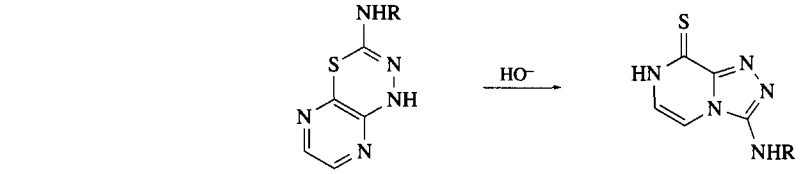
(35)



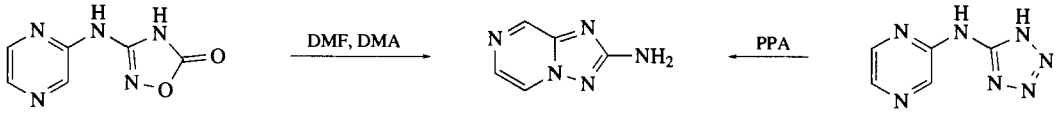
(36)



Scheme 4

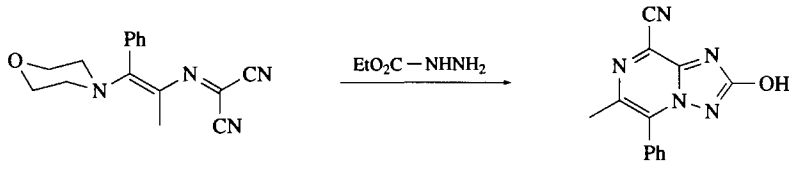


(155) (156) (37)

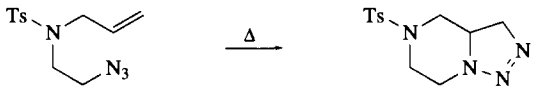


(157) (159) (158)

Scheme 5



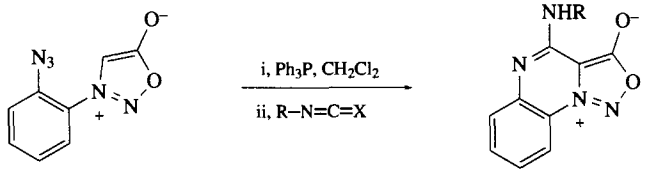
(160) (161) (38)



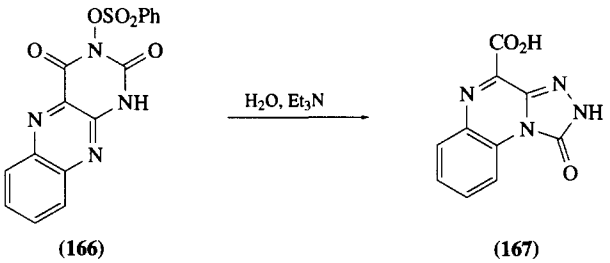
(162) (163) (39)

8.16.5.2.2 Benzologues

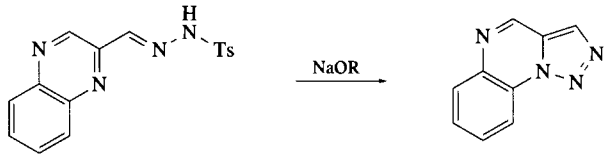
Ring closures to three different benzologues of the bicyclic system discussed in the previous section have been published. Thus, reaction of (**164**) with triphenylphosphine followed by treatment with isocyanate gave [1,2,3]oxadiazolo[3,4-*a*]quinoxalinium-3-olate (**165**) (Equation (40)) ⟨91S745⟩, ring transformation of (**166**) in the presence of aqueous triethylamine afforded the [1,2,4]triazolo[4,5-*a*]quinoxalinone compound (**167**) (Equation (41)) ⟨87JHC1013⟩, and treatment of (**168**) with sodium alkoxide resulted in formation of the unsubstituted tricyclic compound (**25**) (Equation (42)) ⟨87JPC101⟩.



(164) (165) (40)



(166) (167) (41)



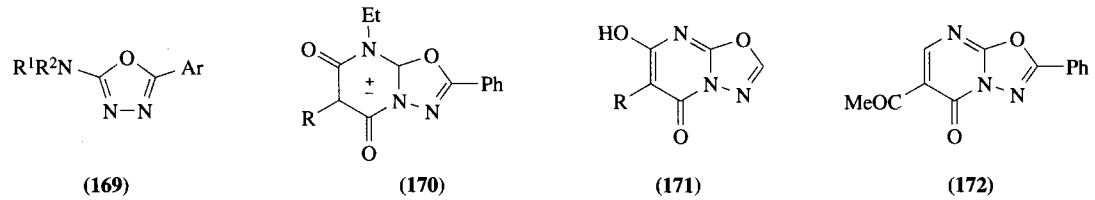
(168) (25) (42)

8.16.5.3 Synthesis of Fused Pyrimidines

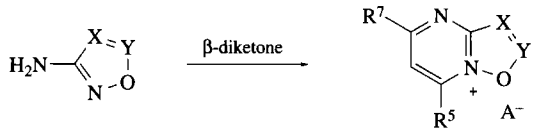
8.16.5.3.1 Oxa-, thia-, and selenadiazoles fused to the a-site of pyrimidine

(i) Bicyclic systems

Several syntheses of derivatives of the new ring system [1,3,4]oxadiazolo[3,2-*a*]pyrimidine (**26**) have been described. Thus, reaction of (**169**) with malonic esters gave the zwitterionic products (**170**) ⟨87JHC1291⟩. Synthetic procedures leading to (**171**) ⟨90M665⟩ and (**172**) ⟨77CPB3360⟩ have also been reported. Reaction of aminooxadiazoles (**173**; X = N, Y = CH) and (**173**; X = C—Ph, Y = N^+—O^-) with β-diketones resulted in formation of [1,2,4]oxadiazolo[2,3-*a*]pyrimidinium salts (**174**; X = N, Y = CH) ⟨86JHC1175⟩ and [1,2,5]oxadiazolo[2,3-*a*]pyrimidinium-2-oxide salts (**174**; X = C—Ph, Y = N^+—O^-) (Equation (43)) ⟨92KGS233⟩. The substituted aminooxadiazole derivative (**175**) underwent ring closure upon heating in the presence of acid and gave 2,5-diphenyl-[1,2,4]oxadiazolo[2,3-*a*]pyrimidin-7-one (**176**) (Equation (44)) ⟨77H(6)107⟩.



(169) (170) (171) (172)

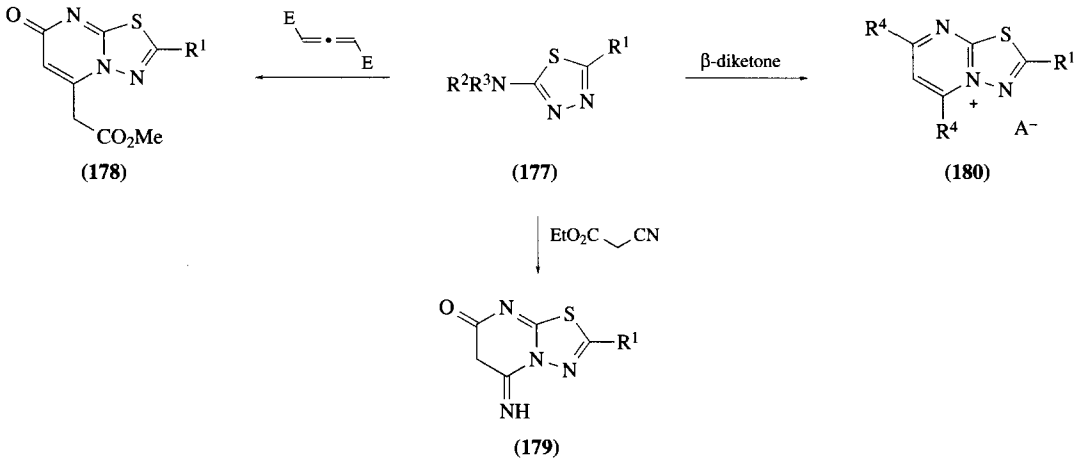


(173) (174) (43)

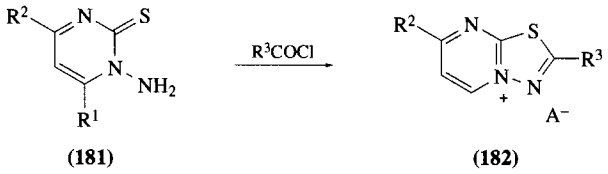


(175) (176) (44)

2-Aminothiadiazoles (**177**) proved to be suitable starting compounds for the ring closures to [1,3,4]thiadiazolo[3,2-*a*]pyrimidines (Scheme 6). Thus, reaction with an allene diester led to (**178**) ⟨88JCS(P1)2993⟩, and a similar conversion was accomplished with ketene ⟨77CPB3360⟩. Reaction of the same starting compounds (**177**) with ethyl cyanoacetate afforded the imines (**179**) ⟨91JHC489⟩, and with β-diketones the heteroaromatic salts (**180**) ⟨83JHC735⟩. Other derivatives (**182**) of the same ring system have been obtained by reacting (**181**) with acid chlorides (Equation (45)) ⟨82JPR942⟩.



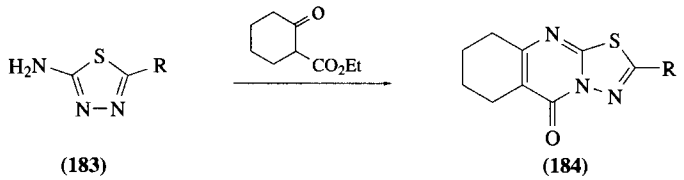
Scheme 6



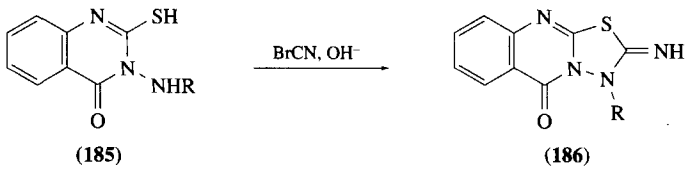
(45)

(ii) Benzologues

Three benzologues of the ring systems described in the previous section have been synthesized. Derivatives of the linearly fused [1,3,4]thiadiazolo[2,3-*b*]quinazoline ring system (**34**) were obtained either by closure of the pyrimidine ring (cyclization of (**183**) to (**184**) (Equation (46)) ⟨88JHC949⟩), or by building up the thiadiazole ring (reaction of (**185**) with cyanogen bromide yielded (**186**) (Equation (47)) ⟨87AP(320)166⟩). Several other examples of this latter ring closure can be found in the literature, for example ⟨86IJC(B)489, 86IJC(B)957, 87MI 816-01⟩.

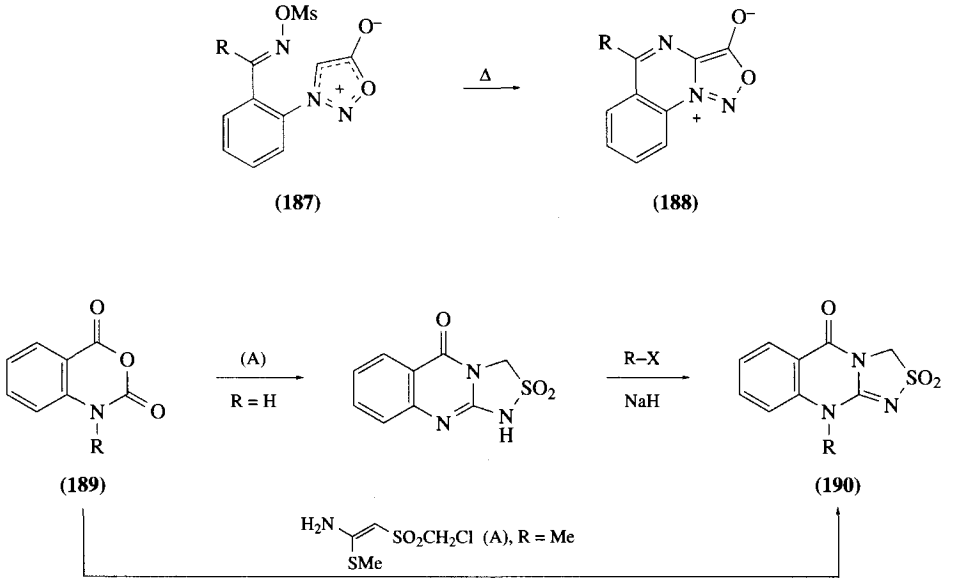


(46)



(47)

Syntheses of two new tricyclic compounds have been reported: thermolysis of the zwitterion (**187**) gave [1,2,3]oxadiazolo[3,4-*a*]quinazolium-3-olate (**188**) (Equation (48)) ⟨86JHC125, 88JHC1817⟩. A condensation reaction of (**189**) afforded the [1,2,4]thiadiazolo[3,4-*b*]quinazoline as a cyclic sulfone (**190**) (Scheme 7) ⟨89JHC1535⟩.

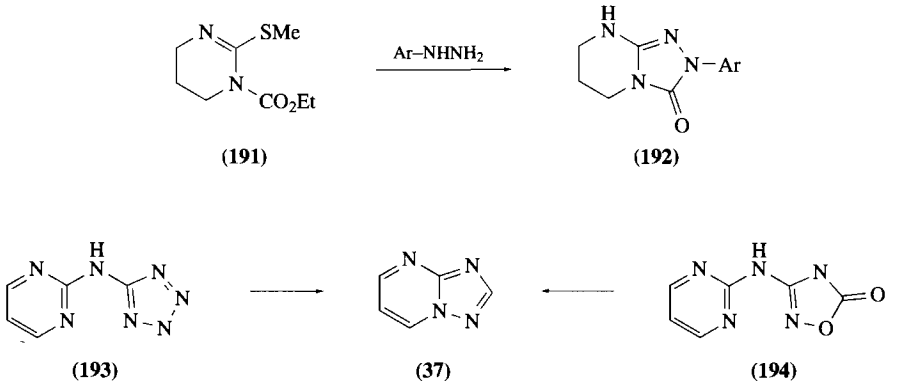


Scheme 7

8.16.5.3.2 Triazoles fused to the a-site of pyrimidine

(i) Bicyclic systems

Most literature data in this section concerns the synthesis of two ring systems: [1,2,4]triazolo[4,3-*a*]pyrimidine (**36**) and [1,2,4]triazolo[1,5-*a*]pyrimidine (**37**); the chemistry of the latter has been reviewed in detail ⟨90ZC305⟩. Two representative approaches to these ring systems by cyclization of the five-membered ring are shown in Equation (49) and Scheme 8. The partially saturated pyrimidine derivative (**191**) can easily be transformed to the ring-closed compound (**192**) by reaction with arylhydrazines (Equation (49)) ⟨86KGS1350, 86JPC331, 88JPC753⟩. Cyclization of the tetrazolylamino- (**193**) and oxadiazolylaminopyrimidines (**194**) gave rise to (**37**) (Scheme 8).

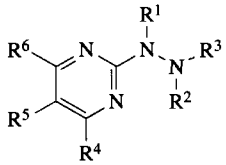


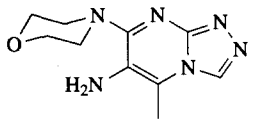
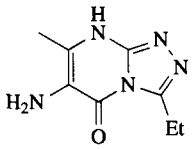
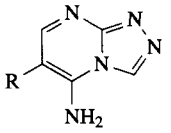
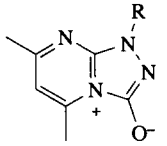
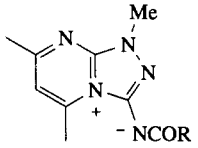
Scheme 8

Various other procedures leading to the above-mentioned two ring systems are known. Those resulting in derivatives of (**36**) are summarized in Table 3, whereas the ring closures to the ring system (**37**) are listed in Table 4.

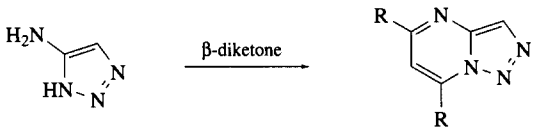
Three major routes to the v-triazole-fused ring system (**38**) have been published. Reaction of (**195**) with β-diketones leads to the neutral product (**196**) (Equation (50)) ⟨83JHC735⟩, whereas oxidative

Table 3 Ring closures to the [1,2,4]triazolo[4,3-*a*]pyrimidine derivatives.

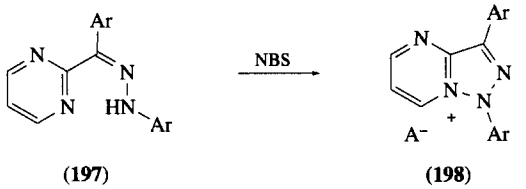


Starting compound	*Reagent*	*Product*	*Ref.*
$R^1 = R^2 = H$, $R^4 = Me$ $R^3 = CHO$, $R^5 = NH_2$, $R^6 =$ morpholino	PPA		86JCS(P1)711
$R^1 = R^2 = R^4 = H$ $R^2 = CHO$ $R^5 = NH_2$, $R^6 =$ morpholino $R^3 = COEt$	PPA		86JCS(P1)711
$R^1 = R^2 = R^3 = R^6 = H$ $R^4 = NH_2$, $R^5 =$ various groups	$HC(OEt)_3$		86H(24)1899
$R^1 =$ alkyl $R^2 = R^3 = R^5 = H$ $R^4 = R^6 = Me$	i, phosgene ii, NH_3		88JCS(P1)351
$R^5 = R^2 = H$, $R^3 =$ —CS—NHCOR $R^1 = R^4 = R^6 = Me$	DCC		93JCS(P1)705

cyclization of the hydrazone (**197**) by NBS gave rise to the triazolopyrimidinium salts (**198**) (Equation (51)) ⟨94JHC1041⟩. Furthermore, reaction of zwitterion (**199**) with diethylaminopropyne was found to give (**202**) as a final product, which was rationalized by proposing formation of intermediates (**200**) and (**201**) (Scheme 9) ⟨90CPB2108⟩.

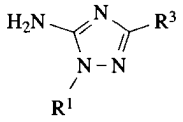


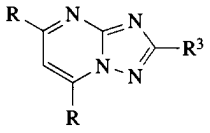
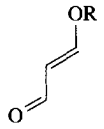
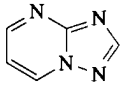
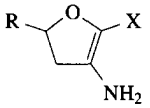
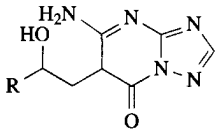
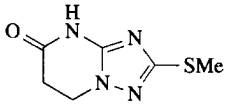
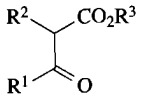
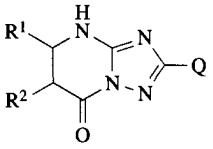
(**195**) (**196**) (50)

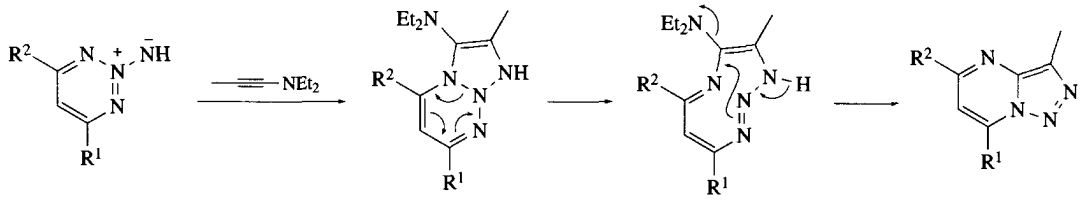


(**197**) (**198**) (51)

Table 4 Ring closures to [1,2,4]triazo[1,5-*a*]pyrimidine derivatives.



Starting compound	*Reagent*	*Product*	*Ref.*
$R^1 = H$, R^3 = various groups	β-diketone		83JHC735
$R^1 = R^3 = H$			83S44
$R^1 = R^3 = H$			81JHC1287
R^3 = SMe $R^1 = (CH_2)_2$—CN	i, OH^- ii, H^+		85JHC385
$R^1 = H$, $R^3 = Q$			90M173

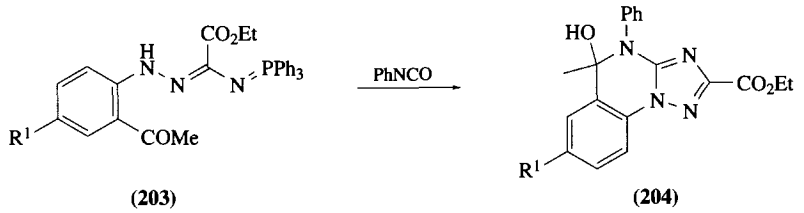


(199) (200) (201) (202)

Scheme 9

(ii) Benzologues

There are three synthetic routes worth mentioning. The reaction of amidrazone (**203**) with phenylisocyanate was found to give (**204**) (Equation (52)) ⟨86JCS(P1)2177⟩. Cyclization of (**205**) with benzoyl chloride in DMF (which acted as the Vilsmeier reagent) selectively gave the linearly fused system (**206**) (Equation (53)): i.e., N(3) of (**205**) reacted, whereas under different conditions a mixture of the possible isomers was formed (i.e., ring closure to N(1) also took place) ⟨86JHC833⟩. The tricyclic compound (**209**) was obtained by a novel technique; alumina-catalyzed cyclization of (**207**) through the intermediate (**208**) (Scheme 10) ⟨85CJC2455, 86CJC250⟩.



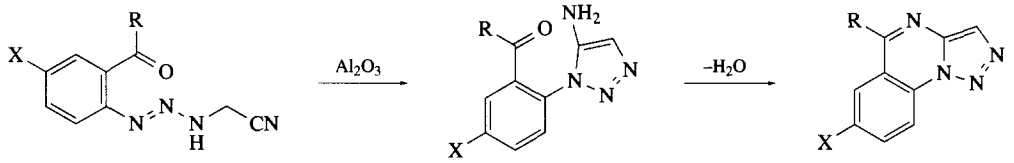
(52)

(203) (204)



(53)

(205) (206)



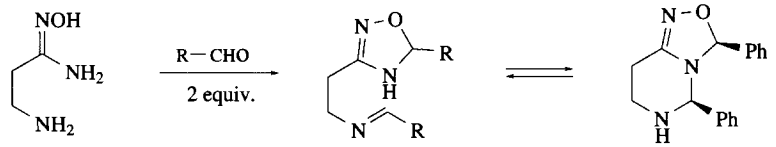
(207) (208) (209)

Scheme 10

8.16.5.3.3 Azoles fused to the c-site of pyrimidine

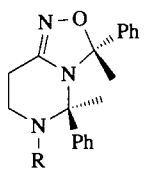
(i) Bicyclic systems

(a) Bicyclic fused oxadiazole and thiadiazoles. The partially saturated compound (**212**) is a representative of a hitherto unknown ring system: [1,2,4]oxadiazolo[4,3-*c*]pyrimidine (**44**). This compound (**212**) was found to be formed from (**211**), prepared from (**210**) with aryl aldehydes, by a ring-chain tautomerism (Scheme 11) ⟨91CB2065⟩. Compound (**213**) containing an R substituent at the pyrimidine nitrogen atom was also formed in an analogous way ⟨92JCS(P1)3069⟩. Thorough instrumental analysis of these compounds revealed that products containing the phenyl rings in a *trans* relationship (e.g., in (**213**)) can also be formed; consequently, ternary equilibria have been observed in these cases ⟨94H(37)2051⟩.



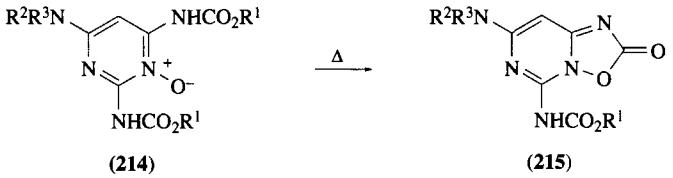
(210) (211) (212)

Scheme 11



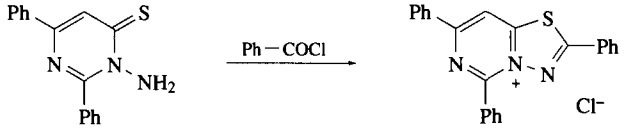
(213)

Pyrolytic heterocyclization of (**214**) led to (**215**) (Equation (54)), whereas treatment of (**216**) with aroyl chloride afforded the [1,3,4]thiadiazolo[3,2-*c*]pyrimidinium salt (**217**), a representative of a new ring system (Equation (55)) ⟨87M485⟩. Compound (**219**), prepared from (**218**) (Equation (56)), also represents a new ring system, [1,2,4]thiadiazolo[4,3-*c*]pyrimidine ⟨86S1027⟩, and similarly, formation of the ring system present in [1,2,4]thiadiazolo[2,3-*c*]pyrimidine (**48**) (cyclization of (**220**) to (**221**) (Equation (57)) ⟨77JHC621⟩) is also reported for the first time.



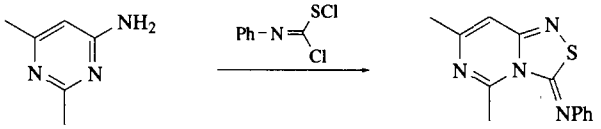
(54)

(**214**) (**215**)



(55)

(**216**) (**217**)



(56)

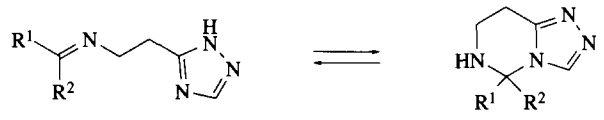
(**218**) (**219**)



(57)

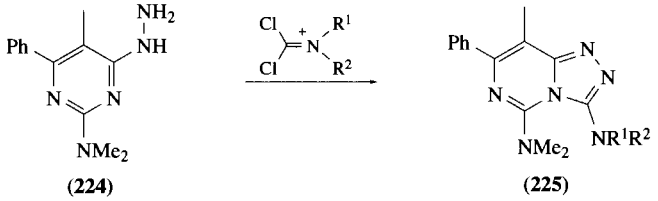
(**220**) (**221**)

(b) Bicyclic fused triazoles. Three such systems exist: (**49**), (**50**), and (**51**). Their most important syntheses are as follows. The ring–chain tautomerism of (**222**) to the partially saturated bicyclic compound (**223**) (Equation (58)) was found to be strongly solvent dependent ⟨92JPC630⟩. The (**223**) : (**222**) ratios were as follows: $CDCl_3$ 1 : 3.3; DMSO 2 : 1; and TFA 1 : 1. Ring closure of (**224**) by phosgeniminium chloride ⟨90T3897⟩ leads to the unsaturated, heteroaromatic compound (**225**) (Equation (59)). [1,2,4]Triazolo[1,5-*c*]pyrimidine-5(3*H*),7(6*H*)-dione (**227**) was obtained by ring transformation of (**226**) under acidic conditions (Equation (60)) ⟨91JHC489⟩ (see Section 8.16.4.2). Reaction of (**228**) with various cyclizing agents (e.g., ethyl chloroformate, bisimidazolylcarbonyl, etc.) proved to be a suitable route to the partially saturated bicyclic derivatives (**229**) (Equation (61)) ⟨92JPC630⟩. For the synthesis of the unsaturated derivatives of the [1,2,4]triazolo[1,5-*c*]pyrimidine ring systems (**50**) and (**51**), two approaches should be mentioned: reaction of (**230**) with Vilsmeier reagent afforded (**231**) (Equation (62)) ⟨90JHC851⟩, whereas the oxidative ring closure of the hydrazone (**232**) with NBS led to the heteroaromatic quaternary salt (**233**) (Equation (63)) ⟨94JHC1041⟩. Other ring closure methods to give derivatives of the ring system (**50**) have also been reported ⟨85CPB2678, 89MI 816-02⟩.

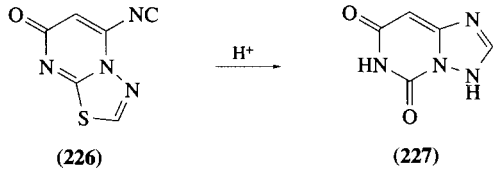


(58)

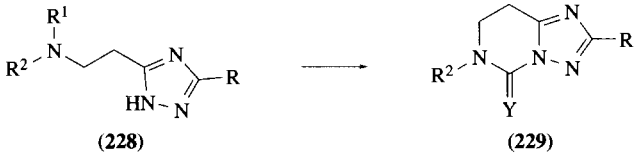
(**222**) (**223**)



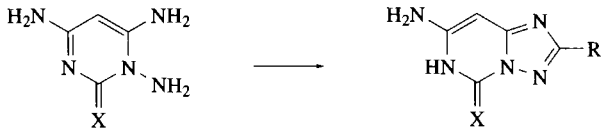
(224) (225) (59)



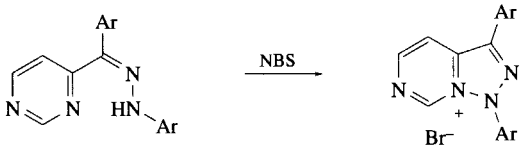
(226) (227) (60)



(228) (229) (61)



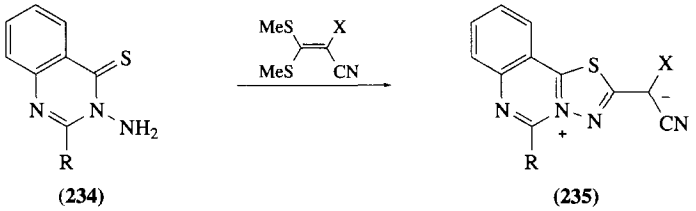
(230) (231) (62)



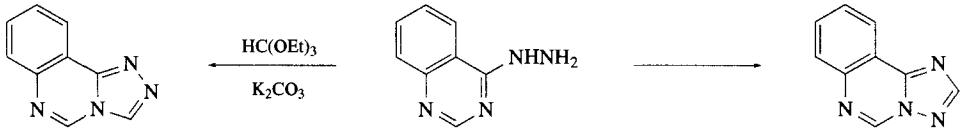
(232) (233) (63)

(ii) Benzologues

Synthesis of five different tricyclic benzologues of the ring systems of the previous section are summarized here. The zwitterionic compound (**235**), a derivative of the new ring system [1,3,4]thiadiazolo[3,2-*c*]quinazoline (**53**), was prepared by cyclization of (**234**) (Equation (64)) ⟨88LA133⟩. Ring closure of (**236**) with various reagents (e.g., with formic acid) results in a Dimroth rearrangement and leads to (**56**); with triethyl orthoformate in the presence of potassium carbonate, no such rearrangement takes place, and (**55**) is formed (Scheme 12). For the synthesis of additional derivatives of (**56**), several other reports have appeared ⟨85H(23)2357, 84S881, 84JCS(P1)1143, 86JHC43⟩. Reaction of the quinazoline-*N*-oxide compound (**237**) was reported to lead to the isocyanate intermediate (**238**) which can undergo ring closure in two directions, to the [1,2,4]oxadiazolo[2,3-*c*]pyrimidine-2-one (**239**) as the main product, and to the isomeric [1,2,4]oxadiazolo[4,3-*c*]pyrimidine-3-one (**240**), the representative of a new ring system (**52**) (Scheme 13) ⟨85H(23)623⟩. Reaction of (**241**) with *t*-butyl-phosphaalkyne represents the first route to a phosphorus-containing fused ring system with bridgehead nitrogen atoms ⟨87CB1645⟩. Formation of [1,2,4]diazaphospholo[1,5-*c*]quinazolin-5(6*H*)one (**242**) was rationalized by supposing a [3 + 2] cycloaddition followed by a rearrangement (Equation (65)).

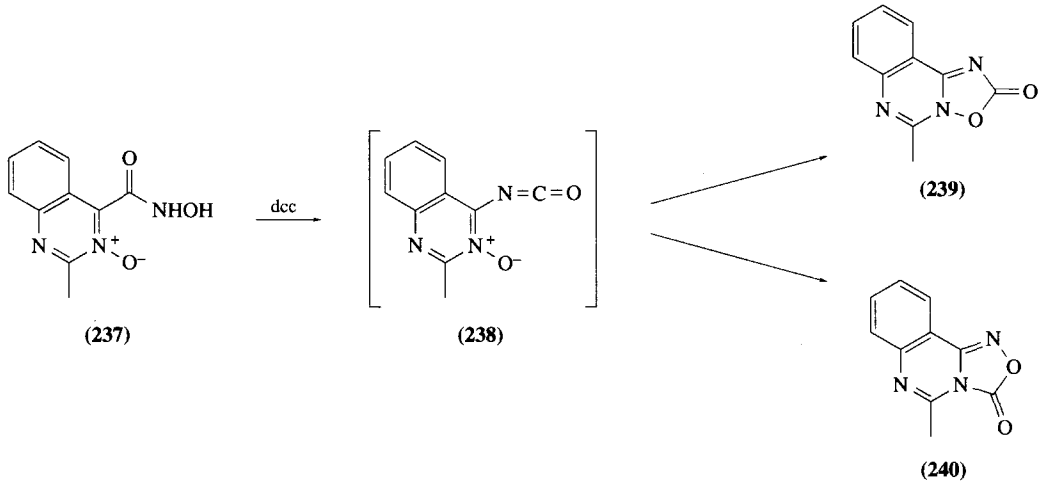


(234) (235) (64)



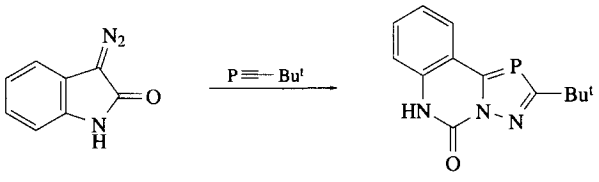
(55) (236) (56)

Scheme 12



(237) (238) (239) (240)

Scheme 13

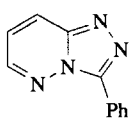


(241) (242) (65)

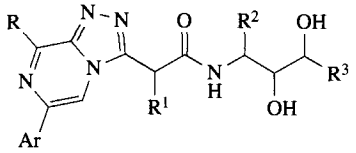
8.16.6 IMPORTANT COMPOUNDS AND APPLICATIONS

Several compounds covered by this chapter have practical applications. 3-Phenyl[1,2,4]triazolo[4,3-*a*]pyridazine (**243**) proved to be an effective herbicide ⟨92EUP483027⟩, whereas the positional isomers of this compound—the 6- and 7-phenyl derivatives (**66a**) and (**66b**) (see Section 8.16.3.6)—have anxiolytic, anticonvulsant, and auxiogenic, convulsant activities, respectively ⟨89MI816-01⟩. The derivative of ring system (**20**) containing a specific side chain in position 3, (**244**) was found to be a human renin inhibitor ⟨93EUP543245⟩. Compound (**245**) simultaneously decreased blood pressure and increased heart rate ⟨78GEP2804519⟩. Three derivatives of the ring system (**30**) proved to be effective in various applications: (**246**) as an immunostimulant ⟨79GEP2755615⟩; (**247**) as an inhibitor of cyclic-AMP phosphordiesterase ⟨81JMC658⟩; and (**248**) as a fungicide which

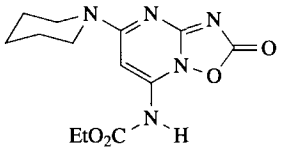
controlled an infection on Chinese mustard caused by *Alternaria brassicicola* ⟨87EUP238059⟩. Finally, some derivatives of (**249**) were found to be antibacterial (R = NH_2, X = N, ⟨87MI 816-01⟩), antihypertensive (R = NH_2, X = N—NH_2, ⟨87AP(320)166⟩), and antifungal (R = CH_2OAr, X = N, ⟨92MI816-01⟩) agents.



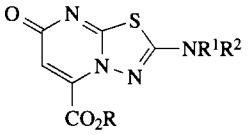
(243)



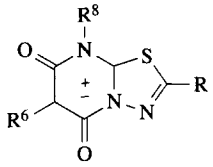
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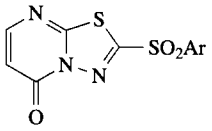
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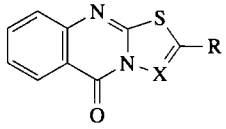
(246)



(247)



(248)



(249)

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8.17
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 1 : 2

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Hungarian Academy of Sciences, Budapest, Hungary

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8.17.1 INTRODUCTION

Due to the wide variation which is possible, the structure, reactivity, and syntheses of 33 different ring systems of which new literature records have been found will be discussed here. These ring

systems are depicted in Figure 1. Some of these have been mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I): imidazo[2,1-*b*][1,3,5]thiadiazine (**2**) ⟨84CHEC-I(5)667⟩, imidazo [2,1-*b*][1,3,4]thiadiazine (**5**) ⟨84CHEC-I(5)666⟩, oxazolo[3,2-*a*][1,3,5]triazine (**12**) ⟨84CHEC-I(6)658⟩, thiazolo[3,2-*a*][1,3,5]triazine (**14**) ⟨84CHEC-I(6)671⟩, imidazo[1,2-*a*][1,3,5]triazine (**15**) ⟨84CHEC-I(5)631⟩, imidazo[1,5-*a*][1,3,5]triazine (**16**) ⟨84CHEC-I(5)659⟩, pyrazolo[1,5-*a*][1,3,5]-triazine (**17**) ⟨84CHEC-I(5)320⟩, imidazo[1,2-*b*][1,2,4]triazine (**20**) ⟨84CHEC-I(5)630⟩, thiazolo[2,3-*c*][1,2,4]triazine (**22**) ⟨84CHEC-I(6)1019⟩, imidazo[2,1-*c*][1,2,4]triazine (**24**) ⟨84CHEC-I(5)630⟩, imidazo-[5,1-*c*][1,2,4]triazine (**25**) ⟨84CHEC-I(5)656⟩, imidazo[1,2-*d*][1,2,4]triazine (**31**) ⟨84CHEC-I(5)564⟩, imidazo[1,5-*d*][1,2,4]triazine (**32**) ⟨84CHEC-I(5)630⟩, pyrazolo[1,5-*d*][1,2,4]triazine (**33**) ⟨84CHEC-I(5)273⟩. The following 19 ring systems, however, have been reported only since 1985 for the first time in the literature: viz. (**1**), (**3**), (**4**), (**6**), (**7**), (**8**), (**9**), (**10**), (**11**), (**13**), (**18**), (**19**), (**21**), (**23**), (**26**), (**27**), (**28**), (**29**), (**30**), and these will be discussed in more detail (see Section 8.17.6).

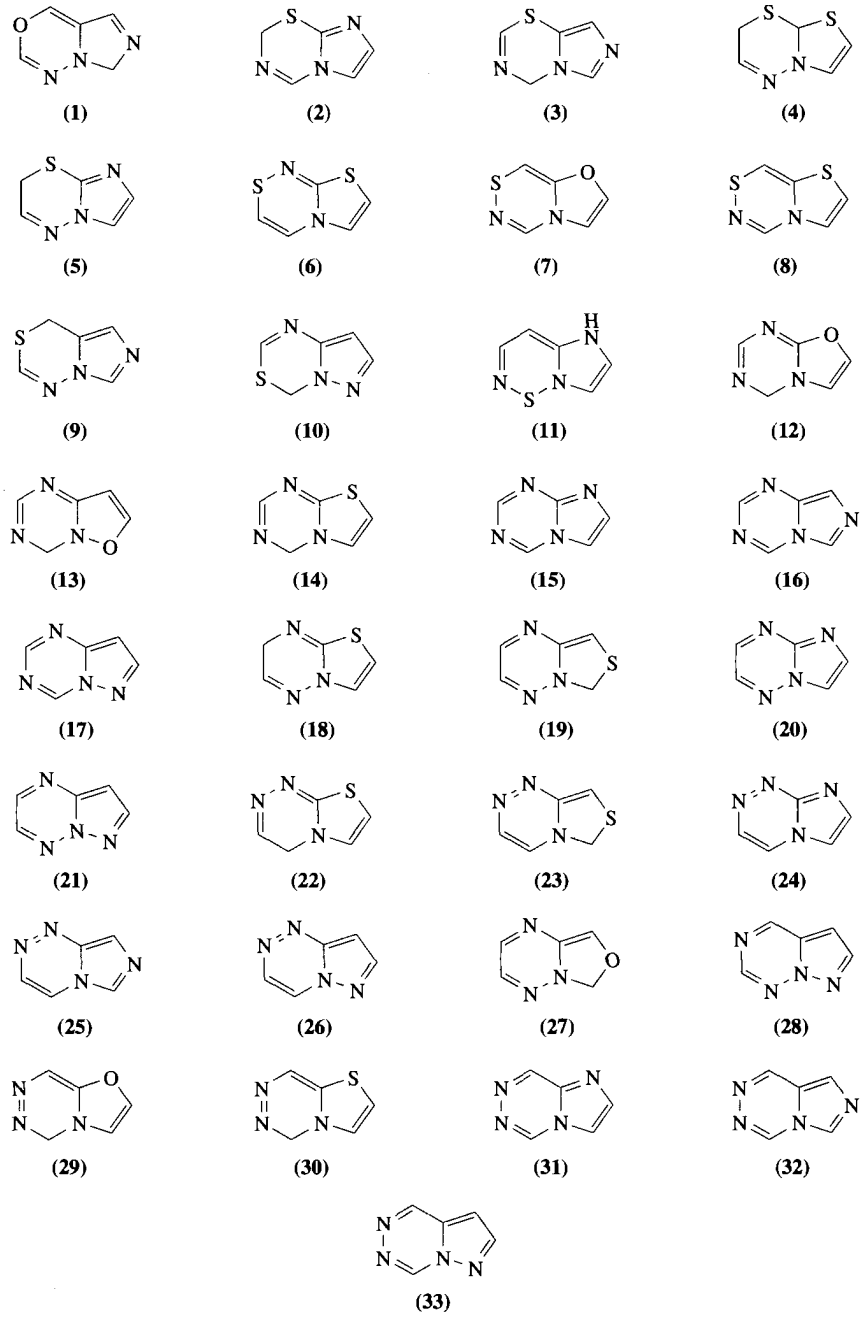


Figure 1 Ring systems discussed in this chapter.

8.17.2 THEORETICAL METHODS

The aromaticity index of the ring system (**20**) has been calculated and compared with related systems ⟨87T4725⟩. Quantum chemical calculation for the formation of some derivatives of ring system (**24**) (e.g., (**130**), see 8.17.6.5.2) suggested that the cyclization is quite asynchronous and can be regarded as a Diels–Alder reaction of inverse electron demand ⟨90JCS(P2)1943⟩.

8.17.3 EXPERIMENTAL STRUCTURAL METHODS

8.17.3.1 Proton NMR Results

Besides routine ^{1}H NMR spectra, compounds shown in Figure 2 were studied in more detail. The most characteristic chemical shifts of these compounds are summarized in Table 1. For the sake of comparison of values of related protons, a common arbitrary numbering has been applied which is shown in structure (**a**) in Figure 2. Additional studies have been published of derivatives of the following ring systems: (**9**) ⟨90T4353⟩, (**26**) ⟨89JHC869⟩, (**28**) ⟨93LA367⟩, and (**33**) ⟨92CPB1411⟩.

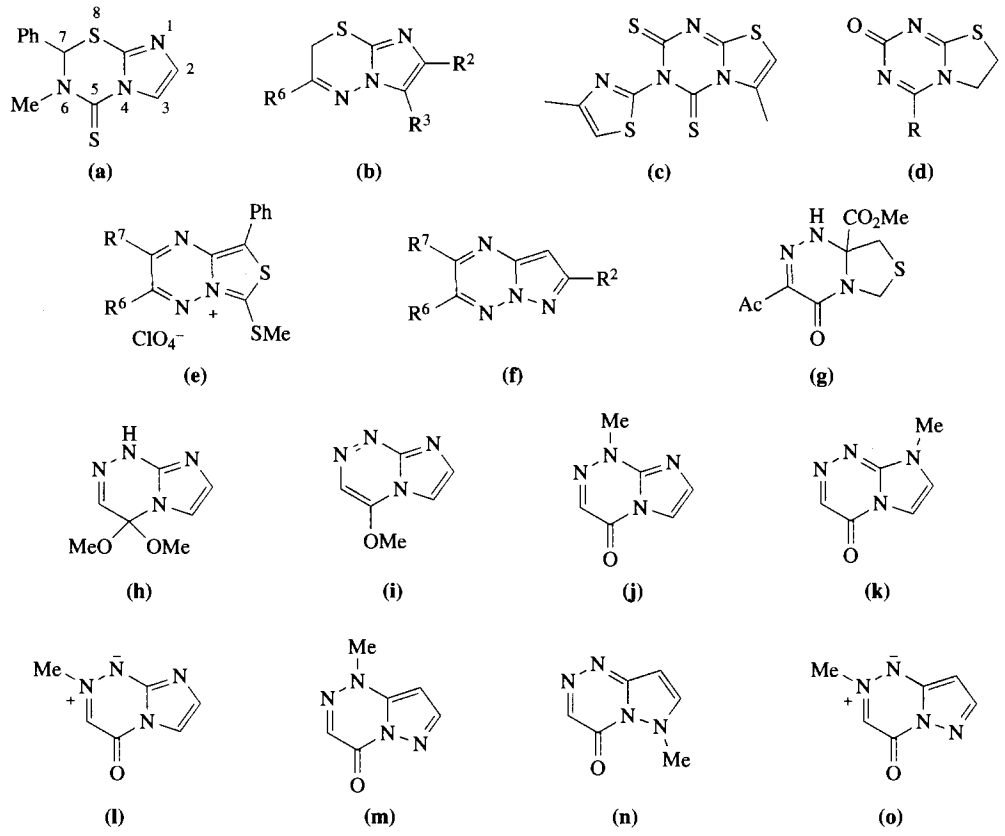


Figure 2 Compounds studied in detail by proton NMR spectroscopy (see Table 1).

8.17.3.2 Carbon-13 NMR Measurements

Compounds listed in Figure 3 have been investigated by ^{13}C NMR spectroscopy, and the assignments are summarized in Table 2. An arbitrary numbering, similar to that used in the previous section, has been applied as shown in structure (**a**) in order to obtain an easy comparison of values of the related carbon atoms. Additional studies have been published for the ring systems (**9**) ⟨90T4353⟩ and (**16**) ⟨83JOC3⟩.

Table 1 Proton NMR shifts of selected compounds (Figure 2) in $CDCl_3$ (unless otherwise indicated).

Compound			*H-1*	*H-2*	*H-3*	*H-6*	*H-7*	*NH*	*N-Me*	*2-Me*	*6-Me*	*7-Me*	*S-Me**	*Ref.*
(a)[a]				7.07	8.12		6.87		3.91					85CCC2170
(b) $R^2 = R^3 =$ Ph	$R^6 =$ Ph						3.94							82H(19)2119
Ph	Me						3.44							
p-Cl-Ph	Ph						4.00							
p-Cl-Ph	Ph						3.94							
(c)				6.24						2.08				82CCC1229
(d) R = Ph				3.42	4.59									92T1953
R = *p*-tolyl				3.43	4.59									
(e)[b] $R^6 =$ H	$R^7 =$ Ph					8.67							2.57	85KGS498
Ph	Me											2.23	2.50	
Ph	H						8.60						2.57	
Me	H						8.06				2.28		2.55	
Me	Me										2.28		2.54	
Me	Ph										2.20		2.48	
(f) $R^2 =$ H, $R^6 =$ H	$R^7 =$ H		6.87	8.25		8.3	8.41							89JHC1109
H, Me	Me		6.63	8.05							2.60	2.61		
H, Ph	Ph		6.88	8.27										
Ph, Me	Me		7.00								2.50	2.50		
(g)[c]			3.86		4.66			10.1						91CC924
					5.17									
(h)				7.04	6.96	6.56		12.5					3.21*	86CC1127
(i)				8.03	7.74	8.50							4.30*	
(j)				7.40	7.76	7.56			3.98					
(k)				7.70	7.70	8.00			3.78					
(l)				7.79	7.93	8.06			4.28					
(m)			6.53	8.05		7.57			3.94					
(n)			6.67	8.32		8.02			4.27					
(o)			6.75	8.17		7.95			4.23					

*OMe protons where indicated by asterisk. [a]in DMSO-d_6. [b]in TFA. [c]in $(CD_3)_2CO$.

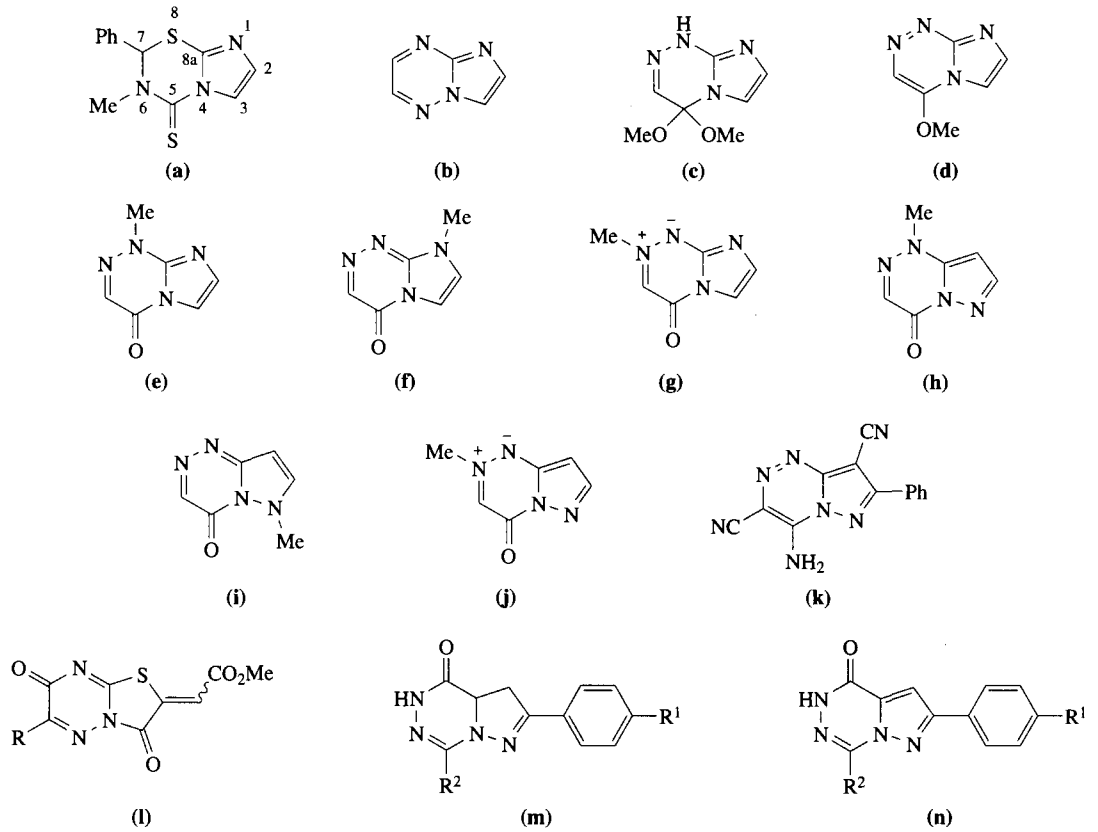
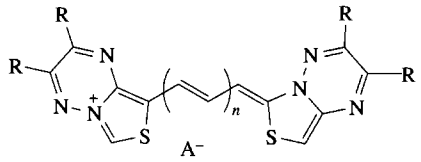


Figure 3 Compounds investigated by carbon-13 NMR spectroscopy (see Table 2).

8.17.3.3 UV Investigations

Detailed UV spectroscopic studies on the deep colored dimers (**34**) and related compounds have been published. The visible and UV absorptions of derivatives with various ethylene chains have been compared ⟨86KGS1693, 88KGS418⟩.



(**34**)

8.17.3.4 Mass Spectral Studies

Such studies have appeared for the derivatives of six different ring systems: (**12**), (**14**), (**15**), (**18**), (**20**), (**21**). These are listed in Table 3.

8.17.3.5 X-ray Elucidations

X-ray structure determinations of derivatives of ring systems of this chapter have been carried out in several cases. The most significant and interesting structures are (**35**)–(**40**). The salt (**35**) was found to contain dimers held together by NH···O=C hydrogen bonds ⟨90T4353⟩. The oxazolotriazinedione derivative (**36**) showed a nearly planar fused bicycle with a dihedral angle of 0.9° between the oxazole and triazine rings ⟨82CPB412⟩. Study of the partly reduced imidazotriazinethione

Table 2 Carbon-13 NMR shifts of selected compounds (Figure 3) in DMSO-d_6 (unless otherwise indicated).

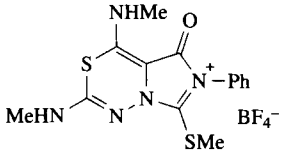
Compound			*C-1*	*C-2*	*C-3*	*C-5*	*C-6*	*C-7*	*C-8*	*C-8a*	*C-Me*	*Ref.*
(a)				129.2	121.88	172.72		63.28			43.35	85CCC2170
(b)[a]				142.8	97.8		136.5	140.9		141.7		89JHC1109
(c)[a]				126.7	107.8	100.9	127.0			143.7	51.7	86CC1127
(d)[a]				137.8	106.2	152.3	115.0			147.0	57.6	
(e)				131.0	109.1	150.6	126.6			142.8	40.9	88JOC887
(f)				123.1	105.4	148.6	133.9			145.8	32.0	
(g)				136.2	108.5	152.0	118.3			149.6	51.2	
(h)			89.2	144.4		148.8	127.4			143.5	42.9	
(i)			94.9	140.5		151.5	134.8			147.9	39.8	
(j)			96.7	145.5		150.9	119.5			149.3	51.5	
(k)			79.3	156.3		142.9	110.4			151.4		88AP(321)851
(l)	R = H				158.03		144.52	159.25		166.24		84JCS(P1)2707
	R = Me			136.35	158.04		153.27	159.80		165.97		
	R = CH_2Ph			136.39	158.11			159.21		166.10		
	R = Ph			136.30	158.07			158.91		165.00		
(m)	R^1 = H	R^2 = H	35.6	153.4		135.3			162.3	56.5		91JHC769
	R^1 = H	R^2 = Me	35.4	152.5		143.1			162.6	56.6		
	R^1 = H	R^2 = Et	35.1	152.4		147.2			162.8	56.7		
	R^1 = H	R^2 = Ph	36.0	151.7		144.3			162.8	56.7		
	R^1 = OMe	R^2 = H	35.8	153.2		135.4			163.8	56.3		
	R^1 = OMe	R^2 = Me	35.5	154.1		144.1			162.2	56.4		
	R^1 = OMe	R^2 = Et	35.4	152.4		147.1			162.3	56.6		
	R^1 = OMe	R^2 = Ph	36.1	151.6		144.4			162.9	56.6		
	R^1 = Cl	R^2 = H	35.6	152.4		135.2			162.3	56.7		
	R^1 = Cl	R^2 = Me	35.3	151.7		143.1			162.7	56.7		
	R^1 = Cl	R^2 = Et	35.2	151.5		147.1			162.9	56.9		
	R^1 = Cl	R^2 = Ph	36.0	150.8		144.2			163.7	56.5		
(n)	R^1 = H	R^2 = H	102.6	154.3		130.3			154.4	135.4		
	R^1 = OMe	R^2 = H	102.0	154.3		130.2			154.4	135.4		
	R^1 = Cl	R^2 = H	102.7	153.2		130.2			154.2	135.5		

[a] in $CDCl_3$.

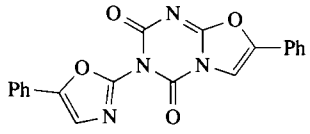
Table 3 Studies on mass spectral fragmentations of derivatives of various ring systems.

Ring system	*Ref.*
(12)	82KGS124
(14)	82KGS124
(15)	81KGS1689
(18)	84JCS(P1)2707
(20)	86JFC(32)299
(21)	86S71

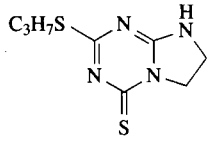
(**37**) revealed that the [1,3,5]triazine ring is essentially planar, whereas the dihydroimidazole moiety adopts a flattened halfchair conformation ⟨87LA721⟩. An additional interesting feature of this structure is that the length of the S—C single bond is 1.739 Å, which is significantly shorter than an ordinary S—C(arom.) bond (177.6 pm). Elucidation of the structure of compound (**38**) unambiguously showed that in the ring closure reaction leading to this product (see 8.17.6.5.2) retention of the configuration occurred, which observation allowed some valuable conclusions to be drawn concerning the reaction mechanism ⟨91CC924⟩. In the 2-substituted imidazotriazinone molecule (**39**), only a small deviation from the co-planar arrangement of the aromatic and heterocyclic rings (9°) was found; this has been correlated with the biological effect of this and related compounds ⟨89JCR(S)206⟩. The partially reduced bicyclic compound (**40**) was found to be composed of a planar imidazole ring fused to the puckered as-triazine with a torsion angle of C(4)—N(3)—N(2)—C(1) = 50° ⟨91MI353⟩. On the other hand, the two bonds extending from the ring junction (i.e., C(8a)—C(8) and N(5)—C(6)) are nearly planar with the imidazole ring. Derivatives of the ring systems (**3**) and (**21**) (one of each, ⟨90H(31)611⟩ and ⟨89JHC1109⟩, respectively) have also been investigated by x-ray diffraction.



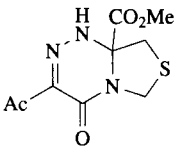
(35)



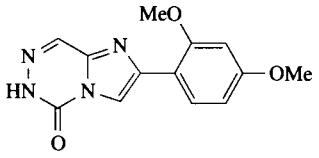
(36)



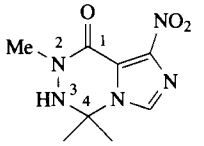
(37)



(38)



(39)



(40)

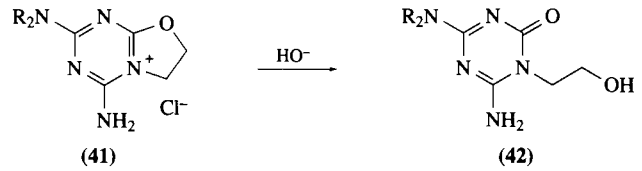
8.17.4 THERMODYNAMIC ASPECTS

Protonation equilibria of imidazo[1,2-*b*][1,2,4]triazines (**20**) have been studied and the pK_a values (found between 0.35 and 2.53) have been determined ⟨87UKZ325⟩. Tautomeric equilibria of pyrazolo[5,1-*c*][1,2,4]triazin-4-ones (i.e., derivatives of (**26**)) and related compounds have also been investigated ⟨89JHC869⟩.

8.17.5 REACTIVITY

8.17.5.1 Ring-opening Reactions

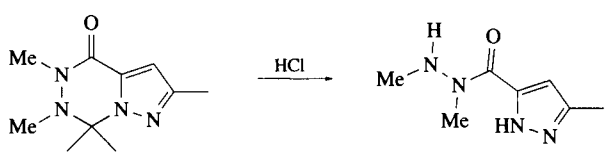
Ring opening reactions of two different ring systems should be mentioned in this chapter. The substituted 5,7-diamino-1,2-dihydrooxazolo[1,5-*a*][1,3,5]triazinium salt (**41**) undergoes hydrolytic cleavage under basic conditions and affords the hydroxyethyltriazinone compound (**42**) (Equation (1)). Reductive ring opening of the triazine ring of the pyrazolotriazine compound (**43**) was observed upon reaction with sodium borohydride, leading to the pyrazole derivative (**44**). The tetramethyl compound (**45**), obtained from (**43**) with methyl tosylate, also underwent ring cleavage (splitting off of acetone) when treated with acid to give the product (**46**) (Scheme 1) ⟨89JHC1045⟩.



(41) (42) (1)



(43) (44)

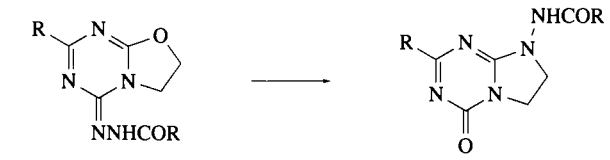


(45) (46)

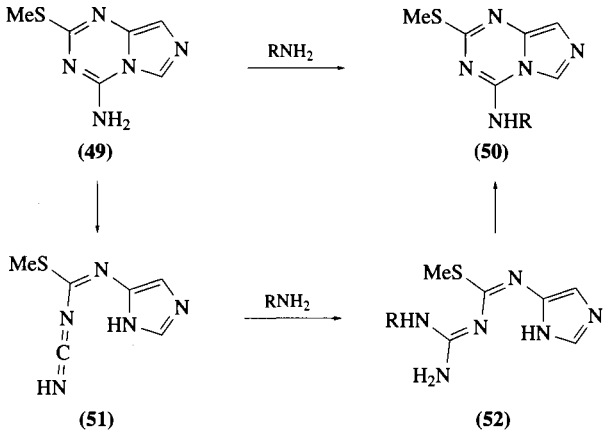
Scheme 1

8.17.5.2 Ring Transformations

Ring transformation of (**47**) was reported to result in the imidazotriazinone derivative (**48**) (Equation (2)) ⟨81KGS1689⟩. An unexpected ring transformation was observed with the attempted substitution of the methylthio group of (**49**) by amines. Instead of the expected product, a formal substitution of the 4-amino group was found which was explained by supposing a ring opening to (**51**) followed by an addition reaction to give (**52**) and ring closure to the final product (Scheme 2) ⟨92JCS(P1)2789⟩.



(47) (48) (2)

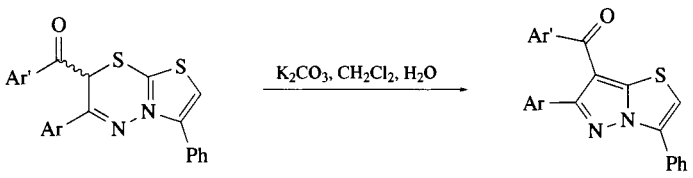


(49) (50) (51) (52)

Scheme 2

8.17.5.3 Ring Contraction Reactions

Ring contraction of (**53**) under basic conditions has been reported to result in the thiazolo[3,2-*b*]pyrazole compound (**54**) (Equation (3)) ⟨88S729⟩.



(53) (54) (3)

8.17.5.4 Formation of Further Condensed Rings

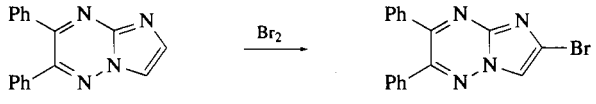
The reaction of the substituted 4-aminoimidazo[1,2-*b*][1,3,5]triazine (**55**) with ethoxymethylene malonate afforded ethyl 4-oxo-4*H*-imidazo[3,4-*c*]pyrimido [1,2-*a*][1,3,5]triazine-3-carboxylate (**56**) (Equation (4)) ⟨92JCS(P1)2789⟩.



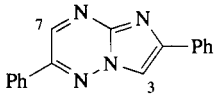
(55) (56) (4)

8.17.5.5 Electrophilic Reactions

In the case of the imidazo[1,2-*b*][1,2,4]triazine ring system (**20**), brominations, nitrations, and hydroxymethylations have been reported. Compound (**57**) reacted with bromine at position 2, i.e., (**58**) was formed, (Equation (5)), and the nitration of the same starting compound showed similar selectivity ⟨84KGS413⟩. Hydroxymethylation of the isomeric diphenyl derivative (**59**) was found to take place at positions 3 and 7 ⟨84KGS1565⟩.



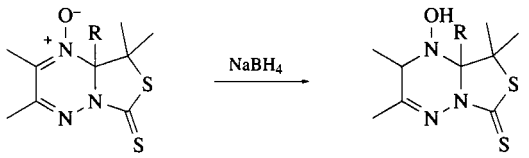
(57) (58) (5)



(59)

8.17.5.6 Reductions

Reduction of the N(1)—C(2) bond in the derivative (**60**) was reported in the reaction with sodium borohydride to yield the *N*-hydroxy product (**61**) (Equation (6)) ⟨87KGS554⟩.



(60) (61) (6)

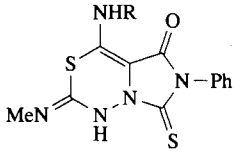
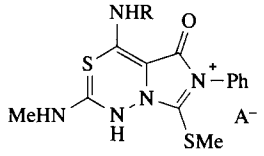
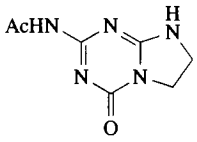
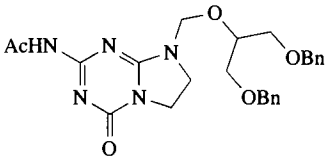
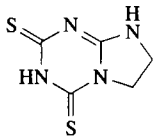
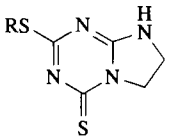
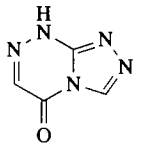
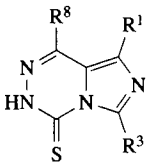
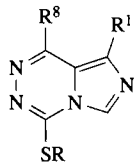
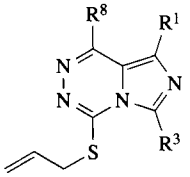
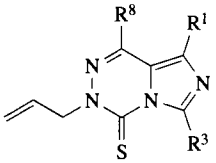
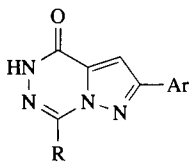
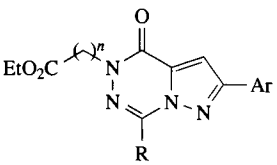
8.17.5.7 Alkylation and Realkylation Reactions

Alkylation and realkylation reactions have been reported for derivatives of five different ring systems. These are summarized in Table 4.

8.17.5.8 Transformations of Substituents of the Various Ring Systems

Several functional group transformations have been published which are summarized in Table 5.

Table 4 Alkylations of derivatives of the various ring systems.

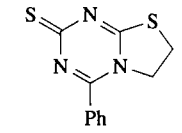
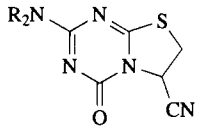
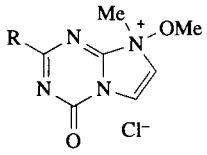
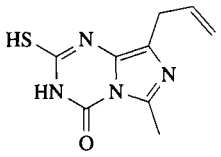
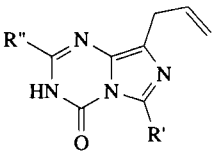
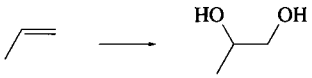
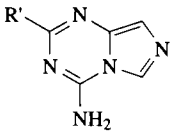
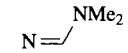
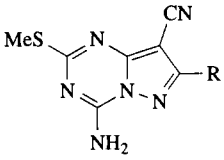
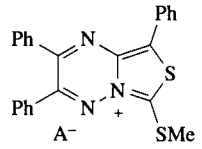
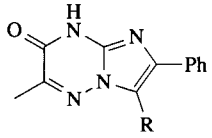
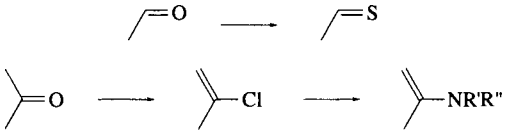
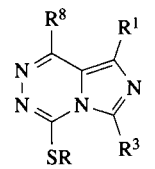
Ring system	*Reactant*	*Product*	*Ref.*
(9)			90T4353
(15)			85JHC1137
(15)			87LA721
(24)		Mixture of methylated products	88JOC887
(32)			85JMC1704
(32)			85JMC1704
(33)			92CPB1411

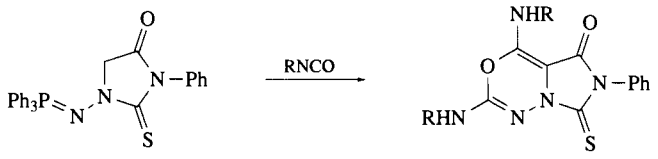
8.17.6 RING SYNTHESES CLASSIFIED BY RING SYSTEMS

8.17.6.1 Synthesis of Fused Oxadiazines and Thiadiazines

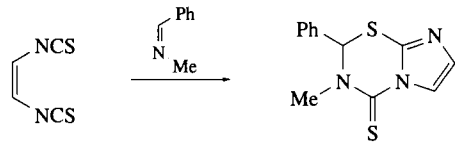
Compound (**63**) represents the first example of the imidazo[1,5-*d*][1,3,4]oxadiazine ring system (**1**) which was obtained by the reaction of (**62**) with isocyanates (Equation (7)) ⟨90T4353⟩. A simple route to (**65**) was found by the cyclization of vinylene diisothiocyanate with *N*-benzylidenemethylamine (Equation (8)) ⟨85CCC2170⟩. Compound (**67**) is the first representative of the imidazo[5,1-*b*][1,3,5]thiadiazine ring system (**3**). This was obtained by reaction of ethyl isocyanoacetate (**66**) and arylsulfenylthiocyanates followed by treatment with triethylamine (Equation (9)) ⟨90H(31)611⟩. The structure of the product was verified by x ray (see Section 8.17.3.5).

Table 5 Functional group transformations of derivatives of the various ring systems.

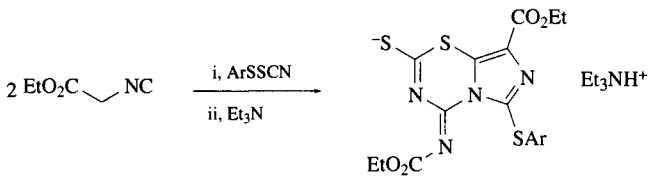
Ring system	*Reactant*	*Transformation*	*Ref.*
(14)			92T1953
(14)			87KGS978
(15)			85KGS1125
(16)			87MI 817-01
(16)			87MI 817-01
(16)			92JCS(P1)2789
(17)			88T7155
(19)			88KGS418
(20)			86KGS981
(32)			85JMC1704



(62) (63) (7)

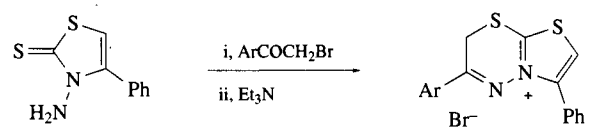


(64) (65) (8)

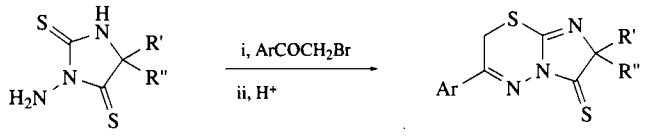


(66) (67) (9)

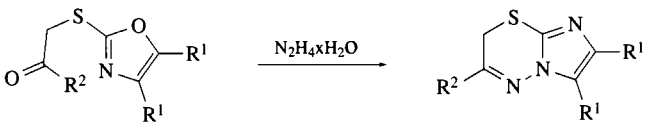
Positively charged derivatives of the ring system (**4**) have been reported ⟨87H(26)1323, 88S729⟩. In these syntheses, *N*-amino-4-phenylthiazol-2(3*H*)thione (**68**) was reacted with phenacyl bromide derivatives to yield the products (**69**) as bromide salts (Equation (10)). The same ring closure principle was applied for the 1,2,6,7-tetrahydroimidazo[5,1-*b*][1,3,4]thiadiazine (**71**)—ring system (**5**)—which was obtained from the dihydroimidazole derivative (**70**) (Equation (11)) ⟨90JCS(P1)3003⟩. The derivative of the same ring system with an aromatic imidazole ring (**73**) was prepared by treatment of (**72**) with hydrazine hydrate (Equation (12)) ⟨82H(19)2119⟩.



(68) (69) (10)

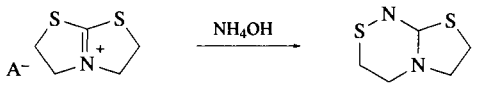


(70) (71) (11)



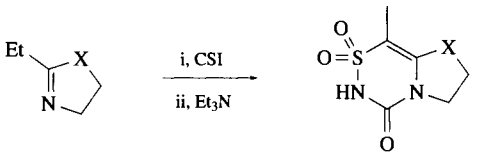
(72) (73) (12)

The totally saturated compound (**75**) represents the first example of the thiazolo[2,3-*c*][1,2,4]thiadiazine ring system (**6**). This compound was obtained as a ring enlargement product in the reaction of (**74**) with ammonia (Equation (13)) ⟨89CL89⟩. Reaction of 2-ethyloxazoline (**76**; X = O) or 2-ethylthiazoline (**76**; X = S) with chlorosulfonyl isocyanate followed by treatment with triethylamine led to the ring closed products (**77**; X = O or S), derivatives of ring systems (**7**) and (**8**), respectively (Equation (14)) ⟨93SC121⟩.



(13)

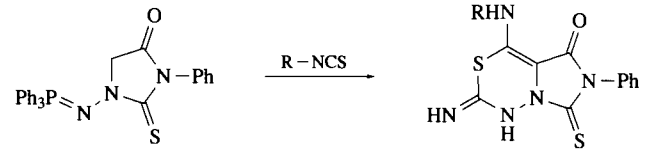
(74) (75)



(14)

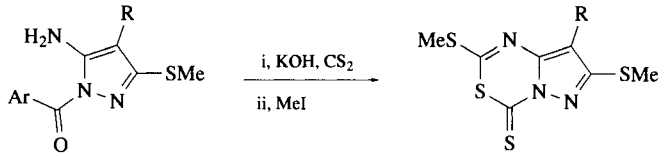
(76) (77)

Reaction of the phosphinimine derivative (**78**) with isothiocyanates also resulted in formation of a derivative of a hitherto unknown ring system: imidazo[1,5-*d*][1,3,4]triazine (**9**). The synthesis of (**79**) (Equation (15)) was explained by intermediate formation of a [5 + 5] fused ring followed by opening and closure to the final product ⟨90T4353⟩. Both the reaction of (**80**) with carbon disulfide to give (**81**) (Equation (16)) ⟨90JHC775⟩ and the ring closure of (**82**) to the sulfone (**83**) (Equation (17)) ⟨89SC3021⟩ represent synthetic pathways to two new ring systems (i.e., derivatives of pyrazolo[1,5-*c*][1,3,5]thiadiazine (**10**) and imidazo[1,2-*b*][1,2,6]thiadiazine (**11**), respectively).



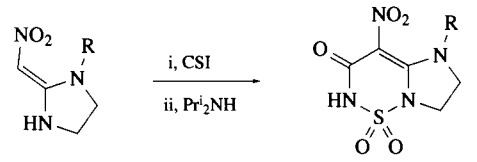
(15)

(78) (79)



(16)

(80) (81)

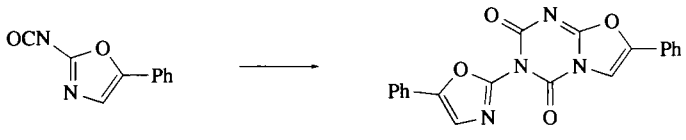


(17)

(82) (83)

8.17.6.2 Synthesis of Oxazolo- and Isoxazolo[1,3,5]triazines

Synthesis of derivatives of the two isomeric ring systems (**12**) and (**13**) are discussed in this section. An example of the ring system (**12**) in unsaturated form was obtained by the dimerization reaction of oxazoloisocyanate (**84**), which afforded (**85**) (Equation (18)) ⟨82CPB412, 82CPB4195⟩, whereas derivatives with a saturated oxazole ring for example, the salt (**87**) prepared from (**86**) (Equation (19)) ⟨92KGS228⟩—have also been reported (see also ⟨81KGS1689⟩).



(18)

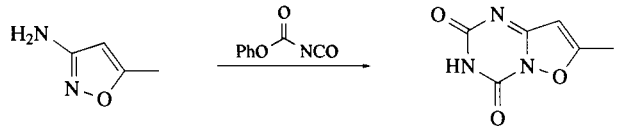
(84) (85)



(19)

(86) (87)

Compound (**89**), the first representative of the ring system isoxazolo[2,3-*a*][1,3,5]triazine (**13**), was obtained by the reaction of (**88**) with phenoxycarbonylisocyanate (Equation (20)) ⟨87JHC501⟩. Other derivatives of this ring system have also been described ⟨90IJC(B)182⟩.

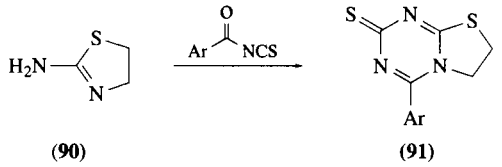


(20)

(88) (89)

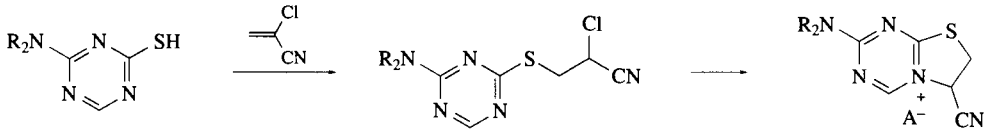
8.17.6.3 Synthesis of Thiazolo[3,2-a][1,3,5]triazines

Principally, two approaches have been applied for the synthesis of these ring systems: (i) closure of the triazine ring as shown by the reaction of aminothiazoline (**90**) with aroylisothiocyanate to give (**91**) (Equation (21)) ⟨83MI 817-01⟩, or (ii) closure of the thiazole ring as realized in the transformation of (**92**) to (**93**) followed by cyclization to (**94**) (Scheme 3) ⟨87KGS978⟩. Several other examples of related ring closures have been published ⟨82AP(315)791, 82CCC1229, 82CPB4195, 82KGS124, 87LA65, 87MI 817-02, 91SC319⟩.



(21)

(90) (91)



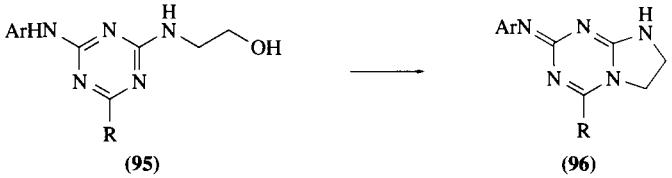
(92) (93) (94)

Scheme 3

8.17.6.4 Synthesis of Imidazo- and Pyrazolo[1,3,5]triazines

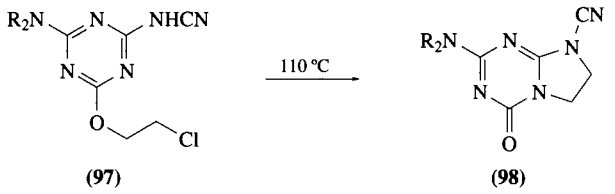
Three ring systems—(**15**), (**16**), (**17**)—belonging to this section were reported in CHEC-I (see Section 8.17.1). Some more important new applications are as follows;

(i) Ring system imidazo[1,2-*a*][1,3,5]triazine (**15**). The hydroxyethylamino compound (**95**) when heated underwent ring closure to (**96**) (Equation (22)) ⟨87NKK40, 88NKK236⟩ and formation of the related *N*-cyano product (**98**) by cyclization of (**97**) was also reported (Equation (23)). Also a partially reduced derivative (**100**) was obtained by the reaction of 2-chloroimidazoline hydrochloride (**99**) with ammonium thiocyanate (Equation (24)) ⟨87LA721⟩. Other syntheses (mostly applications of well-established methods) have also been published ⟨81MI 817-01, 85KGS1125, 87NKK40, 88NKK236, 92KGS228⟩. The ring closure of (**101**) led to formation of the benzologue (**102**) (Equation (25)) ⟨82AP(315)791, 93MI 817-01, 94MI 817-01⟩.



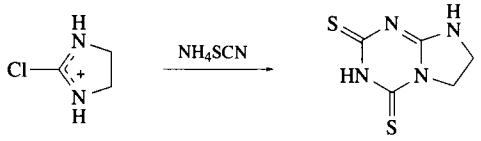
(22)

(95) (96)



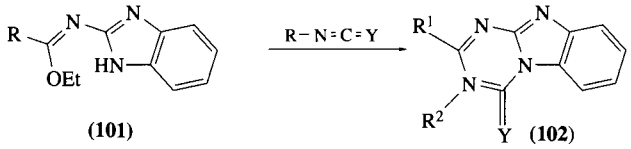
(23)

(97) (98)



(24)

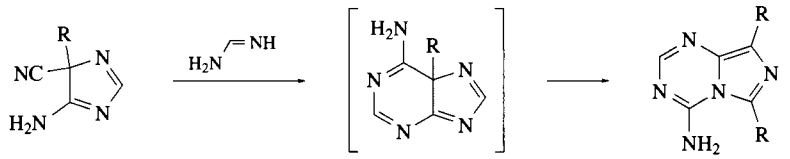
(99) (100)



(25)

(101) (102)

(ii) Ring system imidazo[1,5-*a*][1,3,5]triazine (**16**). Synthesis of derivatives of this ring system using translocative rearrangements has been published ⟨82JA235, 83JOC3⟩: reaction of (**103**) with formamidine gave (**105**) via formation of intermediate (**104**) (Equation (26)). Syntheses of other representatives of this ring system have also been reported ⟨87MI 817-01, 92JCS(P1)2789⟩.



(26)

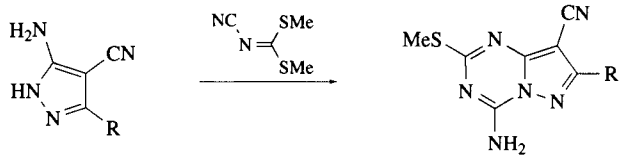
(103) (104) (105)

(iii) Ring system pyrazolo[2,3-*a*][1,3,5]triazine (**17**). Ring closure of the open chain compound (**106**) to (**107**) under basic conditions (Equation (27)) ⟨85LA1962⟩, and conversion of (**108**) into (**109**) (Equation (28)) ⟨88T7155⟩ are two important new routes to these compounds. Other approaches have also been published ⟨84JHC389, 86JHC349, 89AP(322)557⟩.



(27)

(106) (107)



(28)

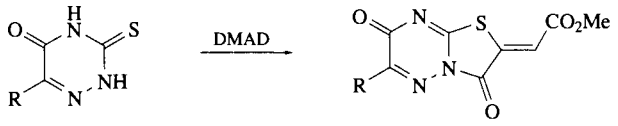
(108) (109)

8.17.6.5 Synthesis of Fused [1,2,4]Triazines

8.17.6.5.1 b-Fused [1,2,4]triazines

Two thiazolo-fused ((**18**) and (**19**)), one imidazo-fused (**20**), and one pyrazolo-fused ring (**21**) belong to this category of systems. Compound (**111**), a representative of the new ring system

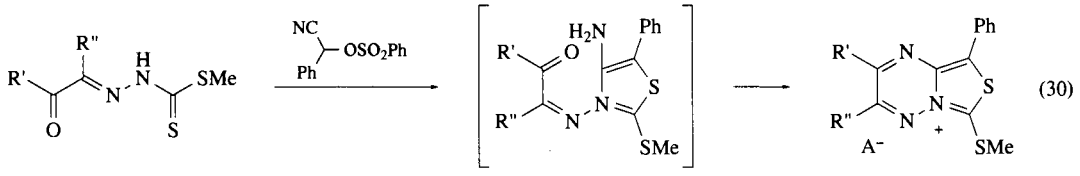
thiazolo[3,2-*b*][1,2,4]triazine (**18**), has been obtained by reaction of (**110**) with DMAD (Equation (29)) ⟨84JCS(P1)2707⟩.



(29)

(**110**) (**111**)

Several syntheses have been described for the isomeric ring system thiazolo[3,4-*b*][1,2,4]triazine (**19**). The heteroaromatic system (**114**) has been obtained by the reaction of (**112**) with *O*-benzenesulfonyl α-cyanobenzylalcohol through the intermediate (**113**) (Equation (30)) ⟨85KGS498, 85KGS1497⟩. The partially saturated derivative (**116**) of the same ring system was prepared by the treatment of (**115**) with diacetyl (Equation (31)) ⟨87KGS554⟩.



(30)

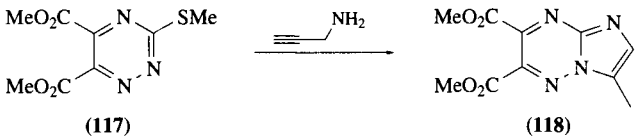
(**112**) (**113**) (**114**)



(31)

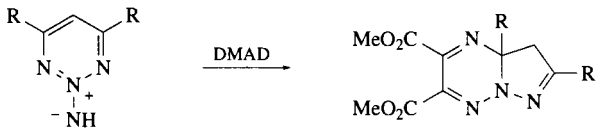
(**115**) (**116**)

Various syntheses have been published earlier for the ring system (**20**). The reaction of triazine diester (**117**) with propargylamine gave (**118**) (Equation (32)). Numerous other works have also appeared in this field ⟨84KGS413, 84MI 817-01, 86JFC(32)299, 87UKZ1095, 88JMC2221⟩. Two major routes to the new ring system pyrazolo[1,5-*b*][1,2,4]triazine (**21**) have been described: reaction of the zwitterion (**119**) with DMAD to yield (**120**) (Equation (33)) ⟨83CPB3759⟩, for which reaction two possible mechanisms have been proposed, and a condensation reaction of (**121**) with dioxo reagents to give (**122**) (Equation (34)) ⟨89JHC1109⟩.



(32)

(**117**) (**118**)



(33)

(**119**) (**120**)



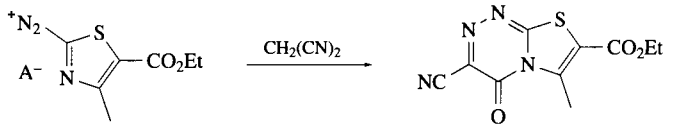
(34)

(**121**) (**122**)

8.17.6.5.2 c-Fused [1,2,4]triazines

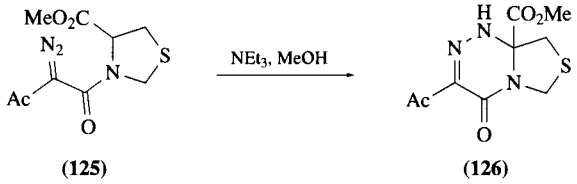
Two thiazolo-fused ((**22**) and (**23**)), two imidazo-fused ((**24**) and (**25**)), and a pyrazolo-fused ring (**26**) are discussed here. While (**22**) has already been described in CHEC-I, a novel approach to its

synthesis should be mentioned here: the reaction of the diazonium salt (**123**) with malononitrile to give (**124**) (Equation (35)) ⟨87SUL125, 89MI 817-01, 91PS(60)119⟩. Other reports have also appeared ⟨84AQ232, 87MI 817-03⟩.

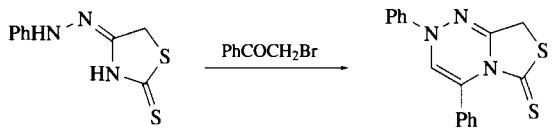


(123) (124) (35)

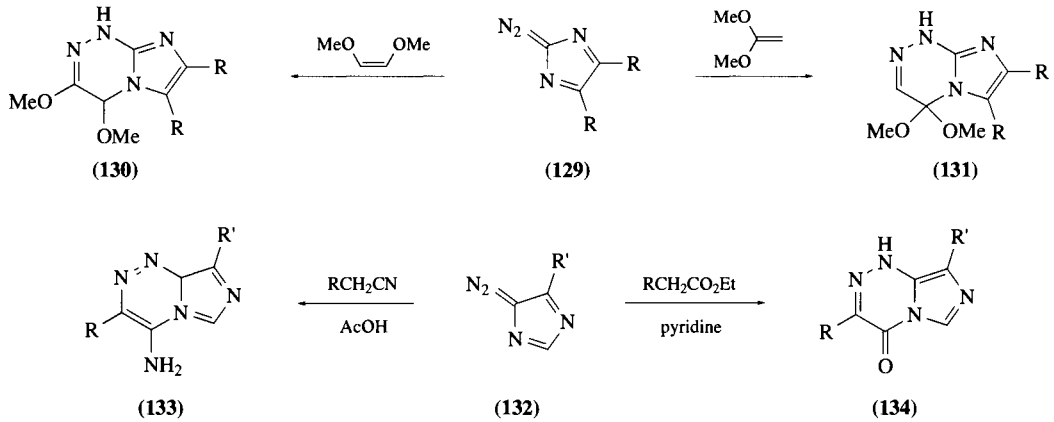
Ring closure of (**125**) to (**126**) under basic conditions (Equation (36)) ⟨91CC924⟩, as well as reaction of (**127**) with phenacyl bromide to yield (**128**) (Equation (37)), are the first examples of synthesis of the thiazolo[4,3-*c*][1,2,4]triazine ring system (**23**) ⟨86PHA101⟩. Derivatives of both imidazo-fused systems (**24**) and (**25**) can be synthesized by reactions of diazoimidazoles (**129**) or (**132**) with alkenes or reagents containing active methylene groups. Thus, reaction of 2-diazoimidazole (**129**) with 1,2-dimethoxyethene gave (**130**) ⟨90JCS(P2)1943⟩, whereas 1,1-dimethoxyethene yielded (**131**) (Scheme 4) ⟨86CC1127⟩. Compound (**129**) was also cyclized with active methylene reagents ⟨88JOC887⟩. 4-Diazoimidazole (**132**), similarly, was cyclized to (**133**) and (**134**) by using substituted acetonitriles or substituted acetic esters (Scheme 4) ⟨87JCS(P1)665⟩.



(125) (126) (36)



(127) (128) (37)



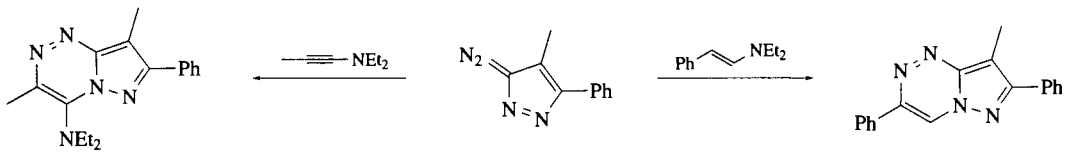
(130) (129) (131)

(133) (132) (134)

Scheme 4

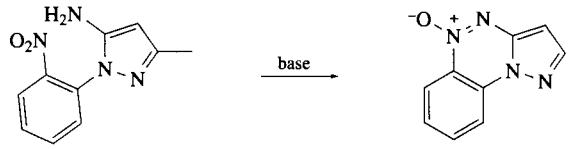
The synthesis of pyrazolo[5,1-*c*][1,2,4]triazines (derivatives of (**26**)) was also accomplished by an analogous method: the diazo compound (**135**) was reacted with ynamines to give (**136**), or with enamines to yield (**137**) after elimination of one molecule of amine (Scheme 5) ⟨83JOC2330⟩. Numerous applications of this very straightforward method have been described ⟨84JHC945, 84M431, 85JHC453, 85LA1962, 87AP(320)850, 88AP(321)851, 88JOC887, 89AP(322)557, 90CCC2790, 91JPR(333)333⟩. The intra-

molecular condensation of (**138**) led to a derivative of the benzologue of system (**26**); pyrazolo[5,1-*c*]benzo[1,2,4]triazine-5-oxide (**139**) (Equation (38)) ⟨82MI 817-01⟩.



(136) (135) (137)

Scheme 5

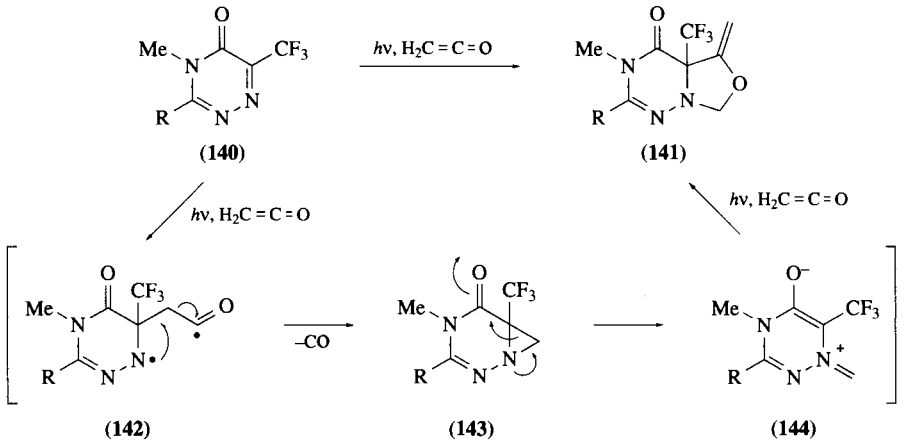


(38)

(138) (139)

8.17.6.5.3 f-Fused [1,2,4]triazines

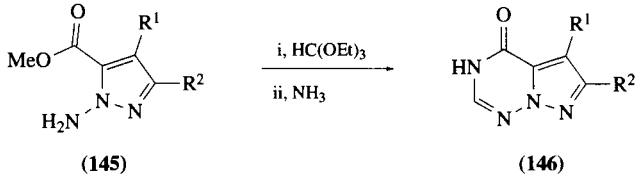
Formation of the oxazolo[3,4-*b*][1,2,4]triazine ring system (**27**) was first observed in the photo-transformation of (**140**) with ketene which gave the product (**141**) (Equation (39)) ⟨88CPB3354⟩. The proposed mechanism involves formation of the biradical (**142**), its cyclization to the fused aziridine (**143**), ring opening of the three-membered ring to give the zwitterion (**144**), which upon reaction with a further molecule of ketene affords the final product (**141**).



(39)

(140) (141) (142) (143) (144)

The first representative of the ring system (**28**), the pyrazolo[1,5-*b*][1,2,4]triazin-1(2*H*)one (**146**), has been synthesized by condensation of (**145**) with triethyl orthoformate (Equation (40)) ⟨93LA367⟩.



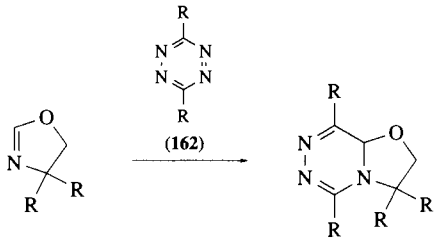
(40)

(145) (146)

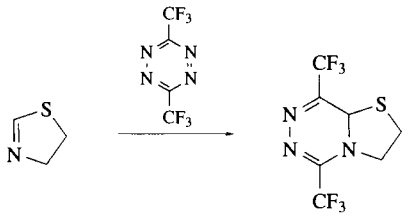
8.17.6.5.4 d-Fused [1,2,4]triazines

Partially saturated derivatives of two of the ring systems belonging to this section (oxazolo[3,2-*d*][1,2,4]triazine (**29**) and thiazolo[3,2-*d*][1,2,4]triazine (**30**)) have been prepared since 1985 for the

first time. Both the oxazoline compound (**147**) and the analogous thiazoline derivative (**149**) were reacted with tetrazines. These Diels–Alder reactions with inverse electron demand yielded the ring-closed products (**148**) and (**150**) (Equations (41) and (42)), respectively ⟨84AP(317)237⟩.

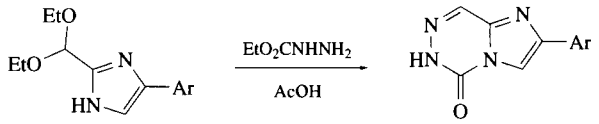


(147) (162) (148) (41)



(149) (150) (42)

A novel synthesis of imidazo[1,2-*d*][1,2,4]triazines has been realized by the ring closure of the imidazole compound (**151**) with urethane to yield the fused triazinone (**152**) (Equation (43)) ⟨89JCR(S)206⟩. Other approaches to this ring system have also been published ⟨84CCC275, 88JIC784⟩.

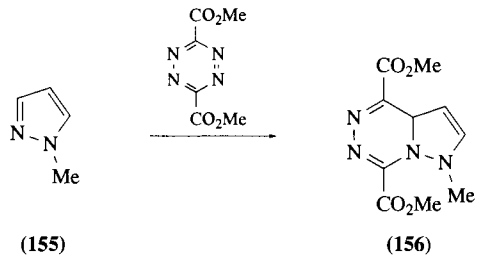


(151) (152) (43)

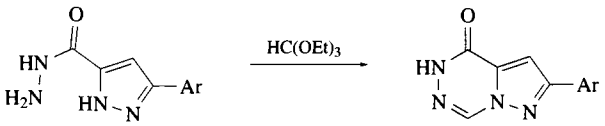
Condensation reactions of (**153**) and related compounds provided a route to derivatives of the ring system (**32**): reaction of (**153**) with acetone yielded (**154**) (Equation (44)). Another analogous ring closure has also been reported ⟨85JMC1704⟩. The Diels–Alder reaction between (**155**) and terazine diester afforded the pyrazole-fused product (**156**) (Equation (45)) ⟨84AP(317)237⟩. A similar condensation reaction as above was also applied for the ring closure to derivatives of (**33**): treatment of (**157**) with ethyl orthoformate yielded (**158**) (Equation (46)) ⟨91JHC769⟩. Another related case has also been reported ⟨89JHC1045⟩. The reaction path from (**159**) to (**160**) involving ring transformation has been described (Equation (47)) ⟨82JHC817⟩.



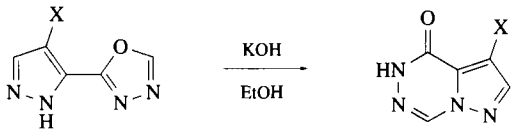
(153) (154) (44)



(155) (156) (45)



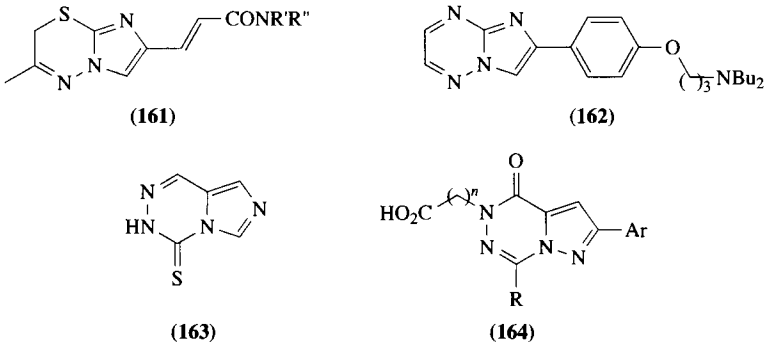
(157) (158) (46)



(159) (160) X = H, Br (47)

8.17.7 IMPORTANT COMPOUNDS AND APPLICATIONS

Four particular derivatives are worth mentioning in this section for their practical applications. The imidazothiadiazine compound (**161**) proved to possess marked antihypertensive and diuretic properties ⟨87GEP3542662⟩. The derivative (**162**) was tested for calcium channel blocking ⟨88JMC2221⟩. Compound (**163**) was found to be a potential antiasthma agent ⟨85JMC1704⟩, and the derivative (**164**) showed significant aldose reductase inhibitory effect ⟨92CPB1411⟩.



(161) (162)

(163) (164)

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8.18
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 3 : 1

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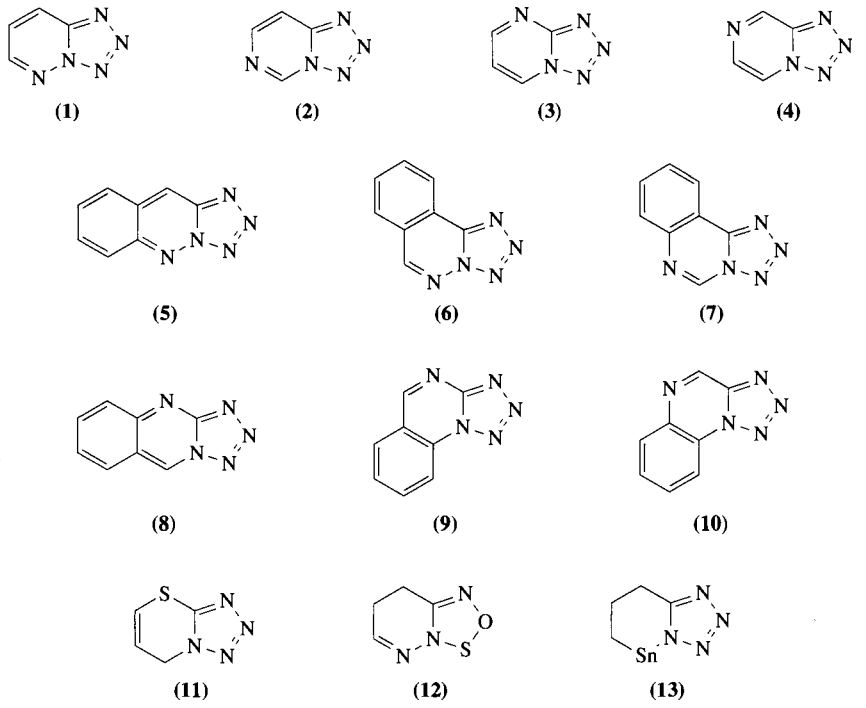
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8.18.1 INTRODUCTION

Thirteen ring systems will be discussed in this chapter. Firstly, four tetrazolodiazines; tetrazolo[1,5-*b*]pyridazine (**1**), tetrazolo[1,5-*c*]pyrimidine (**2**), tetrazolo[1,5-*a*]pyrimidine (**3**), tetrazolo[1,5-*a*]pyrazine, and their six various benzologues (**5–10**). Secondly, three new systems; tetrazolo[5,1-

b]thiazine (**11**), [1,2,3,5]oxathiadiazolo[3,4-*b*]pyridazines (**12**), and tetrazoloazastannine (**13**). A concise survey on the chemistry of (**1–10**) can be found in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(5)860, 84CHEC-I(5)880⟩.



8.18.2 EXPERIMENTAL STRUCTURAL METHODS

8.18.2.1 NMR Investigations

Proton NMR investigations have been published and were referred to in CHEC-I ⟨84CHEC-I(5)854⟩. Some additional reports on this subject have also appeared ⟨76MI 818-01, 78HCA1755, 80AG(E)924⟩.

Detailed ^{13}C-NMR studies on these ring systems have only appeared since 1984. Thus, ^{13}C NMR spectra of the 5-butyl, 5-methyl, and 5-azido substituted tetrazolo[1,5-*a*]pyrimidines ⟨79OMR(12)385, 80AG(E)924, 86IZV1916, 88MRC42, 90KGS1648⟩ as well as the 6-hydroxy and 6-methoxy substituted tetrazolo[1,5-*b*]pyridazines ⟨77JHC1403⟩ and their isomeric azido compounds have been published. This data is summarized in Table 1. In the case of 5-azidotetrazolo[1,5-*a*]pyrimidine (Table 1(d)) the second azido group can also undergo valence bond isomerization to the bis tetrazole (e) which has been identified by the ^{13}C NMR spectroscopic data (see also section 8.18.6.2).

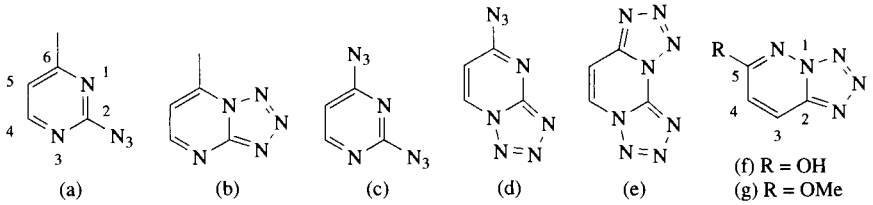
The ^{15}N NMR shifts of tetrazolo[1,5-*b*]pyridazine (**1**), tetrazolo[1,5-*a*]pyrimidine (**3**) ⟨84OMR(22)209⟩, tetrazolo[1,5-*a*]pyrazine (**4**) ⟨87MI 818-01⟩, and tetrazolo[1,5-*c*]quinazoline (**7**) are listed in Table 2 (structures (a), (b), (c), and (d), respectively) ⟨84OMR(22)209⟩.

The 5,5-diphenyl-substituted derivative of tetrazoloazastannine (**85**) was investigated by ^{119}Sn NMR spectroscopy; for the tin atom a shift of −224.3 ppm with respect to Me_4Sn was measured in DMSO solution ⟨89JOM(361)5⟩.

8.18.2.2 Mass Spectral Studies

An electron impact mass spectrometric study of a tetrazolo[1,5-*c*]pyrimidinone derivative has been published ⟨93OMS643⟩. The fragmentation results are shown in Figure 1. These results revealed

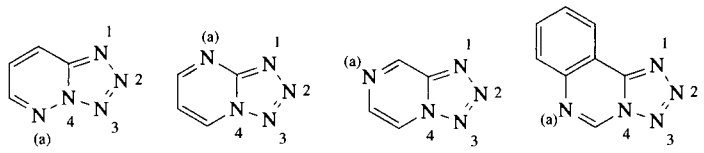
Table 1 Carbon-13 NMR shifts (DMSO) of some fused tetrazolodiazines.



(a) (b) (c) (d) (e) (f) R = OH (g) R = OMe

	C2	*C3*	*C4*	*C5*	*C6*	*C-Me*
a	154.6	–	158.8	112.4	146.8	16.6
b	154.4	–	170.2	114.3	133.7	25.1
c	162.12	160.01	106.51	164.00	–	
d	154.05	–	136.74	106.66	162.39	–
e	145.05	–	130.20	103.48	149.40	–
f	141.09	126.18	120.84	162.54	–	–
g	141.43	126.03	120.87	162.40	–	–

Table 2 Nitrogen-15 NMR shifts of some fused tetrazolodiazines. $CH_3{}^{15}NO_2$ was used as internal standard.



(a) (b) (c) (d)

		N(1)	*N(2)*	*N(3)*	*N(4)*	*N(a)*
(a)	(DMSO)	64.2	−14.5	25.2	99.9	68.9
(b)	(DMSO)	69.6	−22.3	31.7	142.2	103.8
(c)	(DMSO)	63.0	−19.5	30.9	124.8	53.7
(d)	(TFA)	71		30.4		

that both the tetrazole and its valence bond isomeric azide appear as an unfragmented peak when the pyrimidine ring bears a hydrogen atom or methyl group in positions seven and eight, whereas in other cases (e.g. with R′ = 8-halo derivatives) the tetrazole $M^{+}\cdot$ peak was detected only.

8.18.2.3 Additional Methods

Magnetic circular dichroism (MCD) of tetrazolo[1,5-*b*]pyridazine (**1**) and tetrazolo[1,5-*a*]pyrazine (**4**) has been investigated ⟨85JOC302⟩ and was compared with the UV spectra. Good agreement between the observed B terms of the L band of the free bases and the protonated species and the theoretically expected values was found and gave a rationalization for the fairly random variation of the signs and magnitudes of the MCD peaks. These results proved to be suitable also for the prediction of the site of protonation.

The azide–tetrazole equilibria of these systems have also been investigated by UV ⟨88MI 818-01⟩. Enthalpy was found to favor the tetrazole form, but entropy can overweigh the enthalpy and shift the equilibrium towards the azido form. The x-ray analysis of tetrazolo[1,5-*b*]pyridazine (**1**) revealed ⟨78AX(B)1136⟩ that this molecule is near planar, and the N(5)—C(6) and the C(7)—C(8) bonds exhibit double bond character (the bond lengths are 1.298 Å and 1.353 Å, respectively). The diphenyltetrazoloazastannine compound (**85**) also underwent x-ray analysis; the geometry about

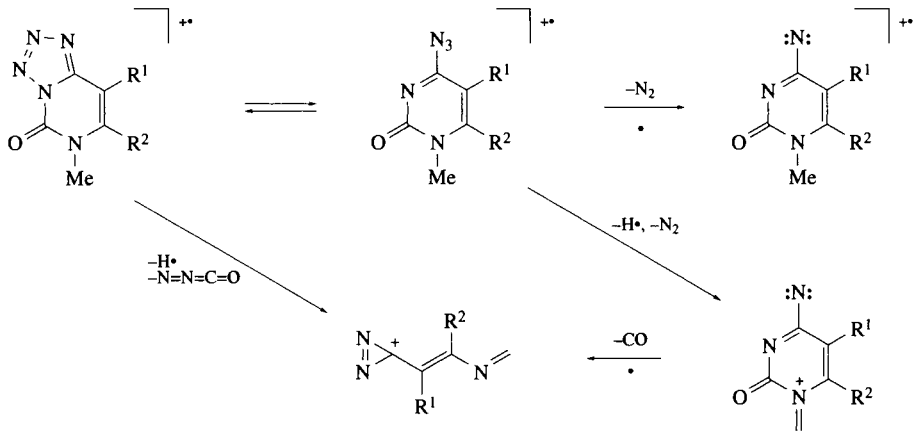


Figure 1 Mass spectral fragmentation of tetrazolo[5,1-*c*]pyrimidin-5(6*H*)one derivatives.

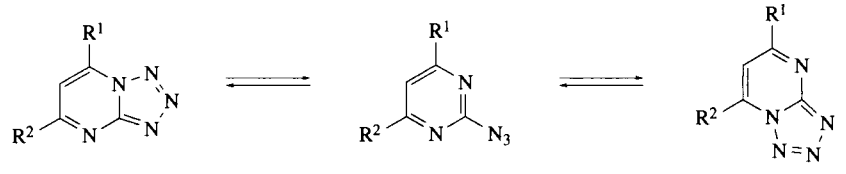
the tin atom was found to be trigonal bipyramidal with equatorial hydrocarbon groups and the N-1 of the tetrazole ring in the apical position.

8.18.3 THERMODYNAMIC ASPECTS

Although the tetrazole–azide equilibrium was the subject of numerous earlier investigations ⟨84CHEC-I(5)860⟩ some novel results have also been published. Interest especially focussed on those cases where the ring closure of the α-azidoazine can occur in two directions (i.e. a ternary azide–tetrazole equilibrium can be formed). (See also sections 8.18.6.1. and 8.18.6.2.)

Study of such a ternary system with the isomers of 2-azido-4-methylpyrimidine (Table 3, in which structure (b) affords (a) and (c)) revealed that the equilibrium is very sensitive and can be easily shifted by an appropriate choice of the solvent ⟨90KGS1648⟩.

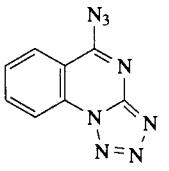
Table 3 The equilibria of unsubstituted and methyl-substituted 2-azidopyrimidines.

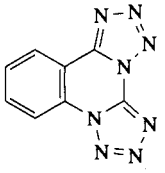


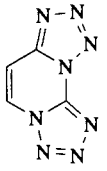
(a) (b) (c)

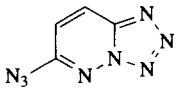
		(a)	(b)	(c)
$R^1 = CH_3 R^2 = H$	CCl_4	25	70	5
	DMSO	70	2	28
$R^1 = R^2 = H$	$CDCl_3$	21	79	
	DMSO	96	4	
$R^1 = R^2 = CH_3$	$CDCl_3$	82	18	
	DMSO	100	0	

The azido–tetrazolo compounds (**14**) can undergo ring closure to the ditetrazole (**15**). For this equilibrium the following thermodynamic parameters were obtained: ($H^{\#} = 80.6$ kJ mol^{-1}, $\Delta H = 13.0$ kJ mol^{-1}, $\Delta S = 35.5$ J mol^{-1} K^{-1}). Similarly, compound (**16**) also forms a stable ditetrazole, whereas the pyridazine derivative (**17**) does not undergo ring closure (see also section 8.18.6.2.) ⟨89IZV2002⟩.


(14)


(15)

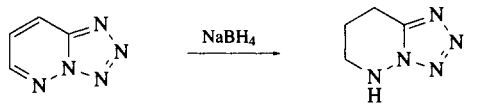

(16)

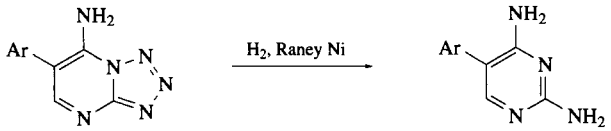

(17)

8.18.4 REACTIVITY OF THE RINGS

8.18.4.1 Reductions

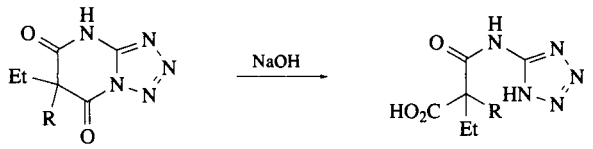
Reduction of tetrazolo[1,5-*b*]pyridazine (**1**) by sodium borohydride was reported to result in the partial reduction of the pyridazine moiety (tetrahydro compound (**18**) was formed) (Equation (1)) ⟨76JHC835⟩. The catalytic reduction of the substituted tetrazolo[1,5-*b*]pyrimidine compound (**19**) afforded the diaminopyrimidine derivative (**20**) (Equation (2)) ⟨85MIP155606⟩.

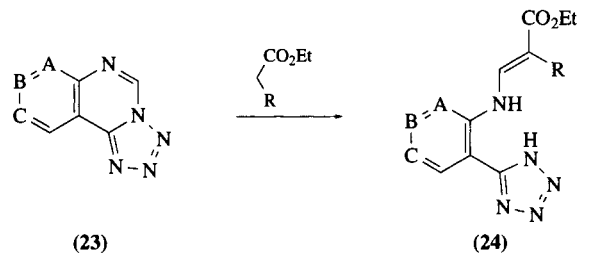

(1) (18) (1)


(19) (20) (2)

8.18.4.2 Ring-opening Reactions

Apart from the well-documented ring opening of fused tetrazoles to azides, ring opening of tetrazoloazines by nucleophilic reagents has often been reported. Such ring opening took place when the barbituric acid derivative (**21**) was treated with sodium hydroxide to give the substituted tetrazole compound (**22**) (Equation (3)) ⟨77ZC96⟩. The pyrimidine moiety was also found to open up in reaction of the azatetrazoloquinazolines (**23**) with reagents with an active methylene group; in these cases substituted aminoazinyltetrazoles (**24**) were formed (Equation (4)) ⟨85M1309⟩.

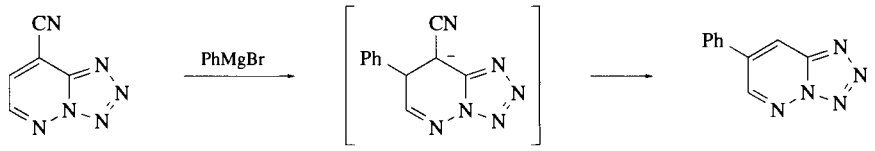

(21) (22) (3)


(23) (24) (4)

	A	B	C
(a)	N	CH	CH
(b)	CH	N	CH
(c)	CH	CH	N

8.18.4.3 Nucleophilic Addition

The reaction of 8-cyanotetrazolo[1,5-*b*]pyridazine (**25**) with Grignard reagent showed quite an unexpected course (Scheme 1) ⟨91T8573⟩. Instead of formation of a ketone side chain, addition of the phenyl group to the ring was observed and the 7-phenyl derivative (**27**) was isolated. The reaction was rationalized by proposing that the addition product (**26**) can undergo a protonation and HCN β-elimination to give (**27**).

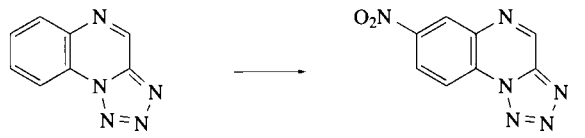


(**25**) (**26**) (**27**)

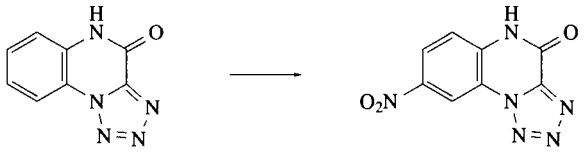
Scheme 1

8.18.4.4 Electrophilic Substitution

Nitration of tetrazolo[1,5-*a*]quinoxaline (**10**) and its 4-oxo derivative (**29**) was investigated and was found to lead to two different selective substitutions; the fully aromatic compound (**10**) gave 7-nitro derivative (**28**) (Equation (5)), whereas the lactam (**29**) afforded 8-nitro product (**30**) (Equation (6)) ⟨92JMC3319⟩. Reactivity of phenyltetrazolo[1,5-*b*]pyridazines was also described ⟨75MIP59122⟩ and nitration of the substituent phenyl ring was reported.



(**10**) (**28**) (5)



(**29**) (**30**) (6)

8.18.4.5 Dipolar Cyclizations

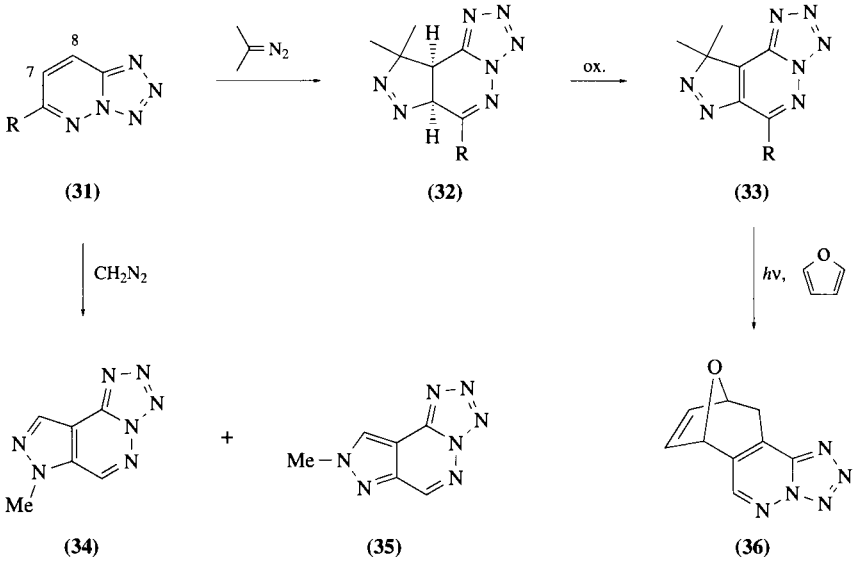
Considerable efforts have been made to explore the double bond character of the C(7)—C(8) moiety of substituted tetrazolo[1,5-*b*]pyridazines (**31**) in reactions with dipolarophiles (Scheme 2) ⟨84CC268, 84H(22)2479, 87AJC2037, 89JHC445, 90JHC2145⟩.

In all these conversions of (**31**) (for example, with diazapropane) a dihydro adduct (e.g. (**32**)) was formed first ⟨84H(22)2479⟩ which upon oxidation afforded a partly unsaturated fused system (e.g. (**33**)). Irradiation of this compound (**33**) resulted in splitting off a molecule of nitrogen and formation of a biradical which, in the presence of furan, could be trapped and the adduct (**36**) was formed. This reaction represents a unique example of a 1,4-addition of a 1,3-diradical to a diene ⟨87AJC2037⟩.

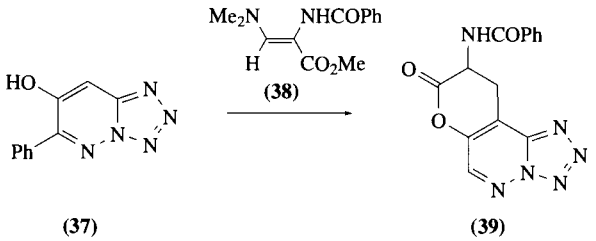
When the tetrazolo[1,5-*b*]pyridazine compound (**31**; R = H) was treated with diazomethane, a similar cycloaddition took place as observed with diazopropane followed, however, by methylation of the nitrogens of the pyrazole ring thus formed. A mixture (i.e., methylated derivatives of the two possible tautomeric products) of (**34**) and (**35**) was obtained.

The same double bond of this ring system (i.e., C(7)—C(8)) in the hydroxyphenyl derivative (**37**) was involved in cycloaddition with the enamine reagent (**38**) (Equation (7)). This reaction led to a derivative (**39**) of the 8H-pyrano[3,2-*d*]tetrazolo[1,5-*b*]pyridazine ring system ⟨93H(35)1331⟩.

Dipolar cyclization of tetrazolo[1,5-*a*]quinoxaline-5-oxide (**40**) with chloroacrylonitrile



Scheme 2



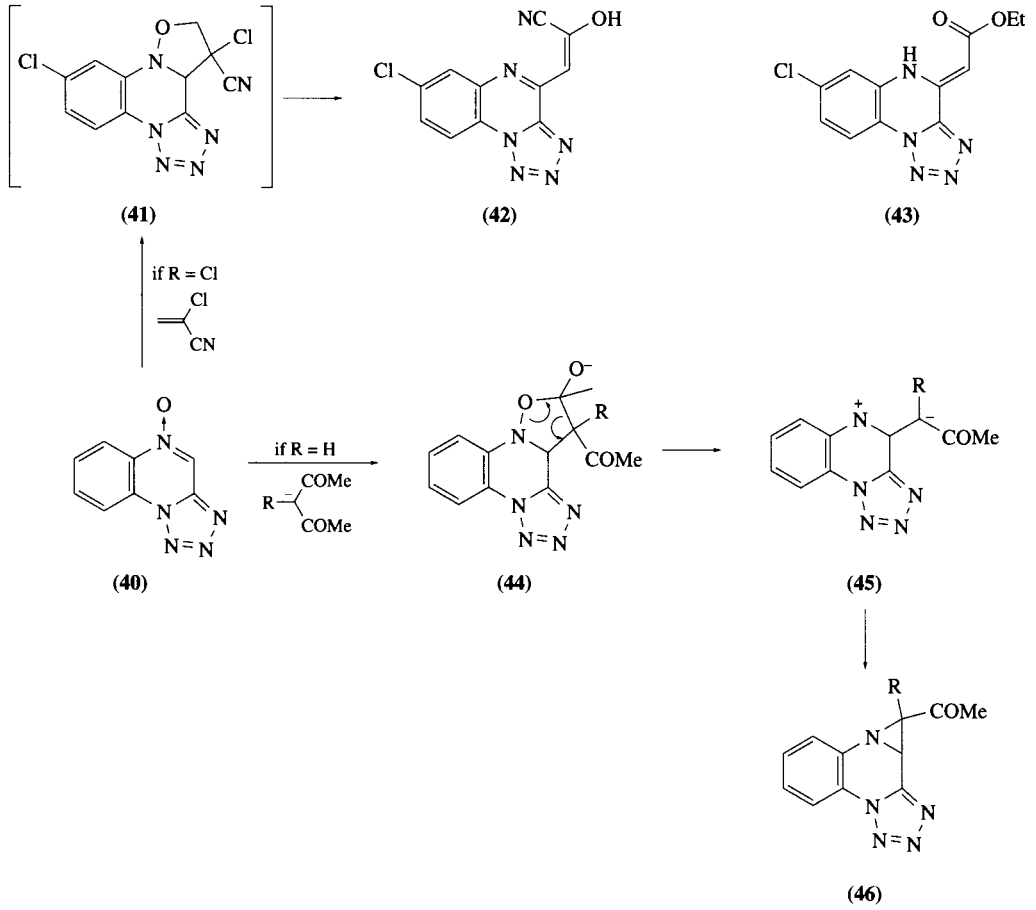
⟨93JHC781⟩ and with substituted β-diketones ⟨90JCS(P1)3049⟩ with participation of the N-oxide function was described (Scheme 3). With the first reagent intermediate (**41**) was proposed, which underwent ring opening to give (**42**), the alcoholysis of which afforded ester (**43**). Cycloaddition of (**40**) with the diketone enolates was reported to proceed similarly, i.e. to lead to the cycloadduct (**44**). This intermediate, however, formed the zwitterion (**45**) which gave the fused aziridino compound (**46**).

8.18.5 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

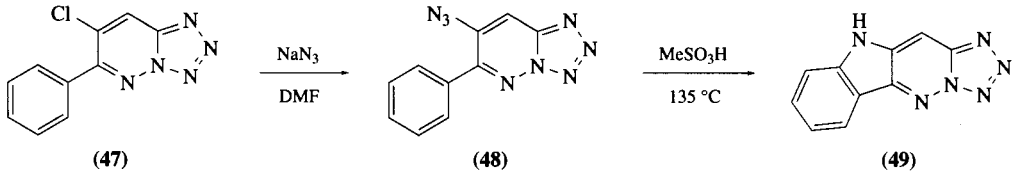
8.18.5.1 Reactivity of Azido Substituents

Various studies appeared on conversions of azido-substituted fused tetrazoles. Some of these reactions resulted in fusion of an additional ring, others afforded decomposition or reduction products. Thus, 7-azido-6-phenyltetrazolo[1,5-*b*]pyridazine (**48**) prepared from the 7-chloro derivative (**47**) was treated with methylsulfonic acid to yield (83%) the tetracycle (**49**) (Scheme 4) ⟨89S781⟩. Conversion of the tetrazolo[1,5-*a*]pyrimidine compound (**50**) bearing an acid azide and an amino group in the *o*-position was transformed to the isocyanate (**51**) which underwent internal ring closure to the imidazo-fused derivative (**52**) (Scheme 5) ⟨86H(24)1899⟩. Formation of a cyanotriazene was reported from 6-azidotetrazolo[1,5-*b*]pyridazine (**53**) (Scheme 6) ⟨80CPB529⟩. Hydrolysis of the anionic product (**54**) with hydrochloric acid in acetone gave the carbamoyltriazene compound (**55**).

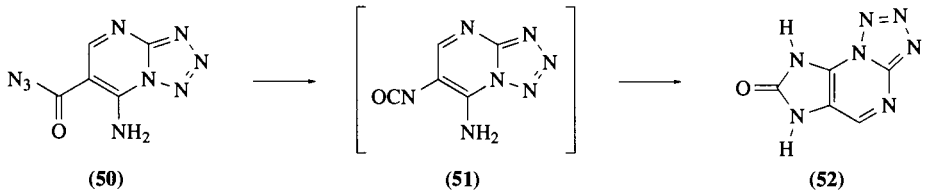
Various other conversions of an azide substituent of these ring systems have been reported, for example reduction to amino derivative by molybdenum(III) reagent ⟨80S830⟩, by titanium(III) reagent ⟨78S65⟩ and by acetonylacetone ⟨77S491⟩, whereas triphenylphosphine afforded a phosphazene ⟨91LA1225⟩ which could also be reduced ("Staudinger reaction") to an amine ⟨89S666⟩. Furthermore, 1,3-dipolar cyclization with β-diketones were carried out to yield new 1,2,3-triazoly derivatives ⟨76MI 818-03⟩.



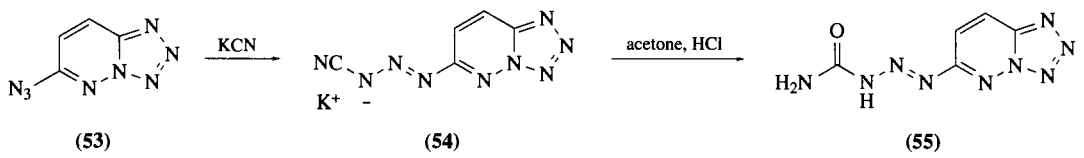
Scheme 3



Scheme 4



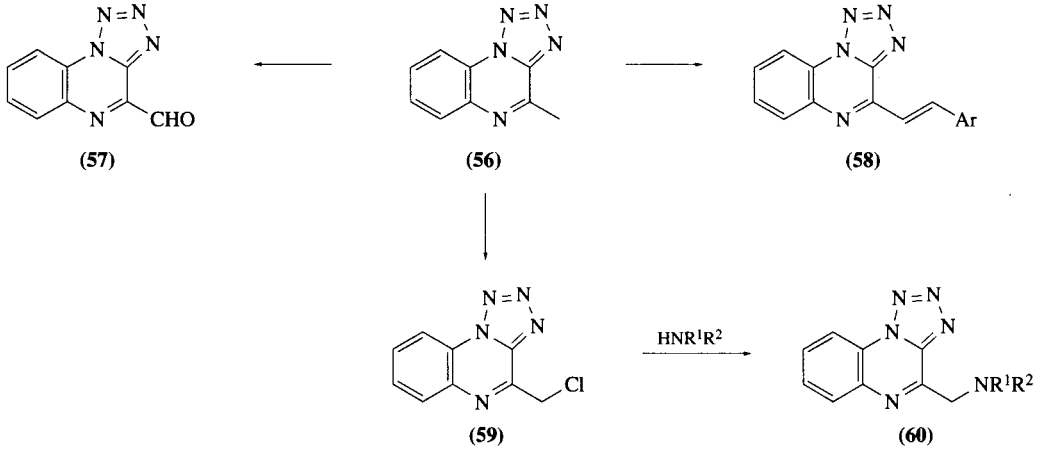
Scheme 5



Scheme 6

8.18.5.2 Reactivity of Methyl Substituents

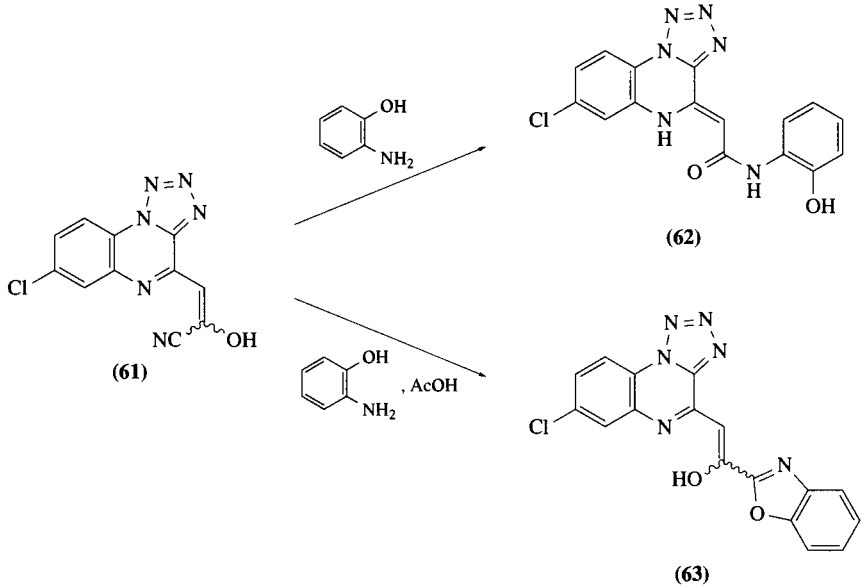
Various conversions (oxidation, condensation, and halogenation) of 4-methyltetrazolo[1,5-*a*]-quinazoline (**56**) were studied in detail (Scheme 7) ⟨82JPR329, 89JPC(331)75⟩. Thus, the starting methyl compound (**56**) was transformed by the "Kröhnke reaction" to the 4-carbaldehyde (**57**). Condensation reactions of the same starting compound (**56**) with aromatic aldehydes afforded styryl derivatives (**58**). Chlorination of the methyl group in (**56**) was also reported, to give the monochloro derivative (**59**) which was isolated and which easily reacted with secondary amines to give (**60**).



(57) (56) (58) (59) (60)

Scheme 7

Considerable interest was devoted to the 4-*β*-cyanoethenyl derivatives of this ring system (**61**) (Scheme 8) ⟨93JHC1149, 93JHC1463⟩. One of the most interesting conversions was found to occur in the reaction with *o*-hydroxyaniline under neutral conditions, the amide (**62**) was obtained, whereas the same reagent in the presence of acetic acid led to a ring closure to the benzoxazolyl compound (**63**). The enamine type of tautomeric form in the derivative (**62**) was also found to be predominant in related cases ⟨81CCC2110⟩.



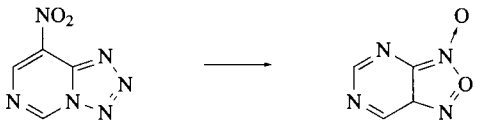
(61) (62) (63)

Scheme 8

8.18.5.3 Conversion of the Nitro Substituent

Similar to the tetrazolo[1,5-*a*]pyridine derivatives (see section 8.15) 8-nitro-tetrazolo[1,5-*c*]pyrimidine (**64**) also proved to be a suitable starting material for an internal ring closure to the

oxadiazolo[3,2-*a*]pyrimidine-1-oxide (**65**) (Equation (8)) ⟨83AF803⟩. The assignment of the position one of the N-oxide function was based on ^{1}H NMR evidence and also supported by theoretical calculations ⟨82CC267⟩.



(64) (65) (8)

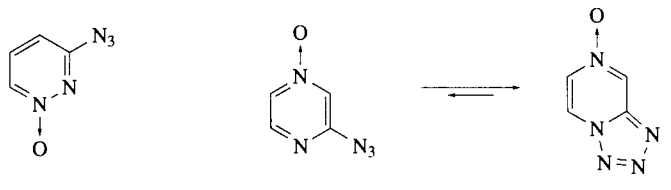
8.18.6 RING SYNTHESES AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

8.18.6.1 Routine Syntheses

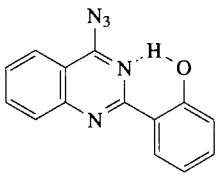
As described in the first edition ⟨84CHEC(5)901⟩ the general routes used for the synthesis of fused tetrazoloazines with bridgehead nitrogen atom proceed through the introduction of an azido group to the azine system. To this end, two main approaches have been widely established: nucleophilic substitution of a halogen by a metal azide (method A) and reaction of a hydrazino compound with nitrous acid (method B). Table 4 lists the applications of these two methods for the synthesis of various ring systems.

8.18.6.2 Results with the Azide–Tetrazole Equilibrium

The electrocyclization of α-azidoazines to fused tetrazoles was well documented and discussed also in the first edition ⟨84CHEC(5)901⟩. Some studies report special cases. Thus, attempts to ring close 3-azidopyridazine-1-oxide (**66**) to tetrazolo[1,5-*b*]pyridazine failed, whereas the 2-azidopyrazine-4-oxide (**67**) was found (in $CDCl_3$ to 85%, in DMSO to 100%) to form the cyclic isomer (**68**) (Equation (9)) ⟨83H(20)1987⟩. Although 4-azidoquinazolines generally undergo ring closure to tetrazolo fused ring systems, in the particular case of the 3-(*o*-hydroxyphenyl) derivative (**69**) no tautomerization to the tetrazole could be detected. The lack of the valence bond isomerization in this case was explained by the blocking effect of the hydrogen bond between the phenolic OH group and N(3) of the quinazoline.



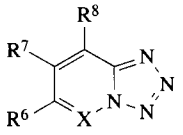
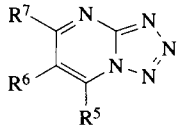
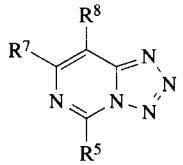
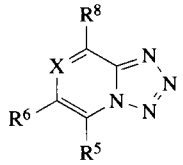
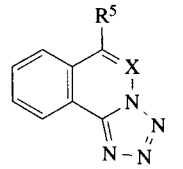
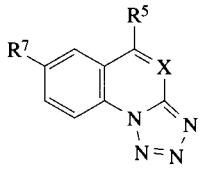
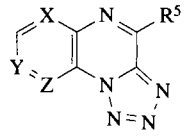
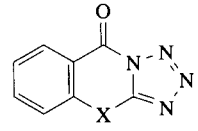
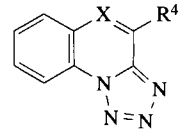
(66) (67) (68) (9)



(69)

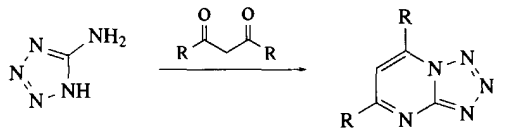
An especially interesting question arises when two azido groups are attached to the azine ring and the formation of a bis-tetrazole is in principle possible. Formation of such tricyclic systems are discussed in Section 8.18.2.

Table 4 Various applications of the synthesis of tetrazolodizines and their benzologues.

		Method	*Ref.*
	X = N, R^6 = Ph, subst. Ph, R^7 = Ph, R^8 = Ph	A	90FES331
	X = N, R^6 = R^7 = H, R^8 = CN	A	88JHC119
	X = N, R^6 = R^7 = H, R^8 = Ph	A	91TB573
	X = N, R^6p-Tolyl, R^7 = R^8 = H	B	77IJC(B)250
	X = N, R^6 = subst. Ph, R^7 = H, R^8 = Me	B	77JPR369
	X = N, R^6 = H, R^7 = Me, R^8 = CH_2R	B	81IJC(B)75
	X = N, R^6 = 2-Thienyl, R^7 = R^8 = H	A	81JHC425
	X = NO, R^6 = R^7 = R^8 = H	B	83H1987
	R^5 = NH_2, R^8 = N_3CO, R^7 = H	B	86H1899
	R^5 = Ph, R^8 = CN, R^7 = NH_2	B	83ZN(B)1556
	R^5 = Ph, R^8 = CN, R^7 = oxo(N-R at pos 8)	B	85JHC189
	R^5 = CH_2Ph, R^7 = Me, R^8 = H	B	91AKZ448
	R^5 = oxo(N-R at pos. 6), R^7 = H, R^8 = Me	A	92BBR1545
	R^5 = R^7 = Ph, R^8 = CH	B	89JHC313
	X = N, R^5 = R^6 = R^8 = H	A	82JAP(K)8259872
	X = N, R^5 = NO_2, R^6 = H, R^6 = Me	B	55ZC431
	X = NO, R^5 = R^6 = R^8 = H	B	83H1987
	X = N-Ph R^5 = oxo	B	52MI187
	X = N R^5 = Me	B	84ACH287
		B	84JHC471
	X = N-Ph R^6 = oxo R^7 = H	B	83PHA367 84PHA567 83PHA25
	X = NH R^5 = Ph R^7 = Cl	B	90PHA370
	unsubstituted	B	84CJC2570
	R^5 = sec. Amines	B	91M849
	X,Y,Z = CH or CCl, R^5 = Ar	A	92CCC1559
	R^5 = OH	A	92JMC3319
	X,Y,Z = CH or N, R^5 = H	B	85M1308
	X = N-Me	B	84PHA867
	X = S	B	88MI 818-02
	X = N, R^4 = CHO	A	90ZC251
	X = N-Me, R^4 = oxo	A	85H2025

8.18.6.3 Ring Closures Starting from 5-Aminotetrazole

Condensation reaction of 5-aminotetrazole (**70**) with reagents having two reactive β-placed double bonds proved to be a general route to the synthesis of tetrazolo[1,5-*a*]pyrimidines (**71**) (Equation (10)) (see also ⟨84CHEC(5)902⟩). Thus, either β-dioxo compounds ⟨83JHC735, 87UKZ319, 93IJC(B)886, 93JHC1267⟩ or the ethers of their enolic tautomers ⟨80AG(E)924⟩ were used to prepare new derivatives of this ring system.



(10)

(70) (71)

The same approach was also successfully applied for N-alkyl-5-aminotetrazoles and led to N-substituted tetrazolopyrimidinium salts. Thus, the 1-alkyltetrazole (**72**) gave the partly benzenoid 3-substituted salt (**73**) (Equation (11)) whereas the 2-alkyl isomer (**74**) afforded the quinonoid (**75**) (Equation (12)) ⟨87UKZ319⟩. The ring closure of the substituted aminotetrazole derivative (**76**) by trimethylsilyl chloride (Equation (13)) represents a novel route to partially reduced tetrazolo[1,5-*a*]pyrimidine derivatives such as (**77**) ⟨93ACH683⟩. A condensation reaction of α-tetrazolylaniline (**78**) with aldehydes (Equation (14)), and subsequent ring closure, was reported for the synthesis of 5,6-dihydrotetrazolo[1,5-*c*]quinazolines (**79**) ⟨88CZ135⟩.

Synthesis of the first derivatives of three new ring systems ((**11**), (**12**), and (**13**)) have been reported. A zwitterionic derivative of the tetrazolo[5,1-*b*]thiazine ring system (**11**), compound (**81**) was obtained by reaction of 1,5-dihydro-1-methyltetrazole-5-thione (**80**) with a ketene derivative (Equation (15)) ⟨80JOC2474⟩. The new [1,2,3,5]oxathiadiazolo[3,4-*b*]pyridazine derivative (**83**) was synthesized (Equation (16)) starting from the pyridazine oxime (**82**) by using thionyl chloride ⟨76CB3564⟩. The tetrazoloazastannine compound (**85**) is a representative of the first tin-containing heterocycle with bridgehead nitrogen atom which has been obtained by heating the open-chain tetrazole (**84**) (Equation (17)) ⟨89JOM(361)5⟩.



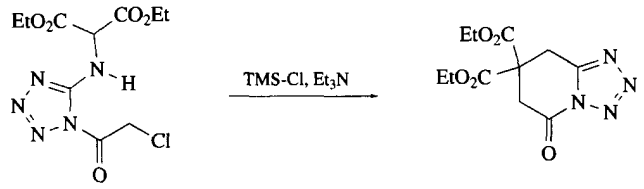
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(72) (73)



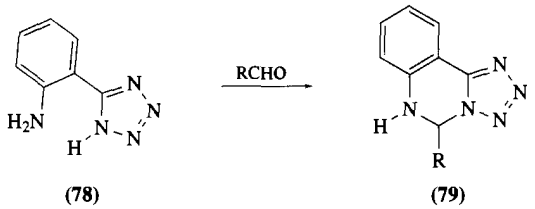
(12)

(74) (75)



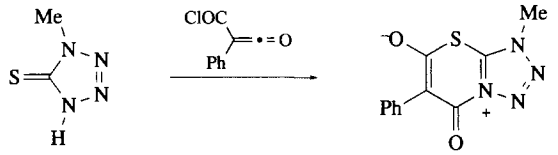
(13)

(76) (77)

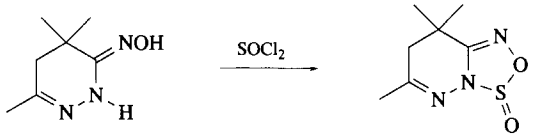


(14)

(78) (79)



(80) (81) (15)



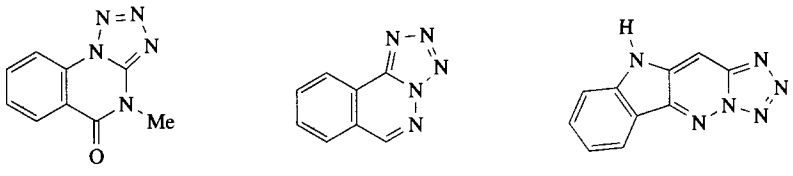
(82) (83) (16)



(84) (85) (17)

8.18.7 IMPORTANT COMPOUNDS AND APPLICATIONS

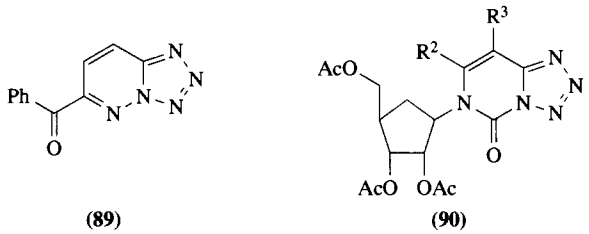
Representatives of derivatives involved in this section were used for various applications. Thus, a number of tetrazolo[1,5-*b*]pyridazine derivatives were built into cephem derivatives as substituents and were evaluated for antibiotic properties ⟨81JAN1456, 85PNA7096, 86JAP61106581⟩. The N-methyltetrazoloquinazolone compound (**86**) showed excellent fungicide effect against *Pyricularia oryzae* ⟨85H(23)2025⟩. Tetrazolo[5,1-*a*]phthalazine (**87**), on the other hand, proved to have a monoamine oxidase inhibitory effect. The fused tetrazolo[1,5-*b*]pyridazine compound (**88**) was found to exhibit anticancer activity ⟨76MI 818-02⟩.



(86) (87) (88)

The tetracyclic compound (**89**) containing a tetrazolo[1,5-*b*]pyridazine moiety proved to be a suitable cyan coupler for silver halide color photographic material of improved light and dark storage stability ⟨91JAP(K)0513964⟩.

Finally, it is important to note in this section that some 6-substituted tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one derivatives (**90**) have been prepared as AZT (azidodeoxythimidine) analogues and tested for activity against HIV virus.



(89) (90)

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8.19
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 2 : 2

GYÖRGY HAJÓS
Hungarian Academy of Sciences, Budapest, Hungary

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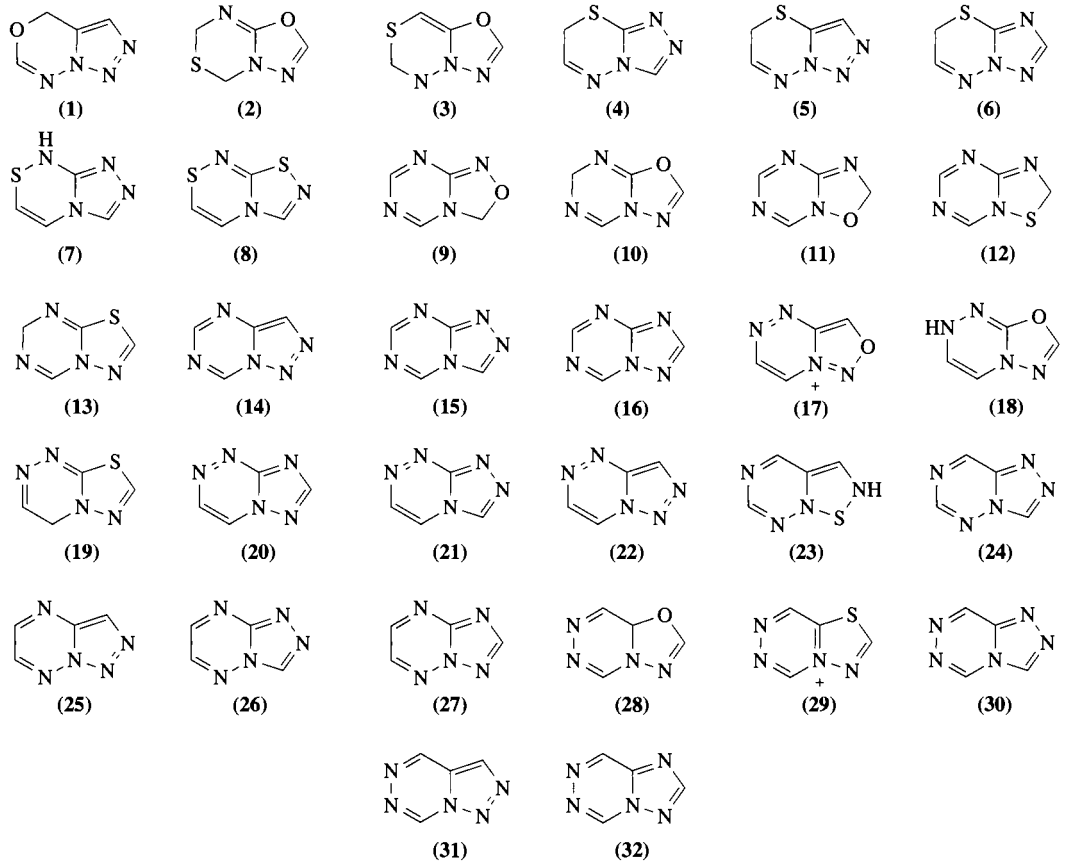
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8.19.6 IMPORTANT COMPOUNDS AND APPLICATIONS 491

8.19.1 INTRODUCTION

Because of the great variety of arrangements of two heteroatoms in each ring of a [5 + 6] fused system this section covers as many as 32 different ring systems (**1**)–(**32**). Three ring systems are discussed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (**8**) ⟨84CHEC-I(6)742⟩, (**18**) ⟨84CHEC-I(6)726⟩, and (**25**) ⟨84CHEC-I(5)853⟩ and as no novel publications on these have appeared up to 1995, they are not discussed below. Eighteen ring systems have already been mentioned in CHEC-I and some new results are described in this chapter. These are as follows: (**4**)

⟨84CHEC-I(5)853⟩, **(9)** ⟨84CHEC-I(3)477⟩, **(10)** ⟨84CHEC-I(3)517, 84CHEC-I(6)727⟩, **(11)** ⟨84CHEC-I(6)724⟩, **(13)** ⟨84CHEC-I(6)568, 84CHEC-I(6)744⟩, **(14)** ⟨84CHEC-I(3)491⟩, **(15)** ⟨84CHEC-I(3)488, 84CHEC-I(5)851, 84CHEC-I(5)859, 84CHEC-I(5)878, 84CHEC-I(5)900⟩, **(16)** ⟨84CHEC-I(3)503, 84CHEC-I(5)851, 84CHEC-I(5)857, 84CHEC-I(5)859, 84CHEC-I(5)878, 84CHEC-I(5)900⟩, **(17)** ⟨84CHEC-I(6)369, 84CHEC-I(6)373, 84CHEC-I(6)714⟩, **(19)** ⟨84CHEC-I(6)568, 84CHEC-I(6)744⟩, **(20)** ⟨84CHEC-I(5)851, 84CHEC-I(5)854, 84CHEC-I(5)857, 84CHEC-I(5)859, 84CHEC-I(5)862, 84CHEC-I(5)878, 84CHEC-I(5)899⟩, **(21)** ⟨84CHEC-I(5)851, 84CHEC-I(5)854, 84CHEC-I(5)857, 84CHEC-I(5)859, 84CHEC-I(5)862, 84CHEC-I(5)878, 84CHEC-I(5)898, 84CHEC-I(5)899⟩, **(22)** ⟨84CHEC-I(5)853⟩, **(24)** and **(26)** ⟨84CHEC-I(5)851, 84CHEC-I(5)854, 84CHEC-I(5)857, 84CHEC-I(5)859, 84CHEC-I(5)878, 84CHEC-I(5)898⟩, **(27)**, **(30)**, and **(32)** ⟨84CHEC-I(5)851, 84CHEC-I(5)859, 84CHEC-I(5)862, 84CHEC-I(5)878, 84CHEC-I(5)900⟩. Furthermore, there are 11 ring systems ((**1**), (**2**), (**3**), (**5**), (**6**), (**7**), (**12**), (**23**), (**28**), (**29**), (**31**)) on which the first publication has appeared during the ten years from 1985 to 1995; these will be referred to later in this chapter.



8.19.2 THEORETICAL METHODS

The aromatic character of (**20**) has been investigated by calculating aromaticity indexes of the ring system ⟨87T4725, 91ZOR114⟩.

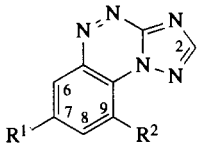
8.19.3 EXPERIMENTAL STRUCTURAL METHODS

8.19.3.1 NMR Measurements

8.19.3.1.1 Proton NMR results

Besides the large number of routine spectral data, a systematic comparison of ^{1}H NMR shifts of the benzologue of (**21**) (i.e. the [1,2,4]triazolo[5,1-*c*]benzo[1,2,4]triazine) with methyl and methoxy substitutions has been published (Table 1) ⟨82JHC61⟩.

Table 1 [1]Proton NMR shifts of some [1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazines in DMSO-d_6.

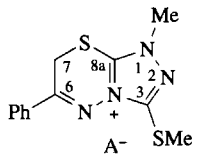


		H-2	*H-6*	*H-8*	*H-9*	*R^1*	*R^2*
R^1 = Me	R^2 = H	8.81	8.46	7.93	8.25	2.62	–
R^1 = OMe	R^2 = H	8.96	8.23	7.88	8.43	4.07	–
R^1 = Me	R^2 = Me	8.84	8.35	7.83	–	2.60	3.00

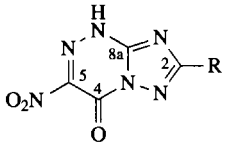
8.19.3.1.2 ^{13}C NMR results

^{13}C NMR assignments have been published for two ring systems (Table 2; 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiazine (**a**), ⟨85CS230⟩, [1,2,4]triazolo[5,1-*c*][1,2,4]triazin-5(8*H*)-ones (**b**) and (**c**), as well as their *N*-methylated derivatives (**d**) and (**e**), respectively ⟨87KGS1543⟩).

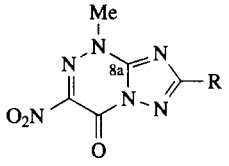
Table 2 ^{13}C NMR shifts of some [1,2,4]triazolotriazines and -thiadiazines in DMSO-d_6.



(a)



(b) R = H
(c) R = Me



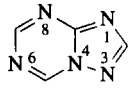
(d) R = H
(e) R = Me

	(a)	*(b)*	*(c)*	*(d)*	*(e)*
C-2	–	154.60	163.18	155.33	165.22
C-3	161.0	–	–	–	–
C-5	–	144.56	143.83	144.24	143.75
C-6	148.7	144.14	144.82	141.65	141.66
C-7	27.6	–	–	–	–
C-8a	161.9	154.26	153.89	152.97	153.04

8.19.3.1.3 ^{15}N-NMR results

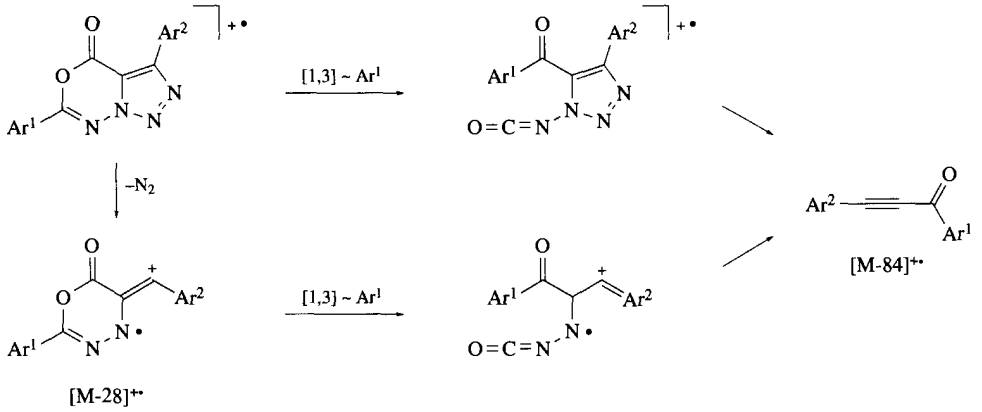
In the case of one ring system (**16**) in this area ^{15}N NMR spectra have been recorded ⟨89IZV2386⟩. The data is summarized in Table 3.

Table 3 ^{15}N NMR data for [1,2,4]triazolo[2,3-*a*][1,3,5]triazine (**16**).

			$J^{15}N$-^1H
	N-1	−149.66	13.6 (H-2)
	N-3	−108.64	15.3 (H-2)
	N-4	−153.73	11.0 (H-2)
	N-6	−135.30	12.7 (H-5)
	N-8	−137.45	–

8.19.3.2 Mass Spectral Studies

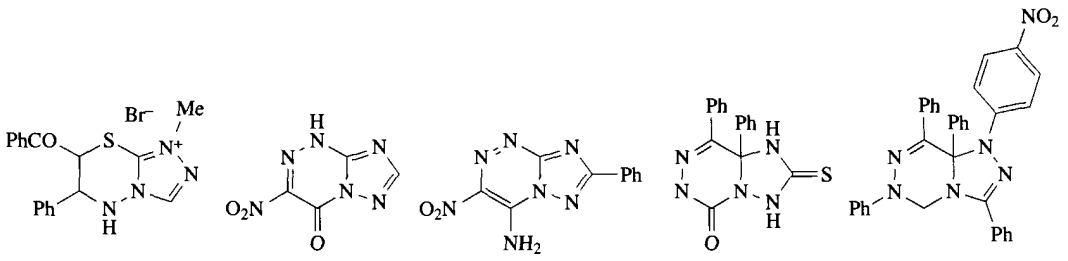
More than routine mass spectral studies appeared for the new ring system: 4*H*-[1,2,3]triazolo[1,5-*d*][1,3,4]oxadiazine (Scheme 1). The oxo derivative of this ring system underwent nitrogen loss and [1,3] aryl shift, with both paths terminating at the same fragmentation product $[M-84]^+ \cdot$ ⟨89OMS(24)424⟩. Similar results were obtained with a related reduced derivative of the same ring system ⟨86OMS(21)95⟩.



Scheme 1

8.19.3.3 X-ray Elucidations

X-ray structure determinations have been carried out for five particular derivatives in this area, (Structures (**a**)–(**e**)).



(a) (b) (c) (d) (e)

Analysis of the bond characters of 7-benzoyl-1-methyl-6-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazole (**a**) suggested that the positive charge is localized at N-1, and the thiadiazine ring conforms as an envelope flapping at C-6 ⟨87JCS(P1)1853⟩. X-ray investigation of two derivatives of [1,2,4]triazolo[3,2-*c*][1,2,4]triazine (**b**) and (**c**) have also been carried out ⟨85KGS682, 87KGS1543⟩. Structure elucidation of the partially saturated [1,2,4]triazolo[2,3-*d*][1,2,4]triazine derivatives revealed interesting structural features: compound (**d**) ⟨92MI 819-02⟩ proved to be nonplanar with the phenyl groups in equatorial and axial positions; the five-membered ring showed an envelope, whereas the six-membered ring had a twisted boat conformation. The related compound (**e**) ⟨91JCR(S)112⟩ showed some strain at the bridgeheads. The angle C(5)—N(4)—C(3) proved to be opened (112.2°), the angle N(4)—C(9)—N(1) reduced (99.2°), and the bond C(8)—C(9) elongated (1.53 A°).

8.19.4 REACTIVITY

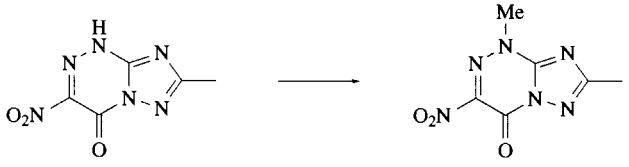
8.19.4.1 Alkylations

Selective alkylations have been reported in two cases: the triazolothiadiazine derivative (**33**) was transformed exclusively to the 1-methyl salt (**34**) by methyl triflate (Equation (1)) ⟨86JHC43⟩, whereas

the triazolotriazinone (**35**) afforded a multicomponent mixture containing the 8-methyl derivative (**36**) as the main product (Equation (2)) ⟨87KGS1543⟩.



(33) (34) (1)



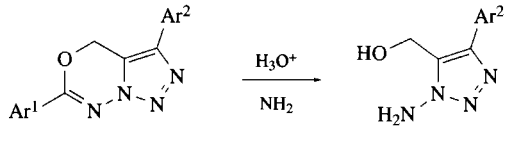
(35) (36) (2)

8.19.4.2 Dimroth Rearrangements

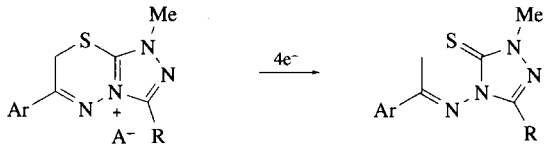
In the case of some fused [1,2,4]triazoles, Dimroth rearrangements to the appropriate isomeric ring systems have been observed. Thus formations of (**16**) from (**15**) ⟨84JCS(P1)993⟩, (**20**) from (**21**) ⟨90JCS(P2)1943⟩, and (**32**) from (**30**) ⟨82JHC1345⟩ have been reported. These transformations are also discussed in the respective sections on synthesis.

8.19.4.3 Ring Openings and Other Transformations

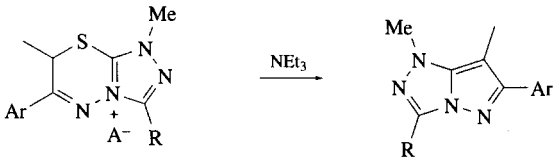
The [1,2,3]triazolo[1,5-*d*][1,3,4]oxadiazole derivative (**37**) underwent hydrolytic ring cleavage when treated with aqueous acid to yield the triazole compound (**38**) (Equation (3)) ⟨85JCS(P1)1167⟩. Ring cleavage, in turn, of the six-membered moiety was found, with the electrochemical reduction of the triazolothiadiazine compound (**39**), to form (**40**) (Equation (4)) ⟨90T5797⟩. Reactivity of the 7-methyl derivative of (**39**) (i.e. (**41**)) towards triethylamine was studied and a ring contraction to the heteroaromatic pyrazolo[3,2-*c*][1,2,4]triazole derivative (**42**) was observed (Equation (5)) ⟨85CS230⟩.



(37) (38) (3)



(39) (40) (4)



(41) (42) (5)

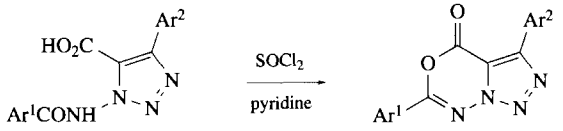
8.19.5 RING SYNTHESES CLASSIFIED BY THE RING COMPONENTS

8.19.5.1 Synthesis of [1,2,3]Triazolo[1,5-*d*][1,3,4]oxadiazine

This ring system was first prepared, in 1985, by ring closure of the diaroylamino-bromomethyl-[1,2,3]triazole compound (**43**) (Equation (6)) ⟨85JCS(P1)1167⟩. A related procedure leading from (**45**) to the oxo derivative (**46**) was published two years later, in 1987, by the same group (Equation (7)) ⟨87JHC1275⟩.



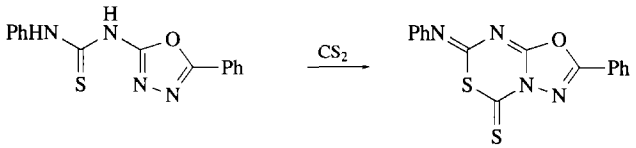
(43) (44) (6)



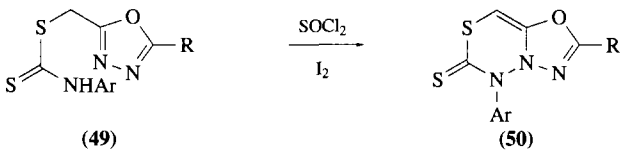
(45) (46) (7)

8.19.5.2 Synthesis of Oxadiazolothiadiazines

Two ring closure procedures resulting in formation of two new title ring systems have been published: treatment of the thioureidooxadiazine (**47**) with carbon disulfide led to the 2-phenyl-7-phenylimino-5,6,7,8-tetrahydro-5-thiooxadiazolo[3,2-*c*][1,3,5]thiadiazine (**48**) (Equation (8)) ⟨81ZC288⟩, and the oxidative ring closure of (**49**) with thionyl chloride ⟨89IJC(B)439, 91MI 819-01⟩ afforded the derivative of the isomeric oxadiazolo[3,2-*d*][1,3,4]thiadiazine, compound (**50**) (Equation (9)).



(47) (48) (8)

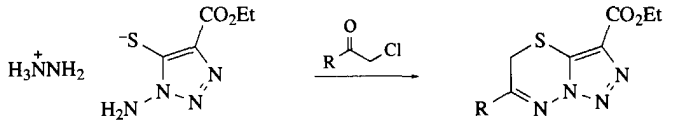


(49) (50) (9)

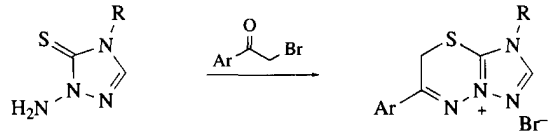
8.19.5.3 Synthesis of Triazolothiadiazines

Three new ring systems belonging to this section have been reported: the *N*-aminotriazolethiolate (**51**) was cyclized to the [1,2,3]triazolo[5,1-*b*][1,3,4]thiadiazine derivative (**52**) (Equation (10)) ⟨89JHC1811⟩, and the analogous transformation of the 4-alkyl-1-amino[1,2,4]triazolethione (**53**) gave the *N*-alkyl salt of the isomeric ring system (**54**) (Equation (11)) ⟨90S707⟩. Synthesis of the third new ring system, [1,2,4]triazolo[3,4-*c*][1,2,4]thiadiazine (**56**), has been accomplished by treatment of the hydrazinothiadiazine (**55**) with dimethylformamide dimethylacetal (Equation (12)) ⟨90JCS(P1)447⟩. Due to the great number of biologically active derivatives of the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine ring system, the literature available for the synthesis of these compounds cannot be surveyed in detail in this chapter. The most important applications for the synthesis of particular derivatives are summarized in Table 4. These involve some structurally more simple cases (a)–(k),

positively charged systems (l), (m) and ring transformations (n), (o). Some additional ring closures to specially substituted derivatives of this ring system have also been reported ⟨82G345, 86IJC(B)283, 88IJC(B)128, 88IJC(B)683, 88MI 819-02, 90SUL239, 91SUL201, 91MI 819-02, 93MI 819-01101⟩.



(51) (52) (10)



(53) (54) (11)



(55) (56) (12)

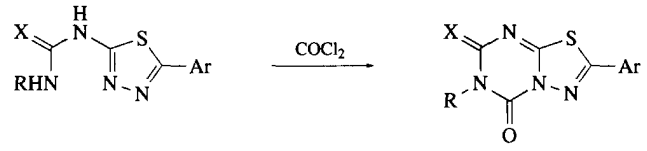
8.19.5.4 Synthesis of Oxadiazolo- and Thiadiazolo[1,3,5]Triazines

All the syntheses published for the oxadiazolo- and thiadiazolo[3,2-*a*][1,3,5]triazine ring systems ((**10**) and (**13**), respectively) utilize the ring closure possibility of ureido or thioureidoazoles by acid chlorides or related reagents.

Thus, treatment of the oxadiazole derivatives (**57**) with ethyl chloroformate gave the ring closed (**58**) (Equation (13)) ⟨87IJC(B)1000, 91M43, 92MI 819-01⟩, whereas the reaction of the analogous thiadiazole compound (**59**) with phosgene afforded the bicycle (**60**) (Equation (14)) ⟨77USP4042372, 87JMC2058⟩. Some additional ring closures to this latter ring system based on the same ring closure principle have also been reported ⟨78FES972, 81IJC(B)518, 88CB1579, 88MI 819-02, 89IJC(B)358, 89IJC(B)200, 90IJC(B)603, 91H(32)1897, 92IJC(B)139⟩.



(57) (58) (13)



(59) (60) (14)

8.19.5.5 Synthesis of Triazolo-fused [1,3,5]Triazines

Three such ring systems exist: [1,2,3]triazolo[1,5-*a*][1,3,5]triazine (**14**), [1,2,4]triazolo[4,3-*a*][1,3,5]triazine (**15**) and [1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**16**). Although as mentioned in the introduction of this chapter all three have been previously reported. Some interesting novel procedures have been

Table 4 Various applications of syntheses of [1,2,4]triazolo[3,2-*a*][1,3,4]thiadiazines.

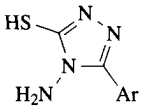
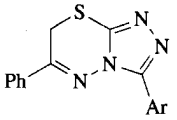
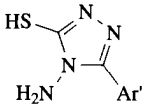
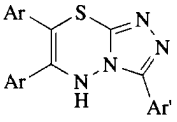
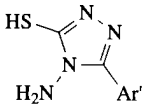
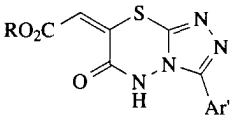
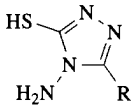
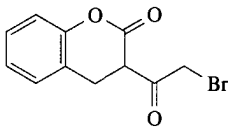
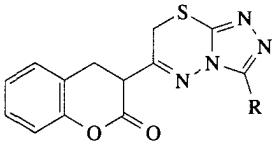
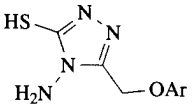
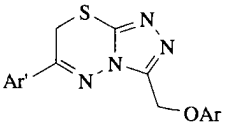
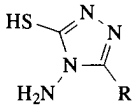
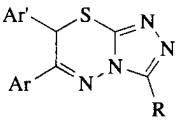
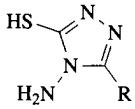
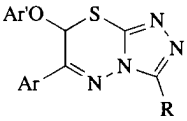
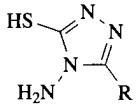
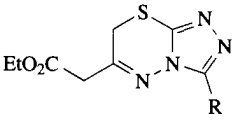
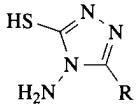
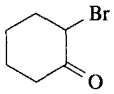
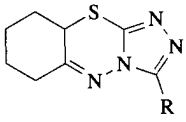
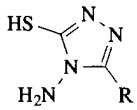
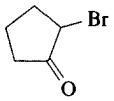
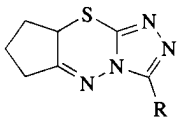
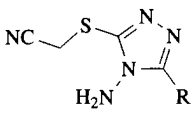
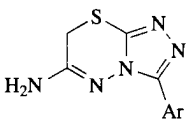
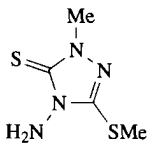
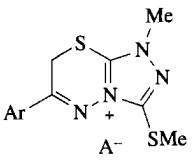
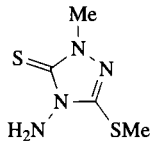
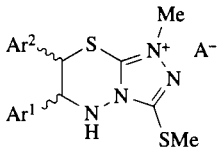
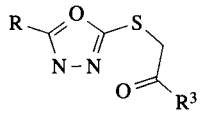
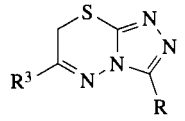
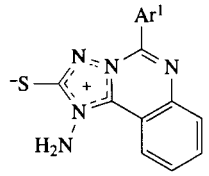
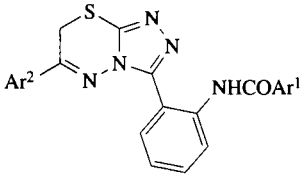
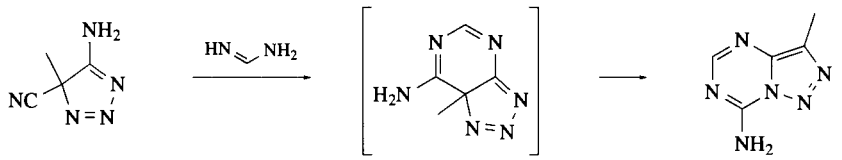
Starting compound	*Reagent*	*Product*	*Range of yields*	*Ref.*
(a) 	$PhCOCH_2Cl$		59–89%	87JHC1173
(b) 	ArCOCH(OH)Ar		30–50%	90H(31)2147
(c) 	ROOC—C≡C—COOR		39–83%	90H(31)2147
(d) 			70–80%	86CCC2214
(e) 	Ar′$COCH_2Br$		61–75%	90IJ782
(f) 	ArCOCHBr—Ar′		65–82%	90JIC695
(g) 	ArCOCHBr—OAr′		60–70%	90JIC220
(h) 	$ClCH_2$—CO—CH_2—COOEt		56–69%	92JHC1101
(i) 			40–52%	91MI 819-03
(j) 			53–68%	91MI 819-03
(k) 	H_2SO_4		60–81%	87JHC1173
(l) 	Ar$COCH_2Br$		64–98%	85CS230

Table 4 Continued.

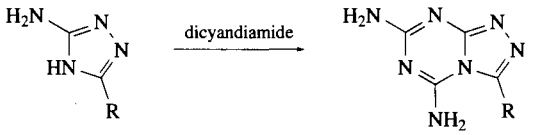
Starting compound	*Reagent*	*Product*	*Range of yields*	*Ref.*
(m) 	1) Ar^1CHO 2) Ar^2COCH_2Br		55–79%	87JCS(P1)1853
(n) 	$N_2H_4xH_2O$		48–100%	82JOC2757
(o) 	Ar^2COCH_2Br		73–78%	86JHC43

published in the ten years from 1985 to 1995. The 4*H*-[1,2,3]triazole compound (**61**) when treated with formamidine ⟨85JOC4986⟩, afforded the expected intermediate (**62**) which, however, underwent ring transformation to the heteroaromatic end product (**63**) (Scheme 2). Derivatives of the ring system (**15**) were prepared either by treatment of aminotriazole (**64**) with dicyandiamide to give (**65**) (Equation (15)) ⟨80MI 819-01⟩, or the ring closure of the hydrazinotriazine compound (**66**) by aldehydes and lead tetraacetate to (**67**) ⟨84JCS(P1)993⟩. This product, interestingly, when reacted with methanolic sodium hydroxide underwent Dimroth rearrangement to the isomeric ring system (**68**) (Scheme 3). The oxo-substituted derivative of this system (**70**) was prepared by treatment of the aminotriazole (**69**) with an *N*-substituted iminoether (Equations (16) and (17)) ⟨88MI 819-01⟩. Several other syntheses e.g. (**71**)→(**72**) ⟨89IZV2386⟩ and others ⟨84JCS(P1)993, 85JPR609, 89IZV2386, 90JHC1553, 91IZV241⟩ have been described for related cases.

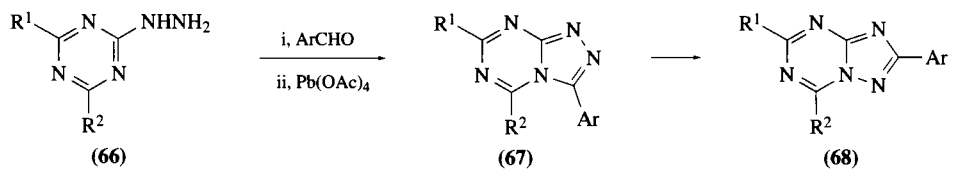


(**61**) (**62**) (**63**)

Scheme 2

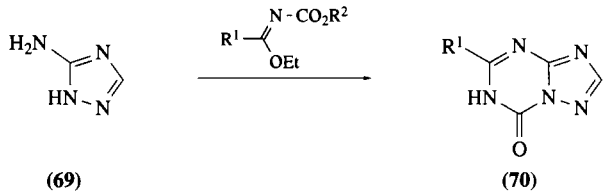


(**64**) (**65**) (15)



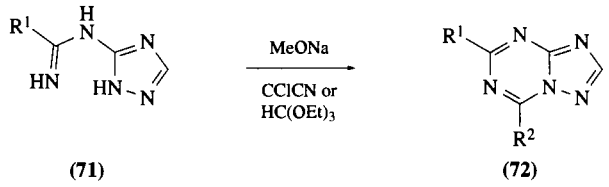
(**66**) (**67**) (**68**)

Scheme 3



(16)

(69) (70)

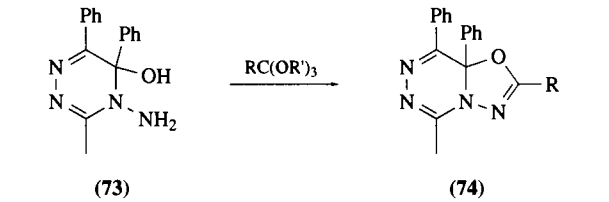


(17)

(71) (72)

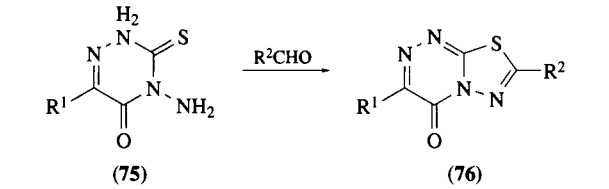
8.19.5.6 Synthesis of Oxadiazolo and Thiadiazolo[1,2,4]Triazines

Synthesis of one oxadiazolo fused (**28**) and three thiadiazolo fused ring systems ((**19**), (**23**), (**29**)) is discussed here. The partially reduced 8*a*H-oxadiazolo[3,2-*d*][1,2,4]triazine derivative (**74**) was prepared by treatment of (**73**) with trialkylorthoformate (Equation (18)) ⟨85LA78⟩. The fused thiazolotriazinium salt (**78**) was formed by ring closure of the thiazole part of the molecule starting from (**77**) (Equation (20)) ⟨91T6747⟩, similar to the derivative (**76**) of the isomeric thiadiazolotriazine ring system which was obtained from the thione (**75**) (Equation (19)) ⟨84JIC552⟩. For the synthesis of these latter derivatives, several additional papers appeared ⟨82JHC1577, 82ZC219, 86H(4)1031, 88H(8)1935, 90SUL185⟩. The first derivative of the [1,2,5]thiadiazolo[3,2-*f*][1,2,4]triazine ring system (**23**) has been accomplished by treatment of the semicarbazone (**79**) with potassium hydroxide to give the cyclic sulfone (**80**) (Equation (21)).



(18)

(73) (74)



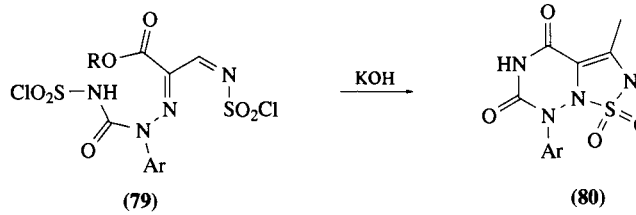
(19)

(75) (76)



(20)

(77) (78)



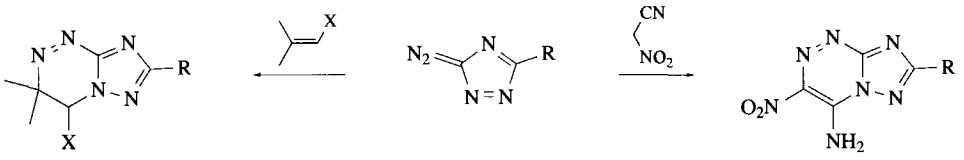
(21)

(79) (80)

8.19.5.7 Synthesis of Triazolo[1,2,4]Triazines

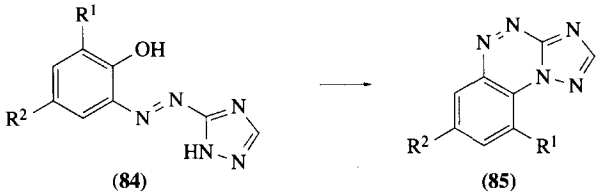
8.19.5.7.1 Systems with c-fusion at the [1,2,4]triazine ring

[1,7]-Dipolar cyclizations with diazotriazoles were the focus of several investigations, and these reactions proved to be suitable for the synthesis of two ring systems belonging to this section: (**20**) and (**22**). Thus, treatment of the diazo compound (**81**) with ethylenes or nitroacetonitrile afforded the ring closed products (**82**) and (**83**), respectively (Scheme 4) ⟨83JOC2330, 85KGS682⟩, whereas treatment of the diazo-v-triazole (**86**) with ynamines gave the heteroaromatic product (**87**) (Equation (23)). Ring closure to the tricyclic system (**85**) was accomplished ⟨82JHC61⟩ starting from the diazo compound (**84**) (Equation (22)). Formation of ring system (**20**) from (**21**) by Dimroth rearrangement ⟨90JCS(P2)1943⟩ as well as by other reactions was reported ⟨83JHC285, 86KGS662, 87KGS1543, 87PHA547, 92KGS674⟩.

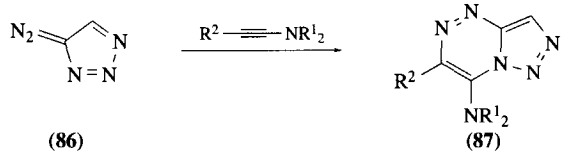


(**82**) (**81**) (**83**)

Scheme 4



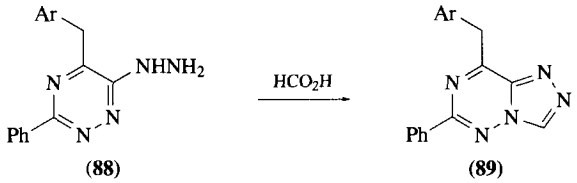
(**84**) (**85**) (22)



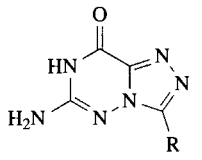
(**86**) (**87**) (23)

8.19.5.7.2 Systems with f-fusion at the [1,2,4]triazine ring

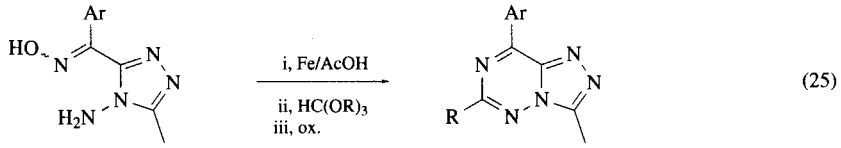
Various approaches for the synthesis of [1,2,4]triazolo[3,4-*d*][1,2,4]triazines have been published. The most important ones are as follows: treatment of the hydrazino compound (**88**) with formic acid ⟨89H(29)2279⟩ to give (**89**) (i.e. closure of the triazole moiety (Equation (24)); the synthesis of the related product (**90**) was also accomplished analogously ⟨86JMC2231⟩); reduction followed by ortho ester treatment of (**91**) affording (**92**) (Equation (25)) ⟨85JHC935⟩, and spontaneous closure of (**93**) to (**94**) was observed upon heating (Equation (26)) ⟨89MI 819-01⟩ (i.e. closure of the triazine moiety). Some additional works have also appeared ⟨85JHC1715, 86JMC2231, 89IJC(B)829⟩.



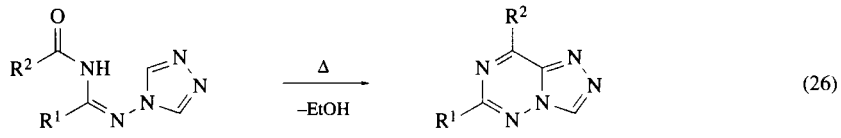
(**88**) (**89**) (24)



(90)



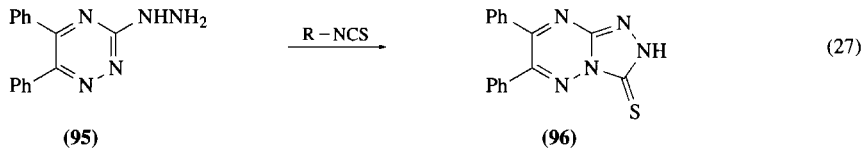
(91) (92) (25)



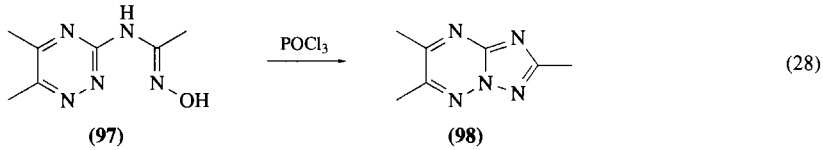
(93) (94) (26)

8.19.5.7.3 Systems with b- and d-fusion at the [1,2,4]triazine ring

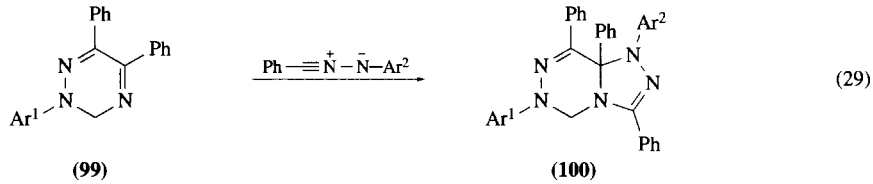
Some well established ring closure methodologies have been described for the synthesis of these ring systems. Thus, treatment of the hydrazinotriazine (**95**) with arylisothiocyanate to the thione (**96**) (Equation (27)) ⟨88M591⟩, phosphorus oxychloride treatment of the amidine (**97**) ⟨82JHC1577⟩ to give the trimethyl-substituted heteroaromatic species (**98**) (Equation (28)), or ring closure of the hydrazone to (**102**) or (**103**) depends on the reagent used (Scheme 5) ⟨88JHC743⟩. The ring system (**32**) has also been obtained by a Dimroth rearrangement of (**30**) ⟨82JHC1345⟩.



(95) (96) (27)

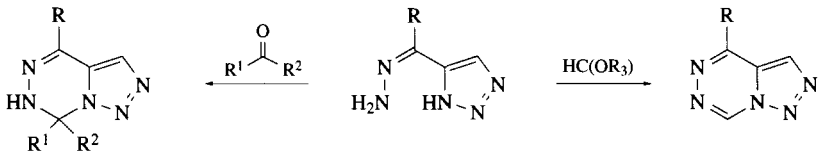


(97) (98) (28)



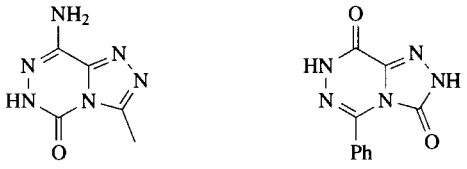
(99) (100) (29)

A fairly unusual triazolotriazine derivative (**100**) has been obtained (Equation (29)) ⟨91JCR(S)112⟩ by dipolar cyclization of (**99**) with diarylnitrilimide (cf. Section 8.19.3.3). Synthesis of the bicyclic products (**104**) ⟨82JHC1345⟩, (**105**) ⟨88S778⟩, and other related derivatives (e.g. ⟨92MI 819-02⟩, see Section 8.19.3.3) have been described.



(103) (101) (102)

Scheme 5



(104) (105)

8.19.6 IMPORTANT COMPOUNDS AND APPLICATIONS

Numerous derivatives of the ring systems belonging to this chapter showed biological activity of various kinds. The most important applications are registered in the case of three ring systems: (a) ring system (**4**): activity against gram negative bacteria ⟨88IJC(B)683⟩ and/or gram positive bacteria ⟨87JHC1173⟩, anti-inflammatory activity ⟨89FES933⟩; (b) ring system (**12**): application as herbicides ⟨87EUP239064⟩; and (c) ring system (**13**): anti-inflammatory ⟨78FES972⟩, fungicide ⟨81IJC(B)518⟩, and herbicide activity ⟨77USP4042372⟩.

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8.20
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 1 : 3

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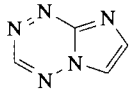
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8.20.1 INTRODUCTION

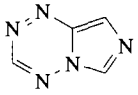
Ten ring systems are discussed in this chapter. Three of these are fused [1,2,4,5]tetrazines: imidazo[1,2-*b*][1,2,4,5]tetrazine (**1**), imidazo[1,5-*b*][1,2,4,5]tetrazine (**2**), and thiazolo[3,2-*b*][1,2,4,5]-tetrazine (**3**). Three others are fused [1,3,4,5]tetrazines: imidazo[1,2-*d*][1,3,4,5]tetrazine (**4**), imidazo[5,1-*d*][1,3,4,5]tetrazine (**5**), and pyrazolo[3,2-*d*][1,3,4,5]tetrazine (**6**). Finally, there are four different fused thiatriazines: oxazolo[2,3-*c*][1,2,4,6]thiatriazine (**7**), thiazolo[2,3-*c*][1,2,4,6]thiatriazine (**8**), imidazo[2,1-*c*][1,2,4,6]thiatriazine (**9**), and pyrazolo[3,2-*c*][1,2,4,6]thiatriazine (**10**). Most of these ring systems have been synthesized in partially saturated form, and a fully heteroaromatic system has been obtained in one case, (**1**), only.

8.20.2 THEORETICAL METHODS

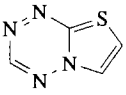
One single report on theoretical work in this area has appeared, in 1992 ⟨92JMC3377⟩: the molecular modeling of the well-known anticancer drug Temozolomide (**12**) has been carried out, and the net charges of the ring atoms have been calculated.



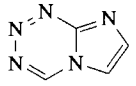
(1)



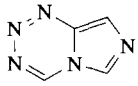
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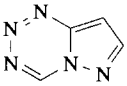
(3)



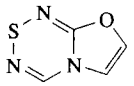
(4)



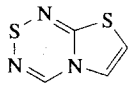
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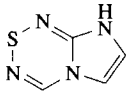
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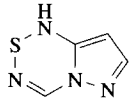
(7)



(8)



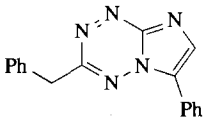
(9)



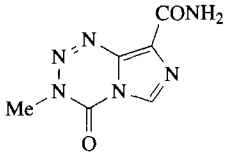
(10)

8.20.3 EXPERIMENTAL STRUCTURAL METHODS

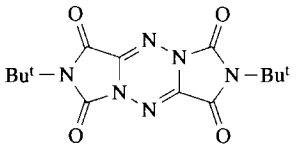
X-ray investigation of the imidazotetrazine compound (**11**) revealed that, in accordance with its heteroaromatic system, an extensive π-delocalization takes place resulting in an essentially planar geometry. Although the C—N lengths vary, all these fall within the common range ⟨79JCS(P1)333⟩. Furthermore, x-ray elucidation of the structure of Temozolomide (**12**) as well as the tricyclic diimidazo[1,2,4,5]tetrazine (**13**) have been published ⟨92JMC3377, 92S879⟩.



(11)



(12)



(13)

8.20.4 REACTIVITY

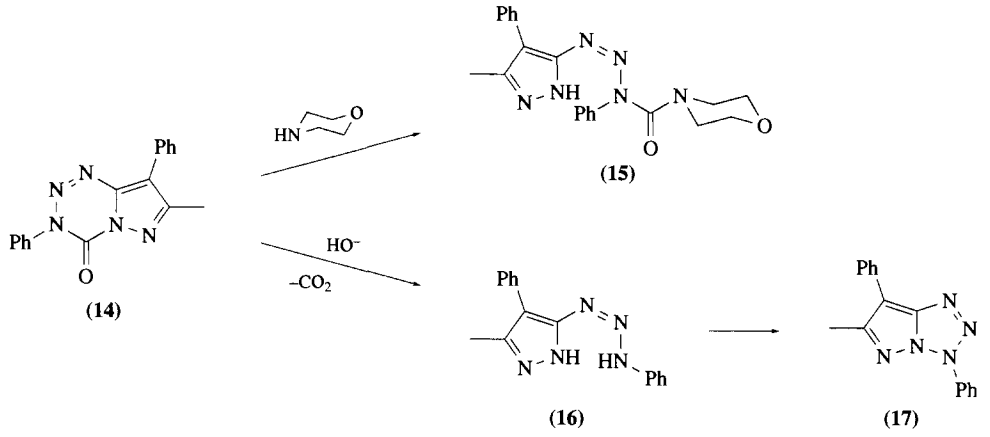
8.20.4.1 Ring-opening Reactions

The pyrazolotetrazinone compound (**14**) was found to react with nucleophiles (e.g., with secondary amines and hydroxide ion), and ring opening of the tetrazine moiety was observed ⟨87JMC357, 87CB1375⟩. Upon reaction with morpholine, the substituted carbamoyltriazene (**15**) was obtained, whereas reaction with hydroxide anion was also followed by decarboxylation to give the phenyltriazene (**16**) (Scheme 1). This compound was oxidized by lead tetraacetate to give the pyrazolotetrazole (**17**) ⟨87CB1375⟩.

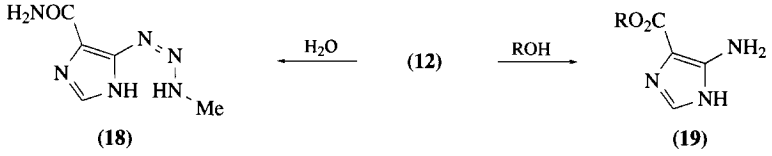
Temozolomide (**12**) ⟨93CC1177⟩ and related compounds ⟨87JMC357⟩ were also found to react with nucleophiles in a similar manner: i.e., with ring opening of the tetrazine part of the molecule. Thus, hydrolysis afforded the triazene compound (**18**), and alcoholysis ⟨84JMC196⟩ yielded an aminoimidazole carboxylic ester (**19**) (Scheme 2).

8.20.4.2 Reactions of the Substituents

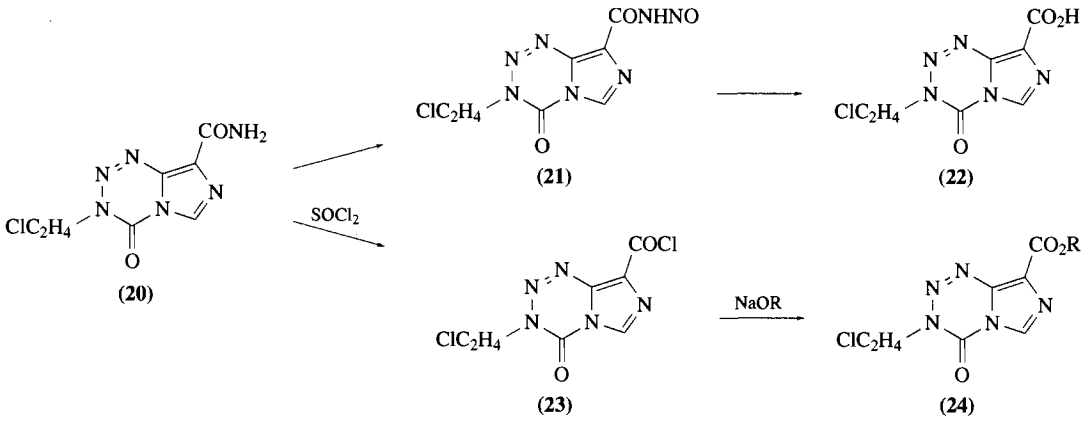
Extensive preparative work was done in order to introduce novel substituents into the acid function of Mitozolomide (**20**) ⟨90JMC1393⟩. Two approaches proved to be particularly successful: nitrosation of the acid amide group to an *N*-nitroso derivative (**21**) followed by hydrolysis to the free acid (**22**); or preparation of the acid chloride (**23**) first and its alcoholysis to the ester (**24**), which proved to react with amines selectively at the acid function without any decomposition of the ring system (Scheme 3).



Scheme 1



Scheme 2

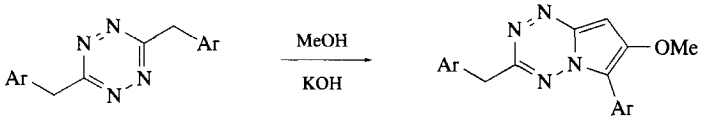


Scheme 3

8.20.5 RING SYNTHESES CLASSIFIED BY THE RING ATOMS OF THE SIX-MEMBERED RING COMPONENT

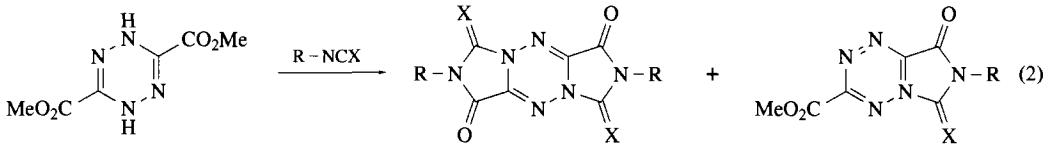
8.20.5.1 Syntheses of Fused [1,2,4,5]Tetrazines

The unexpected formation of the imidazotetrazine compound (**26**) from 1,4-dibenzyl[1,2,4,5]tetrazines (**25**) by methanolic potassium hydroxide (Equation (1)), mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(5)659⟩, has been the subject of several additional publications ⟨82JCS(P1)1165, 85JCS(P1)1081, 88JCS(P1)1439⟩. These studies revealed that a tricyclic ditetrazoloimidazole intermediate is formed by a fairly complicated multistep reaction path, which undergoes ring opening to the end product (**26**). A similar reaction was also carried out with benzyl alcohol instead of methanol.



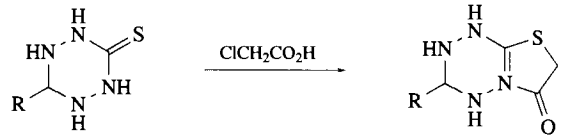
(25) (26) (1)

Reaction of dihydro[1,2,4,5]tetrazine diester (**27**) with isocyanate and isothiocyanate resulted in formation of the bis adduct (**28**) in most cases (Equation (2)). With isothiocyanates (X = S), the bicycle (**29**) was also formed ⟨92S879⟩.



(27) (28) (29) (2)

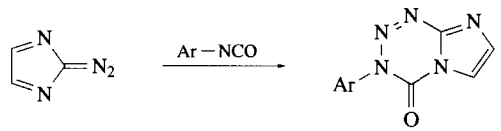
For the synthesis of thiazole-fused [1,2,4,5]tetrazines, another approach was applied as shown by the example of the hexahydrothiazolo[1,2,4,5]tetrazinone (**46**): this compound was prepared by reaction of the hexahydrotetrazine thione (**45**) (R = Ar or $(CH_2)_8CO_2Me$) with chloroacetic acid (Equation (3)) ⟨92MI 820-01, 90IJC(B)148⟩. Another related case leading to the same ring system with an unsaturated thiazole moiety was also reported ⟨92JIC693⟩.



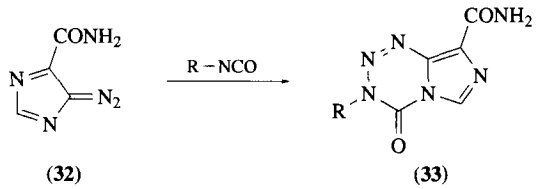
(45) (46) (3)

8.20.5.2 Syntheses of Fused [1,3,4,5]Tetrazines

Because of the known antitumor effect of some azolo[1,3,4,5]tetrazinones, detailed studies have dealt with the synthesis of these compounds. The general principle utilized for this purpose is—as recognized first by Ege *et al.* ⟨79TL4253⟩ and cited in CHEC-I ⟨84CHEC-I(3)535⟩—that diazoazoles, e.g., (**30**), easily undergo [1,7]dipolar cyclization with dipolarophiles via an allowed $[_{\pi}8_s + _{\pi}2_s]$ process. Thus, both 2-diazoimidazole (**30**) ⟨87JOC5538⟩ and 4-diazoimidazole carboxamide (**32**) ⟨84JMC196⟩ react with isocyanates to give the substituted isomeric imidazotetrazinones (**31**) and (**33**), respectively (Equations (4) and (5)).

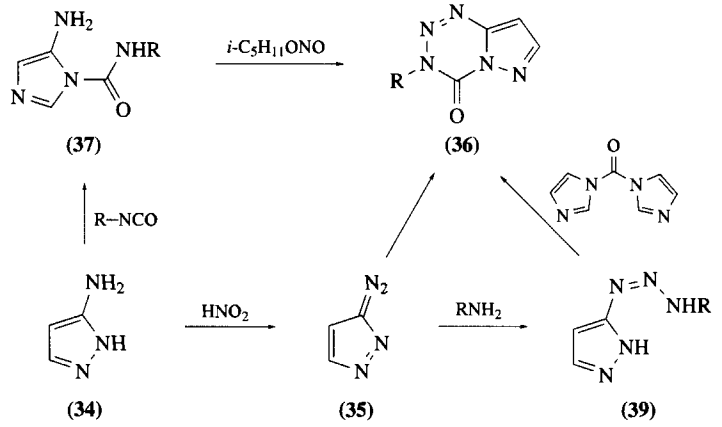


(30) (31) (4)



(32) (33) (5)

Similarly, 3-diazopyrazole (**35**) prepared from 3-aminopyrazole (**34**) gave the analogous pyrazolotetrazine (**36**) ⟨79TL4253, 87CB1375, 87JMC357⟩. This compound was also obtained through two additional routes: addition of the isocyanate reagent to the ring nitrogen atom of (**34**) gave (**37**) which reacted with isoamyl nitrite to give (**36**). Alternatively, (**35**) can be converted with a primary amine to the triazene (**39**), which reacts with carbonyldiimidazole to give the same product (**36**). All these reactions are shown in Scheme 4.

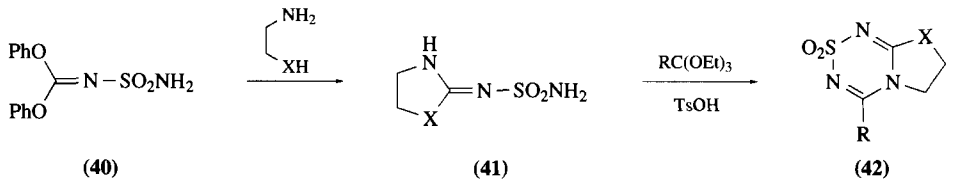


Scheme 4

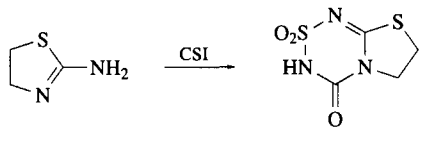
8.20.5.3 Syntheses of Fused Thiatriazines

The main approach for the syntheses of azolothiatriazines starts from a derivative of the five-membered ring component with cyclization being carried out in order to close the six-membered ring.

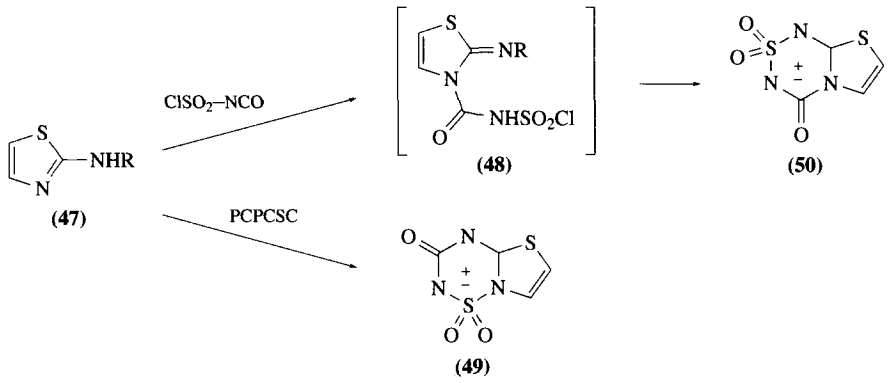
Thus, the saturated azole (**41**) obtained from the sulfonamide compound (**40**) was treated by orthoesters ⟨91S753⟩ to give the azolothiatriazines (**42**) (Scheme 5), and the same procedure was applied for a related case ⟨87S170⟩. Similarly, the ring closure of the six-membered part takes place when the aminothiazoline (**43**) reacts with chlorosulfonylisocyanate to give (**44**) (Equation (6)) ⟨79H(12)1199⟩. A particularly interesting case was described ⟨86H(24)2255⟩ for the reaction of aminothiazoles with chlorosulfonylisocyanate (CSI) and pentachlorophenyl *N*-chlorosulfonyl carbamate (PCPCSC): in the case of CSI the intermediate (**48**) was presumed to lead to the zwitterionic product (**50**). With PCPCSC, however, a similar reaction but of the opposite regioselectivity was observed to yield the isomeric system (**49**). These two reactions are shown in Scheme 6.



Scheme 5



(6)



Scheme 6

8.20.6 IMPORTANT COMPOUNDS AND APPLICATIONS

By far the most important application of compounds in the area of this chapter is the use of some azolo[1,3,4,5]tetrazinones, e.g., (**12**), and (**20**), in anticancer therapy. Use of some pyrazolo[3,2-c]-[1,2,4,6]thiatriazines as photographic couplers is also known ⟨92JAP(K)04116553⟩.

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8.21
Bicyclic 5-6 Systems with One Ring Junction Nitrogen Atom: Five Extra Heteroatoms 3 : 2

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8.21.1 INTRODUCTION

Ring systems containing five heteroatoms located either in the five- or in the six-membered ring are discussed in this chapter. Most of these systems were first synthesized during the period from 1980–1995, therefore only a few representatives have been mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(5)847⟩. According to the distribution of the extra heteroatoms between the five- and the six-membered rings the following classifications can be made:

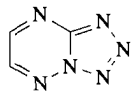
(i) Three extra heteroatoms in the five-membered ring; these ring systems are all tetrazolotriazines: tetrazolo[1,5-*b*][1,2,4]-triazine (**1**); tetrazolo[5,1-*c*][1,2,4]triazine (**2**); tetrazolo[5,1-*f*][1,2,4]-triazine (**3**); tetrazolo[1,5-*d*][1,2,4]-triazine (**4**); and tetrazolo[1,5-*a*][1,3,5]-triazine (**5**).

(ii) Three extra heteroatoms in the six-membered ring; these can be tetrazines (a), or sulfur-containing azines (b).

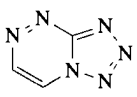
(a) the tetrazines are: [1,2,4]triazolo[1,5-*b*][1,2,4,5]tetrazine (**6**); [1,2,4]triazolo[1,5-*c*][1,2,3,5]tetrazine (**7**); and [1,2,3]triazolo[5,1-*d*][1,2,3,5]tetrazine (**8**).

(b) the sulfur-containing azines are: [1,2,4]triazolo[5,1-*c*][1,2,4,5]dithiadiazine (**9**); [1,2,4]triazolo[5,1-*b*][1,3,4,5]thiatriazine (**10**); and [1,2,4]triazolo[5,1-*c*][1,2,4,6]thiatriazine (**11**).

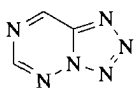
In contrast to the fairly great variety of these ring systems rather little of their chemistry has been described. The available literature is mostly limited to their syntheses, and their spectral data or reactivities have only been published in exceptional cases.



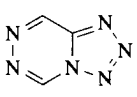
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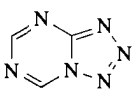
(2)



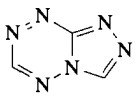
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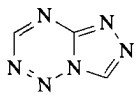
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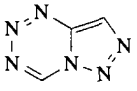
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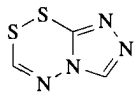
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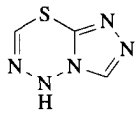
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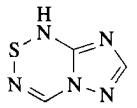
(8)



(9)



(10)



(11)

8.21.2 THEORETICAL METHODS

Such results have only been published for the two isomeric tetrazolotriazines (the "*b*-fused" (**1**) and the "*c*-fused" (**2**)) as well as their benzologues. These compounds form a ternary equilibrium with 3-azido[1,2,4]triazine ⟨84CHEC-I(5)903⟩ which was the subject of numerous investigations of both synthetic and theoretical point of view.

Systematic calculation of heats of formations (by MNDO) of these and other related polyazaazines revealed that the vicinal N—N repulsions are underestimated by these methods and, thus, a correction of 8–10 Kcal mol^{-1} for each vicinal nitrogen pair has been suggested. Allowing for this correction, the results obtained for the *b*- and *c*-fused isomers were very similar with the only difference being that the *c*-fused isomer proved to be less polar. It was concluded that in gas phase the *b*-fused isomer (i.e., **1**) should be the major tautomer, whereas in condensed phase (especially in highly polar solvents) the isomer *c* (**2**) is favored. The calculations at this level proved to be in good correlation with the experimental findings obtained with various benzologue cases ⟨85JOC4894⟩. The same equilibrium was also studied theoretically by another group ⟨83JST(92)255⟩.

In a series of calculations of aromaticity indices ⟨87T4725⟩ a substituted derivative of (**1**) has been compared with related azoloazines.

8.21.3 EXPERIMENTAL STRUCTURAL METHODS

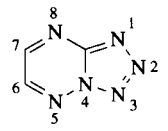
8.21.3.1 NMR Investigations

Two detailed NMR investigations have been published making the assignments of ^{1}H and ^{15}N NMR shifts of (**1**) ⟨89MI 207-01, 89MI 207-02⟩. The results are summarized in Table 1.

8.21.3.2 Mass Spectral Studies

Mass spectral behavior of [1,2,4]triazolo[4,3-*b*]tetrazine (**6**) has been published and interpreted, and sequential loss of N_2, RCN, and NCN was detected ⟨77CJS106⟩. A more complex tricyclic system containing the tetrazolo[5,1-*c*][1,2,4]triazine (**2**) substructure has also been investigated by mass spectrometry ⟨83KGS547⟩.

Table 1 ^{13}C and ^{15}N NMR shifts of tetrazolo[1,5-*b*][1,2,4]triazine (**1**).

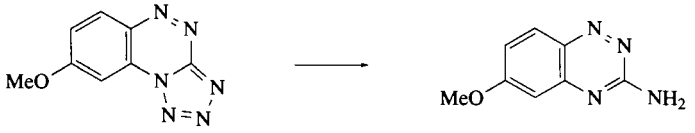


^{13}C-shifts		*^{15}N-shifts*	
C-6	143.3	N-1	−66.7
C-7	153.5	N-2	15.9
C-8a	148.9	N-3	−27.5
		N-4	−117.2
		N-5	−57.3
		N-8	−84.5

8.21.4 REACTIVITY

8.21.4.1 Reduction Reactions and Subsequent Transformations [Et_3NH^+][$Sn(SPh)_3$]

Two new tin reagents, triethylammonium tintriphenyl and dibutyltin dihydride have been found effective in reduction of fused tetrazoloazines to aminoazines ⟨87TL5941⟩. The reaction was interpreted to proceed via ring opening to an azide and subsequent reduction. Thus, the methoxytetrazolobenzo[1,2,4]triazine (**12**) was converted to the amine (**13**), whereas the tetrazolonaphthotriazine derivative (**14**) gave the aminonaphthotriazine (**15**). The yields are near 100% in both cases.



(12) (13) (1)

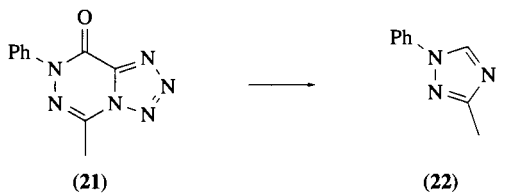


(14) (15) (2)

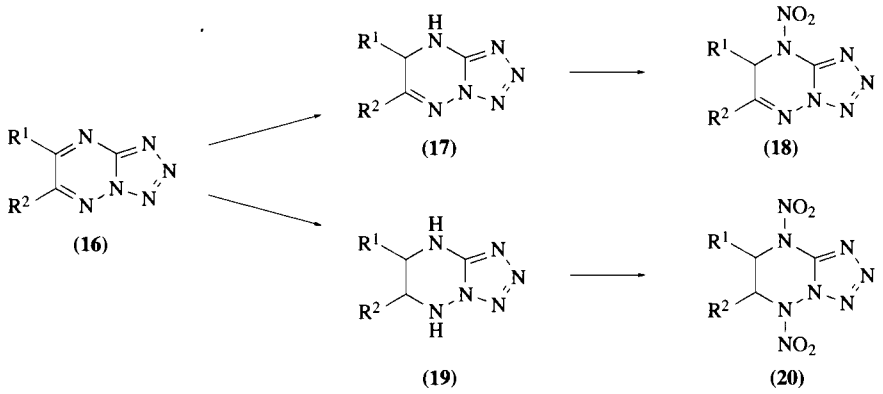
Reduction of tetrazolo[1,5-*b*][1,2,4]triazine derivatives (**16**) was also studied ⟨76JOC41⟩. Catalytic hydrogenation resulted in partial reduction at the C(7)—N(8) bond to give (**17**). Sodium borohydride, in contrast, led to the formation of a tetrahydro derivative (**19**). Behavior of both reduction products (**17**) and (**19**) towards nitration reagent was also studied, and nitrations of the NH groups have been detected (i.e., (**17**) gave the mononitro compound (**18**), whereas (**19**) afforded the dinitro derivative (**20**)).

8.21.4.2 Hydrolytic Ring Opening and Contraction

Ring-opening reaction of a tetrazolo[1,5-*d*][1,2,4]triazinone compound (**21**) by sodium hydroxide was reported ⟨76T2513⟩ to give the [1,2,4]triazole derivative (**22**).



(21) (22) (3)



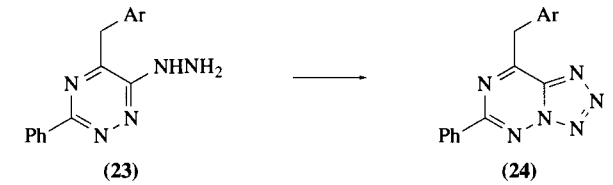
Scheme 1

8.21.5 RING SYNTHESES

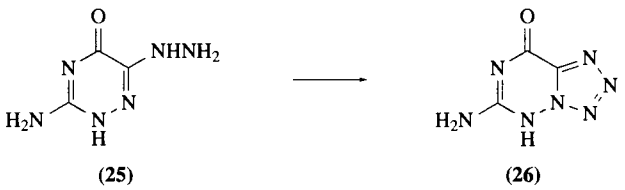
8.21.5.1 Syntheses of Tetrazolotriazines

8.21.5.1.1 Fused [1,2,4]triazines

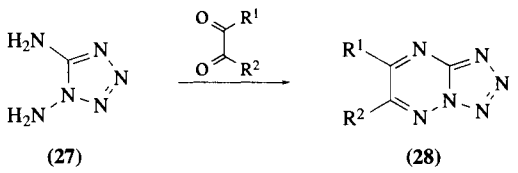
As described in CHEC-I ⟨84CHEC-I(5)903⟩, most of the hitherto known tetrazolotriazines have been obtained via synthesis of the appropriate azidoazine (generally prepared from a hydrazino derivative by nitrous acid or by nucleophilic displacement of a halogen-substituted compound by sodium azide), which then undergoes valence bond tautomerism to the tetrazole. The same route has also been applied for novel tetrazolotriazines. Thus, 6-hydrazino[1,2,4]triazine derivative (**23**) gave the ring closed tetrazolo[5,1-*f*][1,2,4]triazine compound (**24**) ⟨89H(B29)2279⟩. Similarly, the triazinone (**25**) was converted analogously to the tetrazole (**26**) ⟨79JHC555⟩. A different approach, a condensation reaction of diaminotetrazole (**27**) with α-dioxo derivatives was also applied, and a series of tetrazolo[1,5-*b*][1,2,4]triazines containing hydrogen and methyl substituents have been synthesized with all possible combinations of the hydrogen and methyl substituents ⟨88JOC5371⟩. A nitrogen positional isomer of the above ring system has been obtained from a geminal diazidopyrazolone (**29**): thermolysis of this compound afforded the tetrazolo[1,5-*d*][1,2,4]triazinone (**30**).



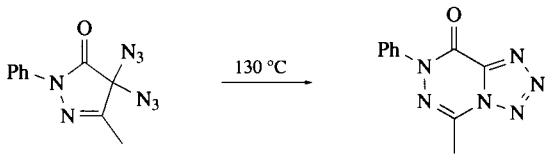
(4)



(5)



(6)

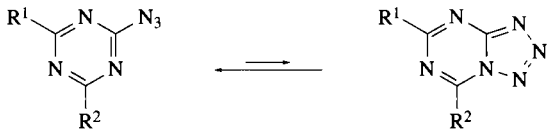


(7)

(29) (30)

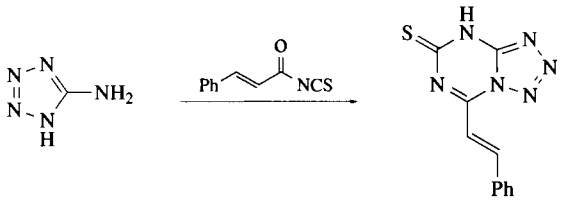
8.21.5.1.2 Fused [1,3,5]-triazines

Attempts to apply the azide-tetrazole isomerism to the synthesis of tetrazolo[1,5-*a*][1,3,5]triazines were published ⟨88IZV491⟩. This equilibrium was found to be shifted generally to the ring opened azides (**31**), and the maximum amount of the tetrazole (**32**) of 15% was detected in DMSO-d_6 at 20 °C in the case of R^2 = H, R^1 = morpholino group. The same tetrazolo ring system was, however, found to be stable with 5-styryl and 7-thio substitution ⟨87LA65⟩: aminotetrazole (**33**) when reacted with cinnamoyl isothiocyanate afforded the tetrazolotriazine-thione (**34**) most likely formed via cyclization of the intermediate thiourea.



(8)

(31) (32)



(9)

(33) (34)

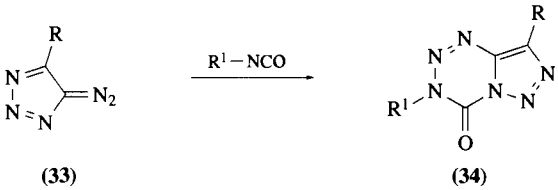
8.21.5.2 Syntheses of Additional Ring Systems

All the syntheses of the derivatives of this section start from aminoazoles which undergo acylation or addition reaction followed by ring closures.

8.21.5.2.1 Triazolotetrazines

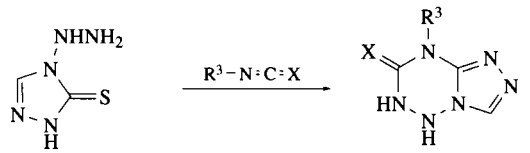
Reaction of the azine (**33**) with isocyanates represented the first synthesis of a fused [1,2,3,5]tetrazine ⟨79TL4253⟩. This methodology was also elaborated for a number of related ring systems and was published in more detail in 1987 ⟨87CB1375⟩.

Synthesis of derivatives (**36**) of the [1,2,4]triazolo[1,5-*c*][1,2,3,5]tetrazine ring system was accomplished by treatment of the *N*-hydrazino[1,2,4]triazolethione compound (**35**) with isocyanates ⟨88MI 821-01⟩.



(10)

(33) (34)

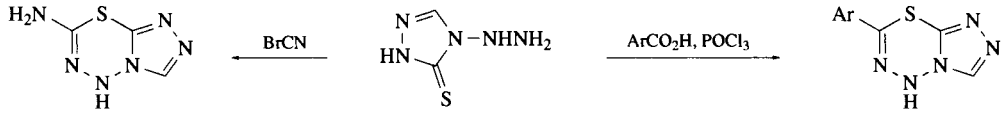


(35) (36) (11)

8.21.5.2.2 Fused azines containing sulfur in the six-membered ring

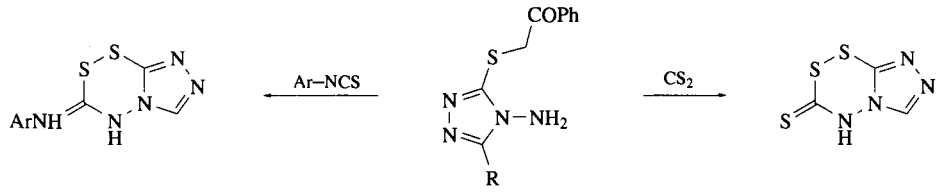
The *N*-hydrazinotriazole (**35**) was also used as a starting material for the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4,5]thiatriazines: reaction with cyanogen bromide led to the amino derivative (**37**), whereas aryl carboxylic acids and phosphorus trichloride afforded the aryl-substituted compound (**38**) ⟨88MI 821-01⟩.

The 3-phenacylthio-4-amino[1,2,4]triazole compound (**39**) proved to be a suitable starting material for the synthesis of [1,2,4]triazolo[1,2,4,5]dithiadiazines ⟨90MI 821-01⟩. With isocyanate the arylimino product (**40**) was obtained, whereas carbon disulfide afforded the thione derivative (**41**).



(37) (35) (38)

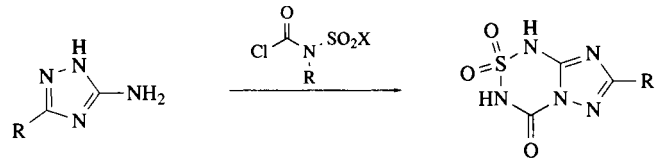
Scheme 2



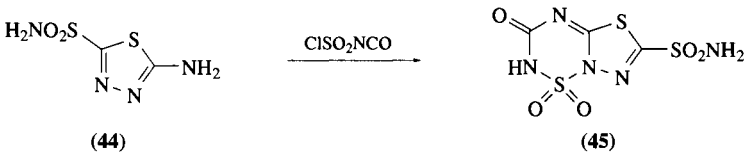
(40) (39) (41)

Scheme 3

Chloro- and fluorosulfonylcarbamoyl chlorides were found to react with aminotriazole (**42**) to give [1,2,4]triazolo[5,1-*c*][1,2,4,6]thiatriazine-1,1-dioxide (**43**) ⟨77JCR(S)238⟩. A thiazole-fused thiatriazine-dioxide (**45**) was prepared from the aminothiazole derivative (**44**) by chlorosulfonylisocyanate. The observed regioselectivity in this reaction was interpreted by the preference for nucleophilic addition at the more electrophilic isocyanate which was followed by the cyclization at the sulfonyl chloride ⟨87JMC2058⟩.



(42) (43) (12)



(44) (45) (13)

8.21.6 IMPORTANT COMPOUNDS AND APPLICATIONS

Potential use of derivative (**45**) as a topically effective carbonic anhydrase inhibitor ⟨87JMC2058⟩, some tetrazolo[1,5-*b*][1,2,4]triazines as antiflammatory agents ⟨81KFZ50⟩, and the triazolodithiadiazines (**40**) and (**41**) for antifungal agrochemical application ⟨90MI 821-01⟩ have been reported.

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8.22
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: No Extra Heteroatom

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Universidad Complutense, Madrid, Spain

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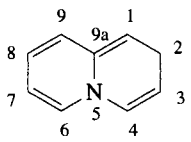
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8.22.10.2 Quinolizidines as Inductors of Chirality 561

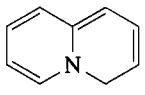
8.22.1 INTRODUCTION

The chapter related to this one in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(2)525⟩ dealt mainly with quinolizinium ion, and quinolizine or quinolizidine were mentioned only as reaction products of the aromatic species. Since that time, new developments in the chemistry of quinolizinium compounds have been relatively scarce, and a number of reviews covering them, together with the earlier work, have appeared ⟨81H(16)803, 82AHC(31)1, 91HOU(E7a)759, 92HOU(E7b)239, 92AHC(55)261⟩. For these reasons, this chapter is devoted mainly to nonaromatic compounds.

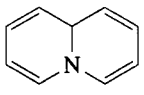
There are three possible structures for the quinolizine system, namely 2*H*-quinolizine (**1**), 4*H*-quinolizine (**2**), and 9a*H*-quinolizine (**3**). None has been isolated as a stable species, although (**2**) may have a transient existence ⟨65TL905⟩. A number of derivatives of these structures are known and have been reviewed ⟨79COC(4)233⟩.



(**1**)



(**2**)



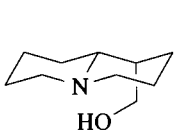
(**3**)

The saturated system, i.e. quinolizidine (**4**), is far more important due to the bewildering profusion of quinolizidine alkaloids in nature; it has been estimated ⟨B-86MI 822-03⟩ that 25–30% of all known alkaloids belong to the quinolizidine–indolizidine group. Some examples of alkaloids containing the quinolizidine structure are given below in structures (**5**)–(**10**): the simple quinolizidine alkaloids lupinine (**5**) and nupharidine (**6**); the *Lycopodium* alkaloid lycopodine (**7**) with a hydrojulolidine

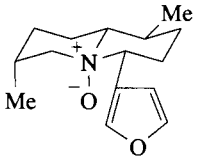
ring system; the tetracyclic *Lupinus* alkaloid sparteine (**8**); the *Lythraceae* alkaloid vertaline (**9**); and the ipecac alkaloid emetine (**10**).



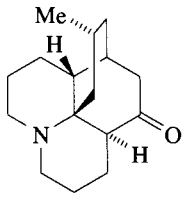
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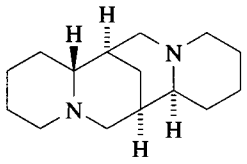
(5)



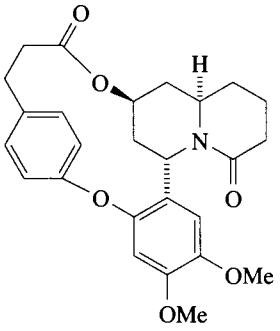
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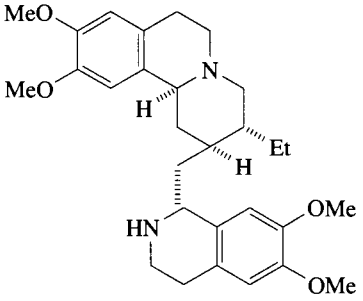
(7)



(8)



(9)



(10)

The occurrence of quinolizidines in nature has stimulated a vast amount of research into their chemistry, biochemistry, and pharmacology, and it is not possible to cover all relevant facts within the scope of a single chapter. For more detailed information, the reader is referred to the numerous comprehensive reviews available on quinolizidine alkaloids and related subjects ⟨B-53MI 822-01, B-53MI 822-02, B-60MI 822-01, B-60MI 822-02, B-71MI 822-02, B-72MI 822-02, B-76MI 822-03, 77H(6)1189, B-81MI 822-02, B-83MI 822-01, B-83MI 822-02, B-84MI 822-01, B-86MI 822-01, B-86MI 822-02, B-93MI 822-02⟩ and to the periodical reviews covering developments in the chemistry of quinolizidine alkaloids, formerly appearing in "The Alkaloids" (Royal Society of Chemistry Specialist Reports) ⟨B-71MI 822-01, B-72MI 822-01, B-73MI 822-03, B-74MI 822-01, B-75MI 822-01, B-76MI 822-02, B-77MI 822-01, B-78MI 822-01, B-79MI 822-01, B-80MI 822-01, B-81MI 822-01, B-82MI 822-01, B-83MI 822-03⟩ and currently in "Natural Product Reports" ⟨84MI 822-04, 85MI 822-05, 87MI 822-03, 89MI 822-01, 90MI 822-01, 91MI 822-03, 93MI 822-01, 94MI 822-01⟩. Periodical reports on other types of alkaloids from the same sources also contain information on certain arenoquinolizine alkaloids like the protoberberine and emetine derivatives, the latter being normally classified as isoquinoline alkaloids.

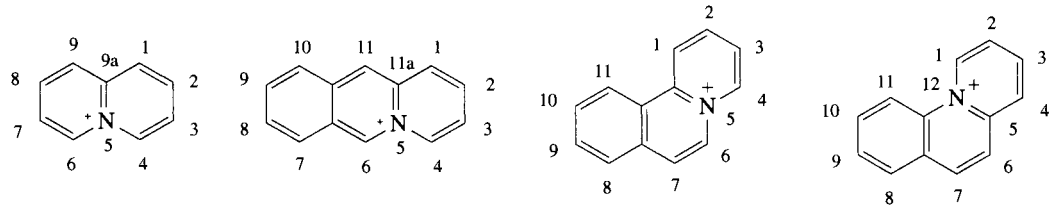
8.22.2 THEORETICAL METHODS

Some theoretical aspects of polycyclic aromatic nitrogen cationic systems, including quinolizinium ion and polycyclic aromatic related systems, are covered in a review ⟨92AHC(55)261⟩.

Delocalization energies of quinolizinium and its benzo derivatives are very similar to the ones calculated for their parent hydrocarbons (Table 1), proving that their aromatic character is similar.

Application of different molecular orbital methods to the calculation of electron densities of quinolizinium ion and its benzo derivatives led to the results summarized in Table 2. It can be appreciated that in these compounds, nitrogen atoms receive electron density from carbon atoms of the opposite parity, as suggested by perturbation theory ⟨92AHC(55)261⟩. Similar Hückel molecular orbital calculations on berberine (**15**) and related alkaloids gave an uncommonly high positive

Table 1 Delocalization energies of quinolizinium compounds.



(11) (12) (13) (14)

Compound	*Delocalization energy/β*[a]
Naphthalene	3.68
Quinolizinium (**11**)	3.89
Anthracene	5.32
Benzo[*b*]quinolizinium (**12**)	5.53
Phenanthrene	5.45
Benzo[*a*]quinolizinium (**13**)	5.66
Benzo[*c*]quinolizinium (**14**)	5.67

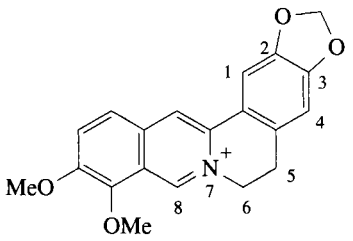
[a]Calculated through the omega method ⟨92AHC(55)261⟩.

charge on the C-8 carbon atom (+0.331 net charge in the case of berberine), which enables these compounds to react easily with nucleophiles in this position ⟨82CJC970⟩.

Table 2 Electron densities of quinolizinium compounds.

Position	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*9a*	*10*	*11*	*11a*	*Ref.*
Quinolizinium (**11**)														
HMO[a]	1.005	0.916	1.011	0.856	1.550					0.874				92AHC(55)261
PPP[b]	1.010	0.976	1.013	0.940	1.185					0.940				81RTC161
PPP[b]	0.939	0.912	0.889	1.065	1.340					1.047				68TCA417
Omega	0.968	0.932	0.973	0.896	1.564					0.898				92AHC(55)261
Benzo[b]quinolizinium (**12**)														
HMO[a]	1.004	0.939	1.013	0.877	1.552	0.791	0.968	1.000	0.968		1.005	1.013	0.905	92AHC(55)261
PPP[b]	0.931	0.950	0.875	1.106	1.333	1.044	0.996	0.908	0.922		0.978	0.897	1.094	70G421
Omega	0.972	0.950	0.978	0.913	1.567	0.865	0.977	0.984	0.973		0.988	0.969	0.922	92AHC(55)261
Benzo[a]quinolizinium (**13**)														
HMO[a]	1.006	0.895	1.011	0.833	1.555	0.901	1.019	1.006	0.977		1.000	0.979		92AHC(55)261
PPP[b]	0.953	0.905	0.916	1.040	1.338	1.139	0.848	0.952	0.930		0.921	0.982		68TCA417
Omega	0.967	0.919	0.971	0.882	1.568	0.930	0.983	0.992	0.980		0.988	0.982		92AHC(55)261

[a]HMO, Hückel molecular orbital theory. [b]PPP, Parisher–Parr–Pople method.

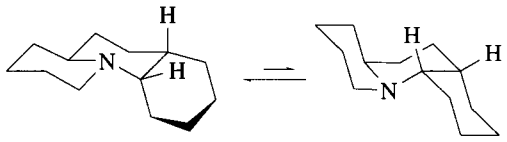


(15)

Theoretical methods have also been used for the study of the UV spectrum of quinolizinium ion and its benzo derivatives ⟨59JCS3654, 69G1078, 71TCA216⟩, and also of berberine alkaloids ⟨82CJC970⟩.

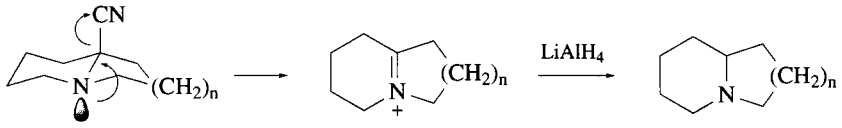
Molecular mechanics has found application in structural studies of quinolizidines. For example, the controversy on the preferred conformation of perhydrobenzo[*c*]quinolizidine ⟨68CPB1889, 78JOC322⟩ was solved in favor of structure (**16**) on the basis of spectral (IR, ^{13}C-NMR) data and

calculation of the energies of both conformers, which showed that (**16**) was more stable than (**17**) in ca. 1.5 kcal mol^{-1}.



(**16**) (**17**)

Such structural studies can also be useful to explain the reactivity of quinolizidine systems. For example, molecular mechanics calculations showed that the more stable conformation of quinolizidine-9-carbonitrile and its indolizidine analogue was the antiperiplanar structure (**18**), which explained the isolation of (**20**) on treatment with lithium aluminum through cleavage of the C—CN bond and subsequent reduction of the iminium ion (**19**) (Scheme 1). On the other hand, the equivalent pyrrolizine derivative, which has a *cis* orientation of the lone pair and the cyano group, is reduced to amine ⟨87JHC47⟩.



(**18**) n = 1,2 (**19**) (**20**)

Scheme 1

8.22.3 EXPERIMENTAL STRUCTURAL METHODS

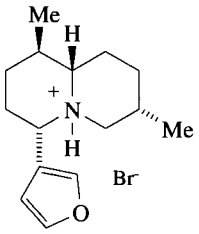
8.22.3.1 X-ray Analysis

Structural characterization of many quinolizidine derivatives has been established by x-ray diffraction. For example, this technique allowed the confirmation of an *R* configuration for (−)-deoxynupharidine hydrobromide (**21**) ⟨70JCS(B)1450⟩ and (+)-nupharidine (**22**) ⟨73MI822-02⟩. The unambiguous assignment of structure (**23**) to petrosine, the main alkaloid isolated from the sponge *Petrosia serrata*, was also performed using x-ray diffraction ⟨82TL4277, 84BSB941⟩. A number of biologically active quinolizidines and benzo[*a*]quinolizidines have also been studied by x-ray diffraction (e.g. compounds (**24**) and (**25**) in order to determine their conformations and absolute configurations, as well as the mean bond lengths and angles ⟨84JMC165, 84AX(C)1965, 87MI 822-02, 88H(27)1653⟩.

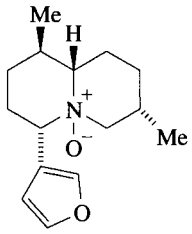
8.22.3.2 NMR Spectroscopy

8.22.3.2.1 Proton NMR spectroscopy

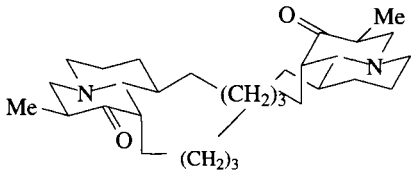
The main application of ^{1}H NMR to quinolizidines has been focused towards the study of their configurational and conformational properties, and has been reviewed ⟨71CR109, B-75MI 822-02, 77H(6)1377⟩. In quinolizidine systems, protons immediately adjacent to the nitrogen show characteristic chemical shifts that are dependent on the dihedral angle between them and the nitrogen lone pair, thus allowing conformational assignments. An antiperiplanar arrangement like the one found in the axial H-4, H-6, and H-9a protons of *trans*-fused systems (**26**) causes a significant upfield shift (δ ca. 2 ppm) relative to equatorial protons (H-4 and H-6) that have dihedral angles of 60° or 120° with the lone pair (typical δ values, ca. 3 ppm) ⟨64TL173, 75OMR(7)191, 77JOC228, 88JOC4452⟩. Although alternative explanations have been put forward ⟨68TL1153⟩, most workers justify the large axial–equatorial $\Delta\delta$ value (ca. 1 ppm) on the basis of the effect of the nitrogen lone pair on the antiperiplanar axial hydrogens ⟨69TL2023⟩. Since protonation reduces $\Delta\delta$ to ca. 0.5 ppm (structure (**27**))



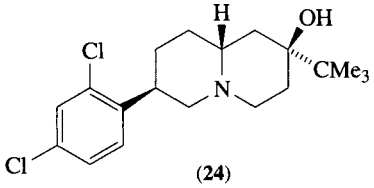
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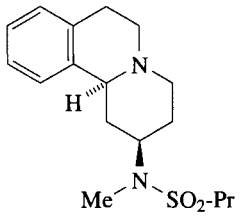
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(23)

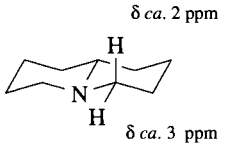


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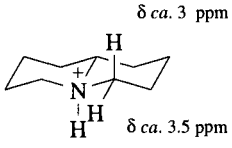


(25)

⟨64TL2553⟩, a value similar to the one found in cyclohexane, the stereoelectronic effect can be quantified as ca. 0.5 ppm.

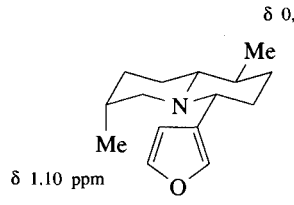


(26)

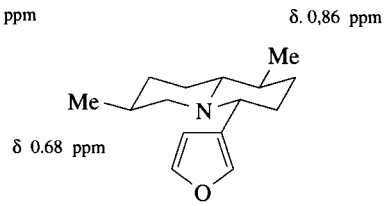


(27)

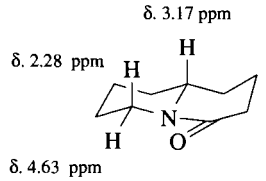
Several quinolizidine derivatives show distinctive features in their ^{1}H NMR spectra. For example, monomethylquinolizidines are known to exist in the *trans*-fused ring conformation (see Section 8.22.4) ⟨62JCS2637, 65JCS6797⟩. In all cases, δ and $J_{CH(Me)}$ values for axial methyl groups are higher than those of their equatorial counterparts ⟨62BCJ1337, 62JCS2637⟩ as, for example, in the methyl resonances of deoxynupharidine (**28**) and 7-epideoxynupharidine (**29**). On the other hand, the large downfield shift of the H-6 equatorial proton, which lies in the same plane of the carbonyl group and is thus anisotropically deshielded, is characteristic of the 4-oxoquinolizidine nucleus (**30**), which is present in many alkaloids. In quinolizidine methiodides, the δ values of the *N*-methyl groups are higher in the *cis*-fused salts (δ: 3.16–3.08 ppm) than in the *trans*-fused analogues (δ: 2.99–2.94 ppm) ⟨68JMC353⟩



(28)



(29)

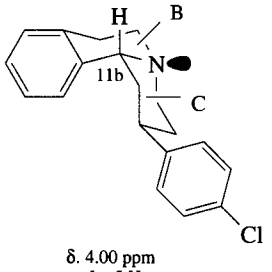


(30)

Selective NOE difference experiments ⟨83JCR(S)208⟩ and two-dimensional techniques ⟨86BAP191⟩ have been used to assign completely the ^{1}H NMR spectra of quinolizidines. Stereochemical assignments of complex quinolizidine alkaloids have been derived from these techniques and other decoupling experiments ⟨83MI 822-06⟩.

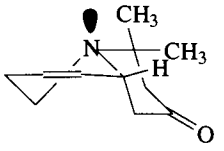
In ^{1}H NMR spectra of benzo[*a*]quinolizidines, the signal due to the C-11b methine proton is particularly important, because its chemical shift value and its coupling constants allow the structural determination of the B/C ring junction ⟨64JA3364, 77OMR(9)322, 79ACH19⟩. Literature examples of the three possible situations are given below (**31**)–(**33**). For *trans*-fused ring systems, δ for C_{11b}-H is

< 3.8 ppm, although in some cases this value can be affected by long-distance substituent effects, as in (**34**) ⟨87H(26)3203⟩, and the criterion must be applied with due caution. The signal is typically a doublet of doublets (e.g. δ: 3.50 ppm, $J = 11.5$ and 3.0 Hz in (**33**)), although long-distance coupling with H-11 often broadens this signal ⟨81JMC79⟩. *Cis*-fused systems show $\delta > 3.8$ ppm for C_{11b}-H. A distinction can be made between the two *cis* conformers such as (**31**), for which H_{11b} is a triplet with $J = 5$ Hz and (**32**), for which this signal is a doublet of doublets with $J_{ax,ax} = 9$–12 Hz and $J_{ax,eq} = 2$–5 Hz ⟨64JA3364⟩. Complete assignment of the ^{1}H NMR spectra of several benzo[*a*]quinolizidines has been achieved through the use of lanthanide shift reagents ⟨81JMC79⟩ and two-dimensional NMR spectroscopy ⟨88H(27)1653⟩.



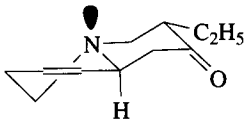
δ. 4.00 ppm
t, J = 5 Hz

(**31**)



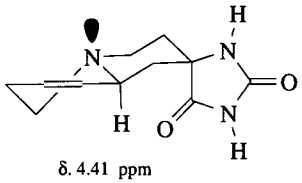
δ. 4.20 ppm
dd, J = 11 and 5

(**32**)



δ. 3.50 ppm
dd, J = 11.5 and 3.0

(**33**)



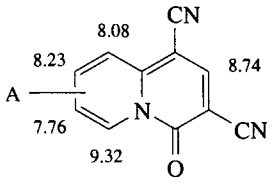
δ. 4.41 ppm
br. d, J = 10

(**34**)

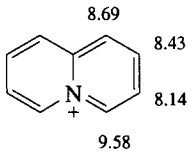
(**32**)–(**34**): Ar = 9,10-$(MeO)_2C_6H_2$

The conformational assignment in dibenzo[*a,g*]quinolizidines (tetrahydroprotoberberine alkaloids) in $CDCl_3$ is hampered by coincidence of the signals due to the CH angular proton and OMe groups present in most of them. However, use of deuterotoluene as solvent causes a downfield shift of methine proton and permits its analysis. Typical δ and J values for these protons are: *cis*-isomers, $\delta = 4.25$–4.37 ppm, dd, $J = 12$ and 4 Hz; *trans*-isomers, δ: 3.50–3.96 ppm, dd, $J = 15$ and 4 Hz ⟨77OMR(9)341⟩.

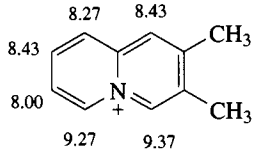
Although quinolizines do not pose stereochemical problems, ^{1}H NMR spectroscopy is also useful for structural studies. Thus, the chemical shifts of C—H signals of ring A in compound (**35**), which appear in the aromatic region, have been used as a measure of the extent of cyclic delocalization ⟨87JHC651⟩. In quinolizinium compounds, such as as (**36**) and (**37**), the positive charge on the nitrogen atom deshields the H-4 and H-6 protons, which resonate at $\delta > 9$ ppm ⟨81H(15)213, 85JHC681⟩.



(**35**)



(**36**)

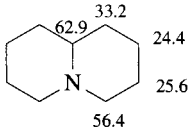


(**37**)

8.22.3.2.2 Carbon-13 NMR spectroscopy

Carbon-13 NMR spectroscopic properties of quinolizidines have been reviewed ⟨B-76MI 822-01, 77H(6)1377, 78H(9)507, B-79MI 822-02⟩, generally with special emphasis on the influence of the *cis* or *trans* arrangement of the ring fusion and of the nitrogen lone-pair orientation on the ^{13}C NMR spectra.

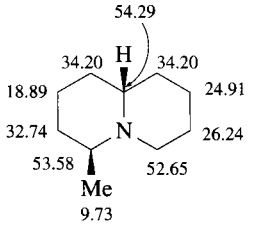
In quinolizidines, carbons α to the nitrogen are deshielded by its inductive effect (**38**). Their chemical shifts are higher for the *trans*-fused ring systems, and the value of $\Delta\delta = \delta_{trans} - \delta_{cis}$ is similar to the one found in decalins. Carbons β to nitrogen are slightly shielded compared to their carbocyclic counterparts ⟨76JA3778⟩; this effect is higher when the carbon atoms are antiperiplanar with respect to the nitrogen lone pair ⟨76CPB2988, 77JOC51, 77OMR(9)322⟩. Finally, γ carbons (C-2,8) located *anti* to the nitrogen atom are shielded with respect to the same atoms in decalin; γ-*gauche* carbons are also shielded, although to a lesser extent.



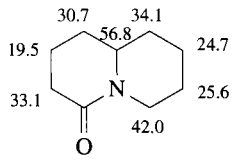
(**38**)

One of the most important structural problems associated with the spectroscopic study of quinolizidines is the determination of their preferred conformation. A general criterion for this kind of stereochemical studies is the value of the $^1J_{C-H}$ coupling constant of the angular carbon adjacent to nitrogen, which is 6–12 Hz larger for the *cis* structure than for the *trans* ⟨78H(9)507⟩. A similar rule is valid for benzo[*a*]quinolizidines (typical *J* values: 126–133 Hz for *trans* and 139–143 Hz for *cis* structures) ⟨76CPB1168⟩, although in these compounds, and also in dibenzo[*a*,*g*]quinolizidines, the chemical shifts of C-6 and C-7 are also of diagnostic value in this respect ⟨77H(6)1377, 78CPB1901, 79CPB3144⟩.

In general, substituent effects on the quinolizidine ring atoms (e.g. (**39**) and (**40**)) parallel those in the carbocyclic series ⟨78H(9)507⟩, with some particular effects due to the nitrogen atom. For instance, the very high-field position of the axial methyl carbon atom of (**39**) is due to the stereoelectronic effect of the β-antiperiplanar nitrogen lone pair, and can be used as a criterion to confirm the *trans* conformation of the ring system.



(**39**)



(**40**)

Chemical shifts of carbon atoms in alkylquinolizidines are linearly correlated to those of decalin, and can be calculated as follows ⟨74CJC3778⟩:

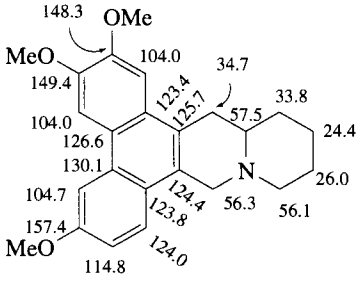
$$\delta_{quinolizidine} = A \times \delta_{decalin} + B$$

Position	*A*	*B*
α	1.013	21.16
α_{bridge}	1.034	17.51
β	0.975	−0.41
γ	0.977	−1.64

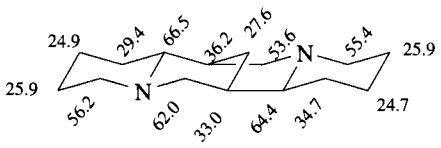
The effect of nitrogen protonation on the conformation of alkyl and arylquinolizidines ⟨76CPB2988, 84BAP339⟩ and benzo[*a*]quinolizidines ⟨78CPB2555⟩ has been studied. In agreement with the behavior of other amines ⟨73JA165⟩, protonation of these quinolizidines normally causes upfield shifts of β, γ, and δ carbons, particularly the β ones. Tertiary α carbon atoms suffer a deshielding effect, while secondary α carbons are only slightly affected. Dependence of ^{13}C NMR spectra on protonation has allowed the determination of the nitrogen inversion rates in benzo[*a*]quinolizidines ⟨78CPB2555⟩.

Carbon-13 NMR spectroscopy has been used for the study of complex quinolizidine alkaloids

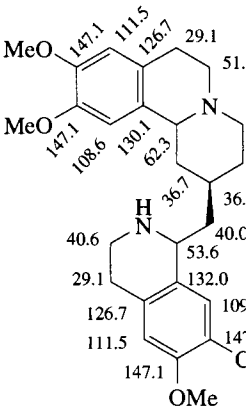
and related compounds. A few representative assignments (compounds (**41**)–(**45**)) are: cryptopleurine (**41**) ⟨82H(19)347⟩; sparteine (**42**) ⟨78H(9)507⟩; (**43**) ⟨78CPB1168⟩; tetrahydro protoberberine (**44**) ⟨89H(29)2257⟩; emetine (**45**) ⟨75JOC2836⟩.



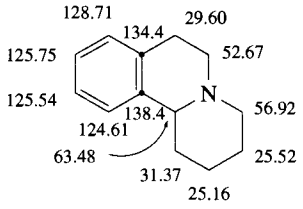
(**41**)



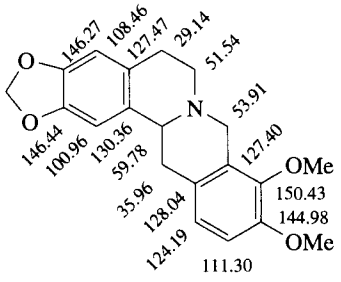
(**42**)



(**45**)



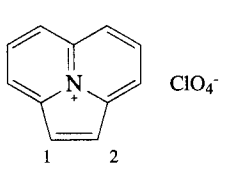
(**43**)



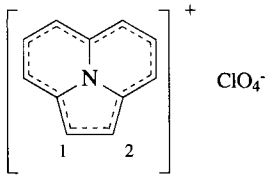
(**44**)

8.22.3.2.3 Nitrogen-15 NMR spectroscopy

Nitrogen-15 NMR data of quinolizinium and related compounds are useful criteria for the study of the extent of the delocalization of their π systems. For example, replacement of the central carbon atom of acenaphthylene by nitrogen leads to pyrrolo[2,1,5-*de*]quinolizinium ([2,3,4]cyclazinylium ion) (**46**). HMO calculations and chemical reactivity (for example, lack of alkenic character in the 1,2 bond) suggest a delocalized π structure (**47**), which is supported by the shielding of the nitrogen atom (22.3 ppm with respect to quinolizinium) in the ^{15}N NMR spectrum of this compound ⟨84JCS(P1)2553⟩.



(**46**)



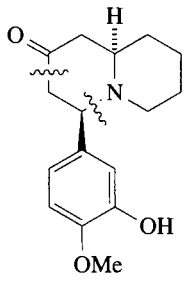
(**47**)

8.22.3.3 Mass Spectrometry

The mass spectra of many alkaloids containing the quinolizidine nucleus have been reported. As an example, the fragmentation pattern for lupinic acid has been worked out ⟨64MC687⟩.

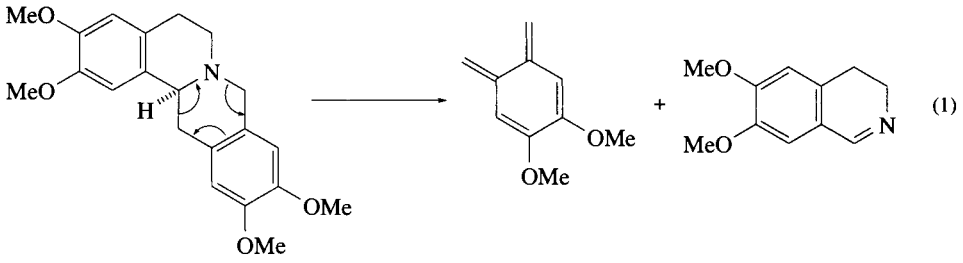
Depending on the functionality present on the quinolizidine nucleus, many other fragmentation

patterns are possible. For example, the base peak for the 2-quinolizidinone derivative (**48**) is formed by cleavage of the C_2—C_3 bond and the benzylic C_4—N bond ⟨82OMS(17)601⟩.



(**48**)

Mass spectra of arenoquinolizidines have also been studied. A typical fragmentation pattern is included in Equation (1) ⟨63JA2807⟩.

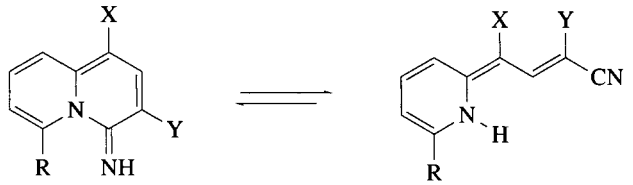


(1)

8.22.3.4 Ultraviolet–Visible and Luminescence Spectroscopy

8.22.3.4.1 Ultraviolet–visible

Comparison of the UV spectrum of the quinolizinium cation with that of naphthalene shows a significant bathochromic shift caused by the cationic heteroatom; benzo, dibenzo, naphtho, and phenanthroquinolizinium systems show a similar behavior with respect to their all-carbon analogues ⟨81H(16)987⟩. Shifts in the UV–visible spectra and changes in the molar absorption of the maxima have been used to prove the ability of arenoquinolizinium systems to interact with DNA ⟨76JMC1261⟩, and a similar study has also been performed on some benzo[*a*]quinolizidine derivatives ⟨91MI 822-02⟩. UV–visible data have also been used to study the equilibrium between 4-iminoquinolizines (**49**) and their monocyclic tautomers (**50**) (Equation (2)) ⟨87JHC655⟩.



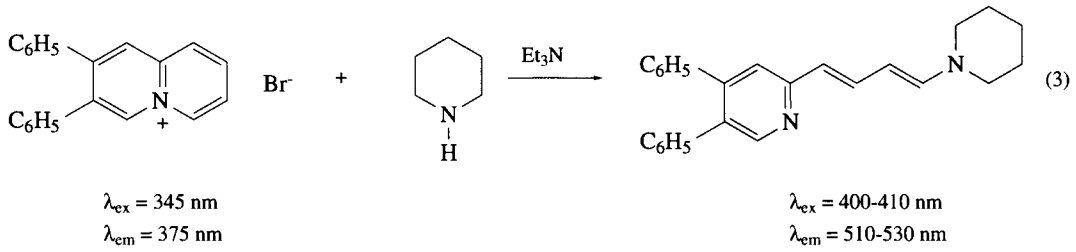
(**49**) (**50**)

(2)

8.22.3.4.2 Luminescence

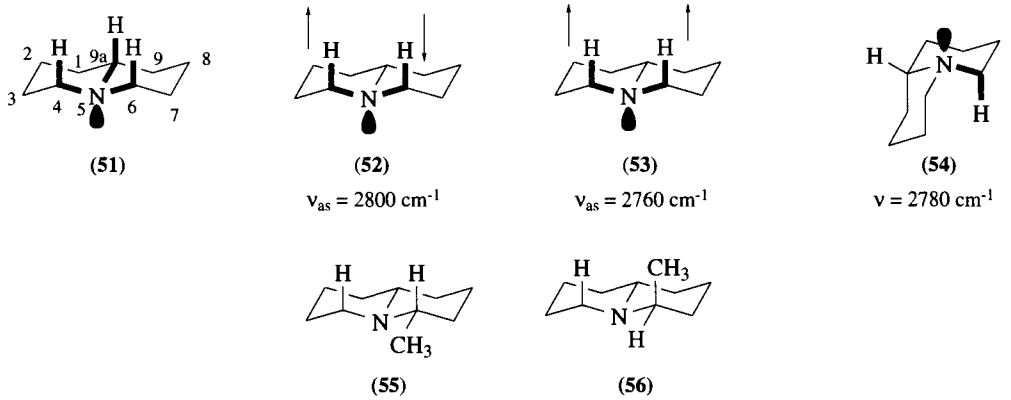
Quinolizines ⟨90JPC8885⟩, quinolizinium derivatives ⟨77ZC450, 79MI 822-03, 85MI 822-03, 88ZC105, 88MI 63, 93TAL1719⟩, and arenoquinolizidines ⟨88MI 822-01⟩ exhibit native luminescence at room temperature and 77 K (Equation (3)). The influence of several environmental properties, including DNA intercalation ⟨88MI 822-02⟩, on the fluorescence intensity of quinolizinium derivatives has been studied ⟨85MI 822-04, 88MI 822-03, 88MI 822-04⟩. Abrupt changes in the native fluorescence occur after

reaction of 2,3-diphenylquinolizinium salts with nucleophiles due to opening of the quinolizinium system, a property that allows the use of this reagent in the fluorimetric quantitation of amines (Equation (3)) ⟨85MI 822-03, 91MI 822-01, 92MI 822-01, 92BSB677⟩.



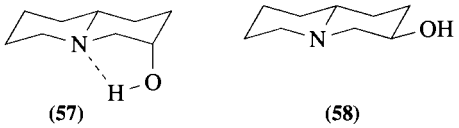
8.22.3.5 Infrared Spectroscopy

Infrared spectroscopy was the first physical technique employed in the study of conformational and configurational problems in quinolizidine derivatives. Bohlmann ⟨57AG541, 58CB2157⟩, after examining the IR spectra of a large number of quinolizidines, stated as a general rule that those compounds with a *trans* ring junction show a characteristic series of bands between 2700 and 2800 cm^{-1}, which are lacking in the *cis* systems. Through preparation of deuterated quinolizidine derivatives ⟨64TL173⟩, these bands were related to the C_{4ax}—H and C_{6ax}—H bonds antiperiplanar to the nitrogen lone pair, which exist only in the *trans* geometry. A detailed study by Wiewiorowski and co-workers ⟨68T5439⟩ revealed a slightly more complex picture; according to these authors, in *trans* quinolizidines all three axial C_α—H bonds participate in charge delocalization through stereoelectronic effects and the whole system is coupled (**51**). However, the study of deuterated model systems showed that the contribution of the C_α—H methine group (C_{9a}—H) is negligible. The well-defined maxima observed in *trans*-quinolizidines are due to coupled asymmetric (2800 cm^{-1}) (**52**) and symmetric (2760 cm^{-1}) (**53**) stretching vibrations of the H_{ax}—C_4—N—C_6—H_{ax} system. Replacement of one of these hydrogens by deuterion still leaves a weak band at ca. 2780 cm^{-1}, and a similar band is also observed in *cis*-quinolizidines (**54**). These facts contradict Bohlmann's statement that two C_α—H axial bonds are necessary for absorption bands to be observed in this region, which was probably due to the low resolution of his spectrometer. Later studies of quinolizidine alkaloids ⟨71CRV109, 86JCS(P1)447⟩ by IR have confirmed Wiewiorowski's conclusions. For example, epimyrtine (**55**) displays strong Bohlmann bands at 2790 and 2745 cm^{-1}, while myrtine (**56**) lacks these signals but shows an absorption at 2810 cm^{-1} ⟨81T4287⟩.



Once the preferred ring fusion is determined through examination of Bohlmann bands, IR may allow the deduction of the configuration of substituents placed on the quinolizidine system. For instance, (**57**) displays an intramolecularly bonded OH signal at 3527 cm^{-1}, while the corresponding signal in (**58**), due to a free hydroxyl group, appears at 3609 cm^{-1} ⟨64JOC2264⟩ and therefore the

hydroxyl must be axial in (**57**) and equatorial in (**58**). This criterion can be extended to other 1- and 3-hydroxyquinolizidines.



(**57**) (**58**)

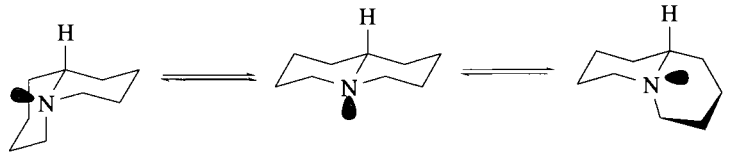
The use of Bohlmann bands for the conformational analysis of quinolizidines is unreliable in some cases due to their low intensity. Furthermore, these bands are absent in *trans*-quinolizidines with distorted rings ⟨67JOC1248, 73H(1)257⟩ or lacking two axial hydrogens α to nitrogen ⟨77H(6)1377⟩. For these reasons, the uncritical application of Bohlmann's rule has led to erroneous conclusions. Studies on the application of Bohlmann bands to condensed systems, such as benzo[*a*]quinolizidines ⟨78CPB1901⟩ and dibenzo[*a*,*g*]quinolizidines ⟨76CPB3185⟩, as well as polycyclic saturated systems related to sparteine ⟨68T5439, 88BAP295⟩, are also available.

Infrared data of conjugated systems, such as 4*H*-quinolizines ⟨87JHC655⟩ and quinolizinium salts ⟨85JHC681⟩ have also appeared in the literature.

8.22.4 THERMODYNAMIC ASPECTS

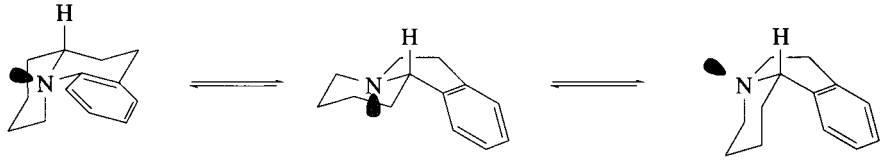
Due to the biological interest of many quinolizidine derivatives, a vast amount of chromatographic and other analytical data (melting and boiling points, color tests, etc.) are available (see, for example, ⟨B-81MI 822-03⟩ for an analytical profile of emetine).

The quinolizidine system poses an interesting conformational problem, due to the presence of the stereochemically mobile nitrogen atom. Three structures (**59**)–(**61**) are possible (Scheme 2), one of them with a *trans* arrangement between the nitrogen lone pair and the angular hydrogen atom and two others with a *cis* ring fusion. A similar situation occurs in arenoquinolizidines (e.g. structures (**62**)–(**64**) (Scheme 3) for benzo[*a*]quinolizidines and (**65**)–(**67**) (Scheme 4) for dibenzo-[*a*,*g*]quinolizidines). Although the configuration of benzo- and dibenzoquinolizidines is the opposite in the *cis* and *trans* structures, they are usually described as conformers due to the fact that nitrogen inversion allows both enantiomers to be in equilibrium. For spectroscopic criteria that allow the assignment of the *cis* and *trans* structures see Sections 8.22.3.2 and 8.22.3.5.



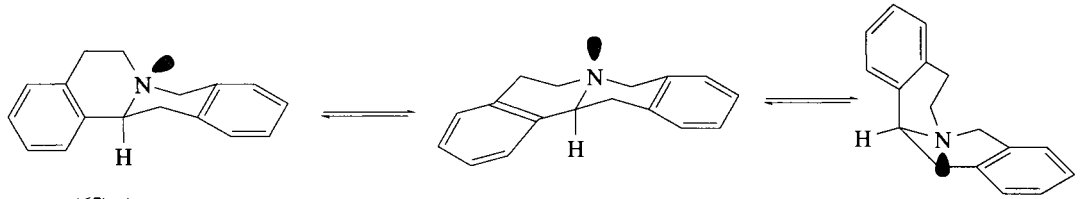
(**59**) *cis* (**60**) *trans* (**61**) *cis*

Scheme 2



(**62**) *cis* (**62**) *trans* (**64**) *cis*

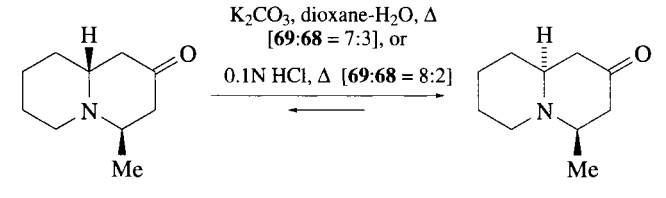
Scheme 3



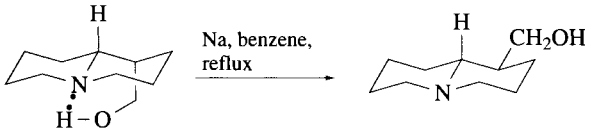
(**65**) *cis* (**66**) *trans* (**67**) *cis*

Scheme 4

Most quinolizidine compounds tend to adopt conformations with a *trans* ring junction, unless this leaves the bulkier substituents in an axial position. For example, racemic epimyrtine (**69**) is thermodynamically more stable than its isomer myrtine (**68**), as shown by the results of equilibration experiments through retro-Mannich or retro-Michael pathways (Equation (4)), both in basic and acid media. This can be attributed to the higher stability of the structure with a *trans* ring junction and an equatorial methyl group, with respect to other isomers ⟨81T4287⟩. Similarly, (±)-lupinine (**70**), with a *trans* ring junction and an axial 1-hydroxymethyl group, epimerizes to (±)-epilupinine (**71**) when refluxed with sodium in benzene solution; the stereochemistry of (**70**), and hence that of (**71**), is confirmed by the evidence of hydrogen bonding in its IR spectrum and by chemical reactivity studies (Equation (5)) ⟨79COC(4)233⟩.

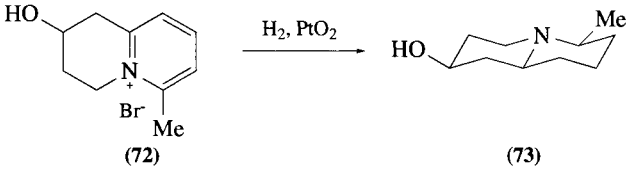


(±) Myrtine (**68**) (±) Epimyrtine (**69**) (4)

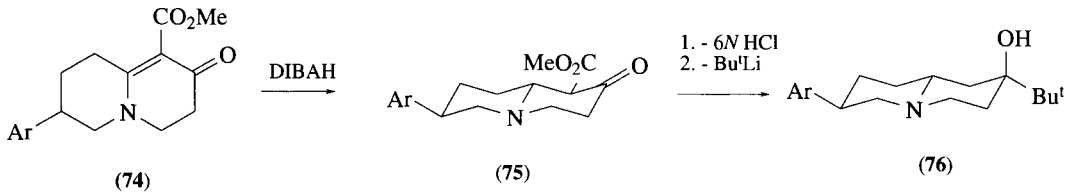


(**70**) (**71**) (5)

The stability of the final product usually controls the stereochemistry of reactions leading to quinolizidine derivatives. For example, catalytic hydrogenation of tetrahydroquinolizinium salt (**72**) ⟨85JMC1843⟩ gives predominantly the hydroxyquinolizidine (**73**) with equatorial hydroxy and methyl groups (85% by ^{1}H NMR) (Equation (6)). Similarly, (**74**) is stereospecifically reduced to (**75**) (*trans*-fused, with equatorial substituents), which can be transformed into (**76**) through another stereospecific addition to the carbonyl group (Scheme 5) ⟨84JMC165⟩.



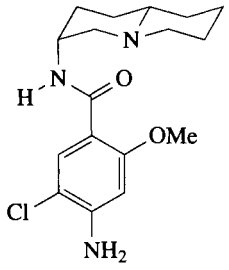
(**72**) (**73**) (6)



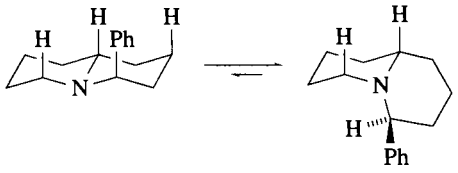
(**74**) (**75**) (**76**)

Scheme 5

Not all substituents demand to be placed in an equatorial position. For example, 7-phenyl-2-quinolizidinone exists in a *trans* chair–chair conformation, with the phenyl group axial ⟨86JCS(P1)447⟩, and compound (**77**), a gastric prokinetic agent with a potency similar to that of metoclopramide, displays a similar conformation, as shown by spectral evidence and molecular mechanics ⟨85JMC1843⟩. However, an increase in the number of 1,3-diaxial interactions may cause an axial disposition of the aryl group to be too unstable, as in the case of 4-phenylquinolizidine. This compound exists predominantly in the *cis*-fused conformation (**79**) in order to avoid the severe interaction between the phenyl group and the three axial protons in the *trans*-fused structure (**78**) (Equation (7)) ⟨65TL2703⟩. Other steric interactions may give rise to surprising situations. For instance, porantherilidine (**80**) exhibits a *trans* chair–chair conformation although this leaves the bulky pentyl side chain in an axial position ⟨73MI 822-01, 80M143⟩.

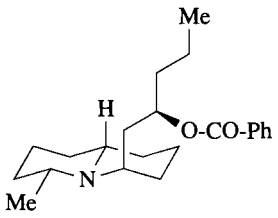


(77)



(78) (79)

(7)



(80)

The influence of polar effects may be important in determining the preferred conformation of quinolizidines. Thus quaternization of the nitrogen atom in quinolizidine systems causes the conformational equilibrium to shift towards the *cis* structure ⟨83H(20)1239, 83JST(101)127, 84JST(117)193⟩ due to the presence of unfavorable 1,3-diaxial interactions affecting the N^+-R group in the *trans* conformers. *N*-Oxidation ⟨71JA2501⟩ and, sometimes to a lesser extent, protonation ⟨71JCS(C)2541, 78CPB2555, 84BAP339⟩ also cause a shift of the conformational equilibrium towards *cis*-fused species.

Regarding the stability of quinolizine derivatives, it was mentioned in the introduction that the unsubstituted systems (e.g. **2**) have very low stabilities and, at best, have transient existence, probably due to their enamine structures. Electron-withdrawing groups increase their stability and, for example, the 4*H*-quinolizine-1,2,3,4-tetracarboxylic esters are stable. This can be explained by resonance involving the carboxylate groups at C-1 and C-3, whose conjugation with nitrogen makes them vinylogous carbamates.

8.22.5 REACTIVITY OF FULLY CONJUGATED RINGS

Due to the scarcity of new information on the reactivity of quinolizinium systems since the appearance of CHEC-I, the reader is referred to the corresponding chapter of this work ⟨84CHEC-I(2)525⟩ and to the reviews cited in the introduction (Section 8.22.1).

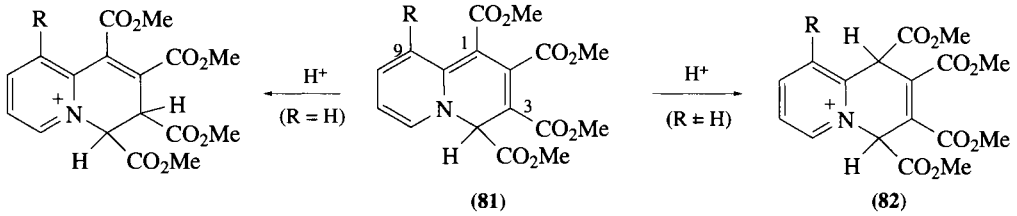
8.22.6 REACTIVITY OF NONCONJUGATED RINGS

8.22.6.1 Reactivity of Partially Saturated Quinolizinium Systems and their Benzo Derivatives

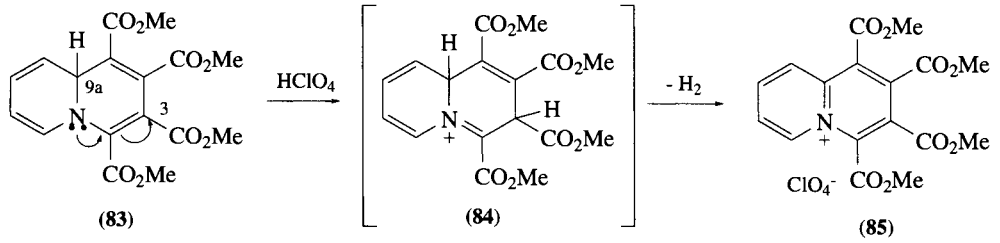
8.22.6.1.1 Basicity

Compound (**81**) protonates on C-3 carbon, which is the end of a conjugated π system towards which the nitrogen atom acts as a donor (Scheme 6). However, the presence of substituents at C-9

alters the extent of conjugation (as proved by changes in the UV spectrum), and protonation then takes place at C-1 to give (**82**). On the other hand, 9a*H*-quinolizines (**83**) are converted into quinolizinium salts (**85**) if perchloric acid is used ⟨79COC(4)233⟩ because simple protonation at C-3 would give a nonaromatic structure (**84**) (Scheme 7). Under other conditions, they can be transformed into their 4*H*-isomers through a [1,5] sigmatropic rearrangement ⟨82JA4671⟩.



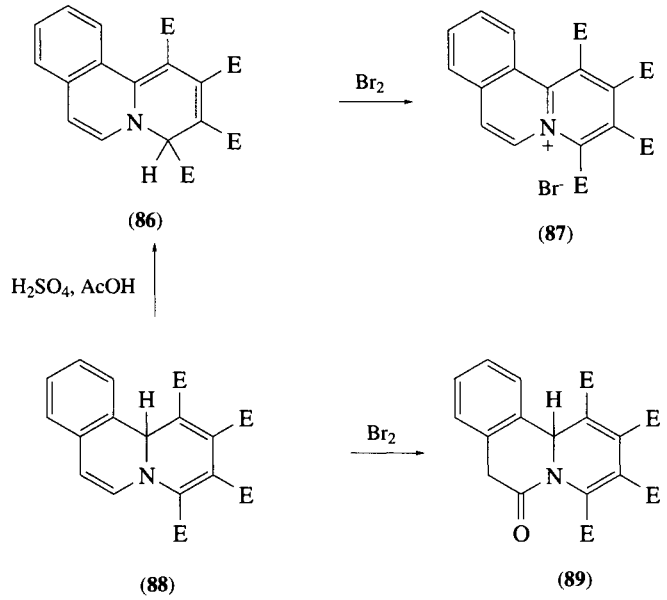
Scheme 6



Scheme 7

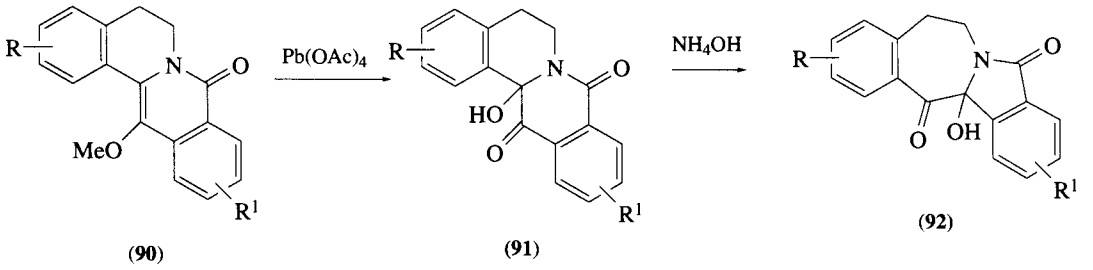
8.22.6.1.2 Oxidation

4*H*-Quinolizine derivatives are readily transformed into quinolizinium salts in the presence of mild oxidants, like perchloric acid (see Scheme 7). The benzo[*a*]derivative (**86**) undergoes a similar transformation in the presence of aqueous bromine to yield compound (**87**), but the 11b*H*-isomer (**88**) gives a quinolizinone derivative (**89**) ⟨62JCS748⟩. These reactions are summarized in Scheme 8.



Scheme 8

Prolonged treatment of oxyprotoberberines (**90**) with lead tetraacetate gives 8,13-dioxo-13a-hydroxytetrahydroprotoberberines (**91**) in excellent yield (Scheme 9) ⟨84JOC2642⟩. One of these compounds rearranged in the presence of ammonium hydroxide to give an indolobenzazepine (**92**) ⟨82TL39, 84JOC2642⟩.

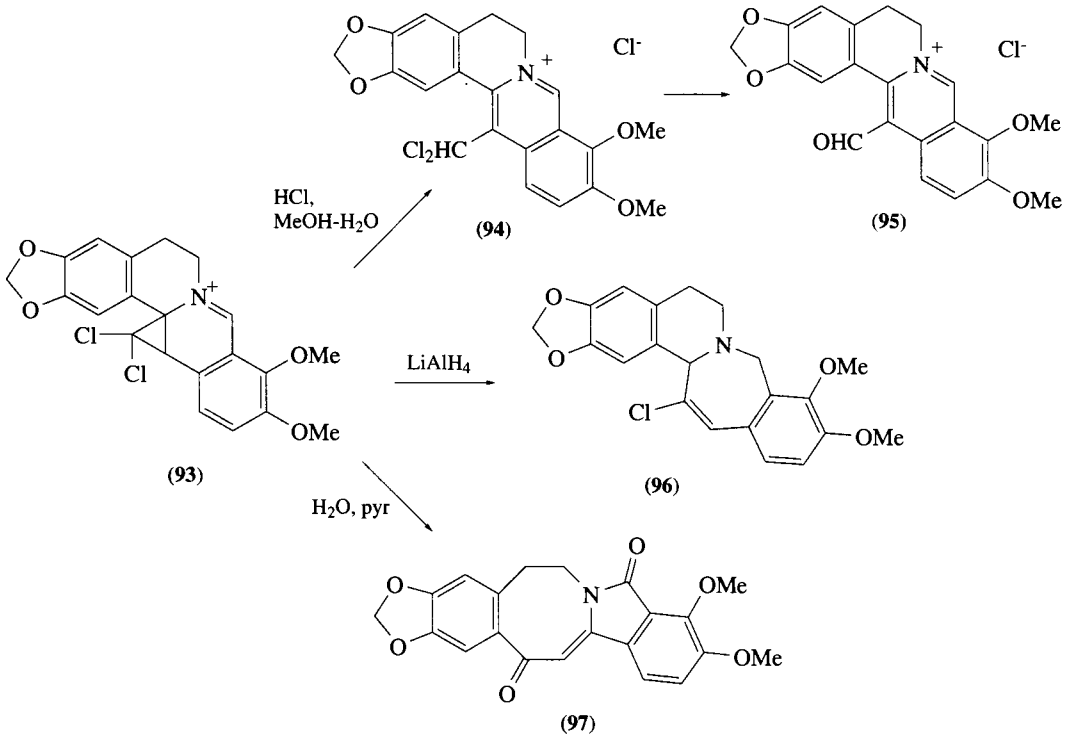


(**90**) (**91**) (**92**)

Scheme 9

8.22.6.1.3 Carbene addition

Treatment of berberine with dichlorocarbene afforded the dichloro adduct (**93**), an interesting starting material for the preparation of formylated derivatives but also of unusual berberine derivatives ⟨81JOC386⟩. Thus, treatment of (**93**) with dilute hydrochloric acid in methanol gave the 13-formyl derivative (**95**) through the intermediacy of (**94**). On the other hand, lithium aluminum hydride reduction of (**93**) afforded the C-homoberberine (**96**), and reaction of (**93**) with aqueous pyridine led to the keto lactam (**97**) (Scheme 10).

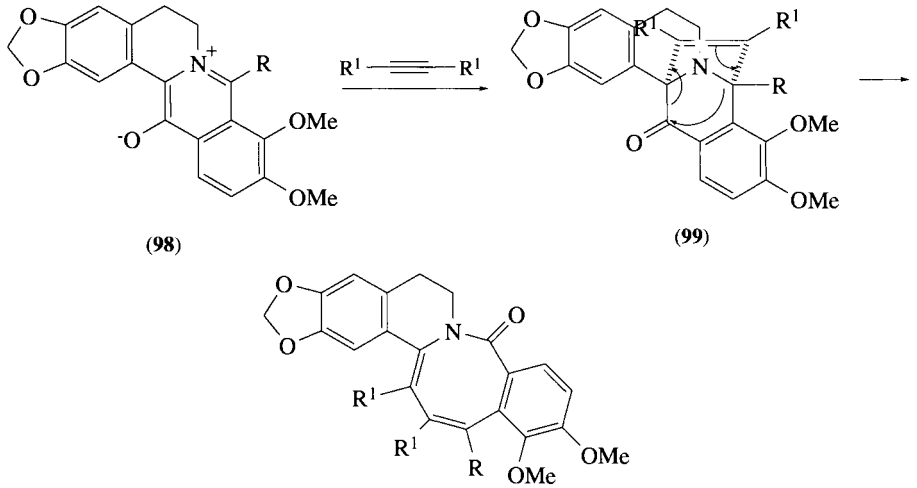


(**93**) (**94**) (**95**) (**96**) (**97**)

Scheme 10

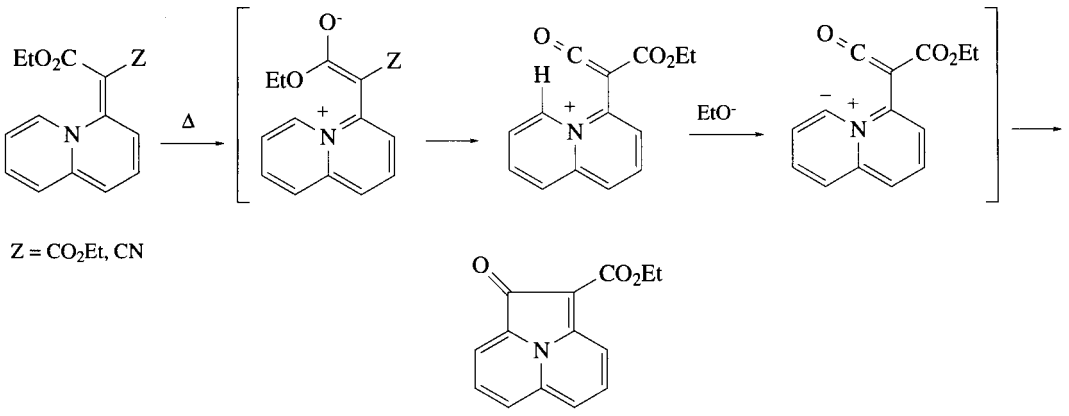
8.22.6.1.4 Cycloaddition chemistry of partially saturated quinolizinium betaines

3-Hydroxyquinolizinium bromide gives a mesomeric betaine that shows 1,3-dipolar reactivity ⟨65JOC526⟩. Similarly, 8-methoxyberberine phenol betaine (**98**) undergoes 1,3-dipolar cycloadditions with acetylenic compounds to give cycloadducts (**99**). These compounds, on heating in ethanol, were transformed into 8*H*-isoquinolino[2,1-b]benzazocines (**100**) (Scheme 11) ⟨79H(12)174, 79H(12)511⟩. A related intramolecular cycloaddition of a betaine onto a ketene group allowed the preparation of ethyl 1-oxo-pyrrolo[2,1,5-*de*]quinolizine-2-carboxylate (**101**) (Scheme 12) ⟨84JCS(P1)2553⟩.



(**98**) (**99**) (**100**)

Scheme 11



Z = CO_2Et, CN

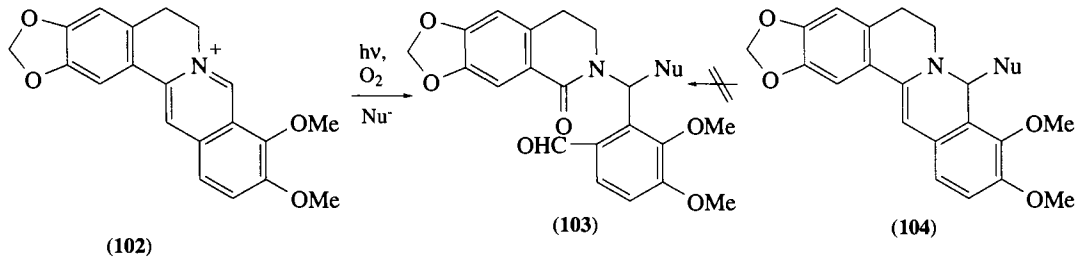
(**101**)

Scheme 12

8.22.6.1.5 Photochemistry

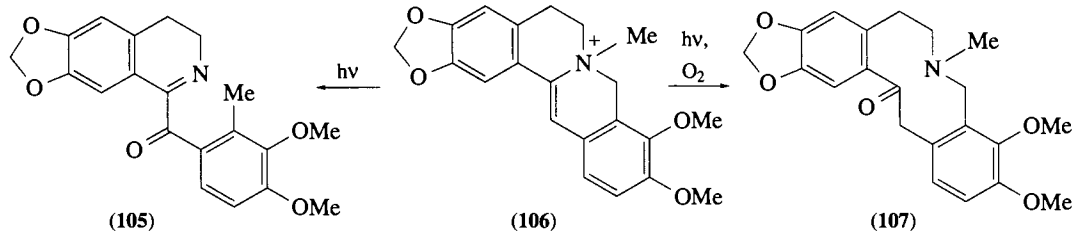
Photochemical transformations of partially saturated quinolizinium systems have received much attention, particularly in the field of berberine alkaloids.

Nonsensitized photochemical oxidation of dihydrodibenzo[*a*,*g*]quinolizinium compounds such as berberine (**102**) in the presence of nucleophilic reagents affords isoquinoline lactam aldehydes (**103**) (Scheme 13) ⟨84H(22)101⟩. A mechanistic proposal ⟨81H(16)1735⟩ involving the intermediacy of the dihydroberberine (**104**) was rejected on the basis of the results of direct irradiation of this compound. Participation of singlet oxygen was also excluded.

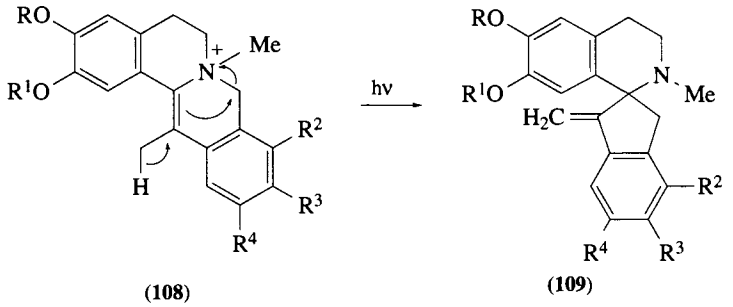


Scheme 13

Some tetrahydro dibenzo[*a*,*g*]quinolizinium compounds, like the *N*-methyldihydroberberine salts (**106**) also undergo ring opening on exposure to sunlight, yielding isoquinolines (e.g. **105**), or ring-cleaved berberines (e.g. the alkaloid allocryptine **107**) if the same treatment is performed in the presence of oxygen (Scheme 14) ⟨79PJC79⟩. On the other hand, C-13 methylated derivatives (**108**) followed a different route, affording spiroisoquinolines (**109**) (Equation (8)) ⟨78TL3419, 82TL3619⟩.

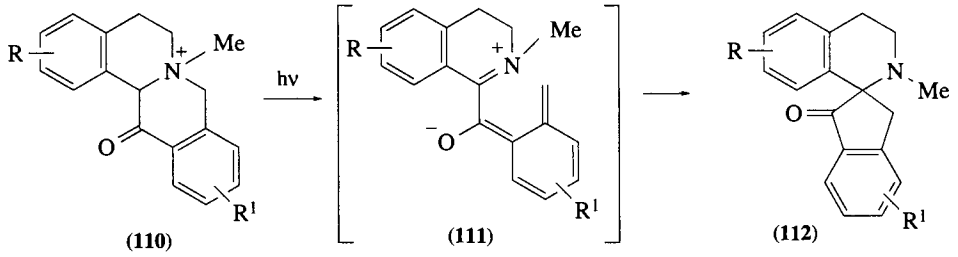


Scheme 14

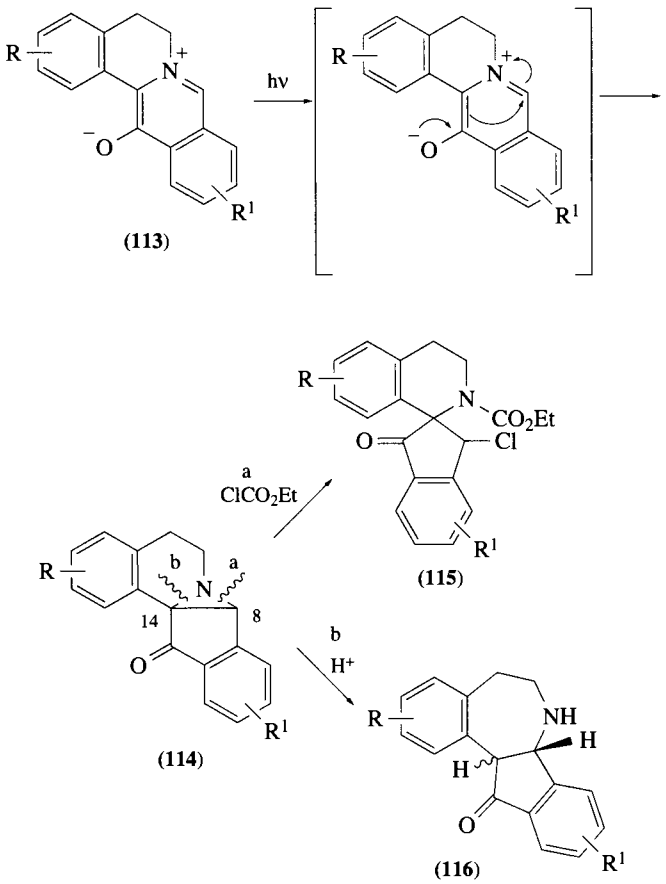


(8)

Similarly, irradiation of phenolbetaines derived from 13-oxotetrahydroprotoberberines (**110**) affords spirobenzylisoquinolines (**112**) through an *o*-quinodimethide intermediate (**111**) (Scheme 15) ⟨73JCS(P1)1464⟩. A slightly different phenolbetaine (compound **113**) gave 8,14-cycloberbine (**114**) upon irradiation (Scheme 16) ⟨79TL3794⟩. The aziridine structure of this compound makes it a versatile synthetic intermediate, which can be transformed into a number of interesting compounds through regioselective cleavage of the C_8—N and C_{14}—N bonds. Thus, (**114**) has been transformed into spirobenzylisoquinolines (**115**) by treatment with ethyl chloroformate, or to diastereomeric mixtures of benzindenoazepines (**116**) by protonation or reaction with other electrophiles (Scheme 16) ⟨80H(14)1455, 81TL3131, 82CPB3446, 82H(19)313⟩.



Scheme 15



Scheme 16

Oxygen functions can be introduced in the C-13 position of protoberberines by direct photooxygenation ⟨76H(6)953, 77H(7)945, 80JCS(P1)911⟩. Thus, irradiation of (**117**; R^1 = H) in the presence of oxygen and Rose Bengal afforded the 13-oxido derivative (**118**), together with berberine. Further irradiation of (**118**) furnished the dibenzo[*a*,*g*]quinolizidine (**119**) and the dihydroisoquinolone (**120**) (Scheme 17). In contrast, 13-oxidocoralyne (**121**), obtained from 5,6-dehydrocoralyne, underwent photooxygenation to give the papaveraldine derivative (**123**) through the suggested intermediacy of (**122**). Similar irradiation of the starting material or (**121**) in the presence of sodium methoxide led to a mixture of (**124**) and (**125**), presumably again through an epidioxy intermediate (Scheme 17) ⟨76H(6)953, 77H(7)945, 80JCS(P1)911⟩.

8.22.6.2 Reactivity of Quinolizidines and Arenoquinolizidines

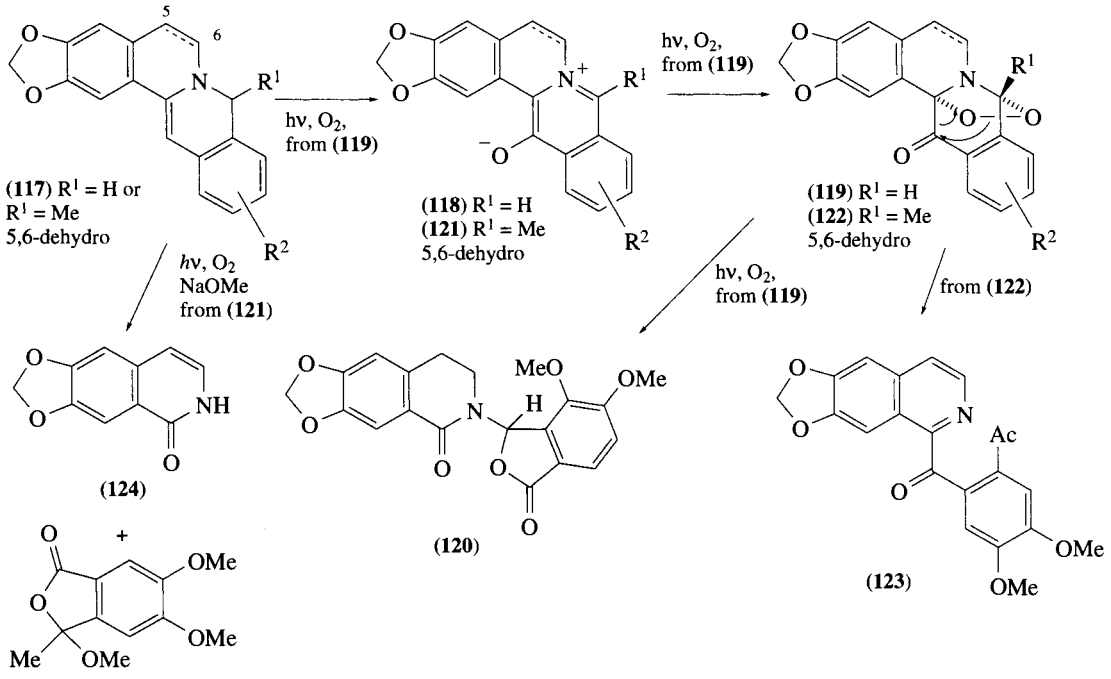
8.22.6.2.1 Basicity

Quinolizidine behaves as a tertiary cycloaliphatic amine, and its protonation leads to the quinolizidinium cation (**126**). This basicity allows resolution of optically active quinolizidines with chiral acids. As an example, optical resolution of butaclamol analogues (**127**) was accomplished with (+)- and (−)-binaphthyl phosphoric acids ⟨51JA3681⟩.

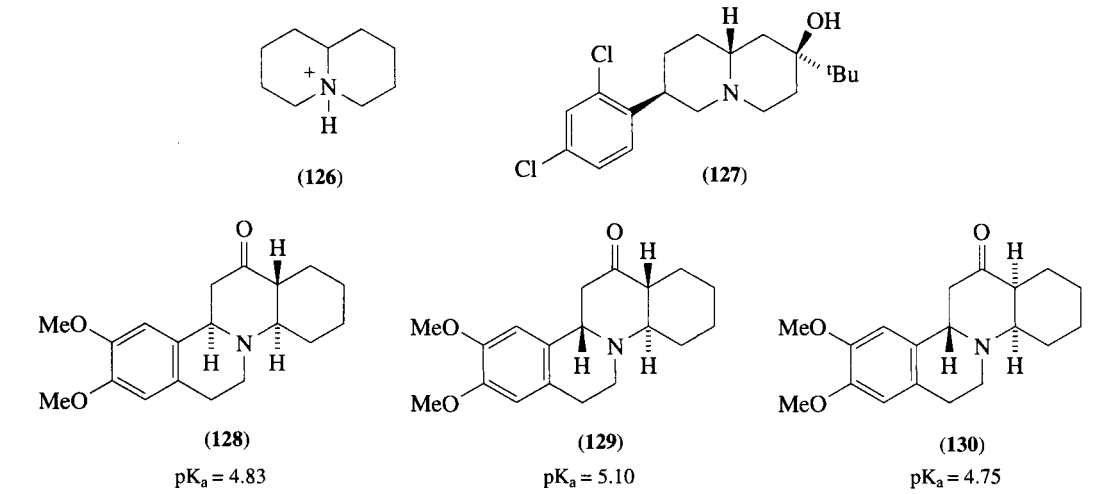
The basicity of more complex quinolizidines is related to the accessibility of the nitrogen lone pair and can therefore be related to their stereochemistry. For example, among the stereoisomeric 8-aza-homosteroids (**128**)–(**130**) the most basic compound is (**129**), in which the nitrogen lone pair is most accessible. This was confirmed by chemical reactivity studies, since (**128**) and (**129**) were completely methylated with methyl iodide in DMF at room temperature, while conversion of (**130**) was only partial ⟨76ACH139⟩.

8.22.6.2.2 Quaternization

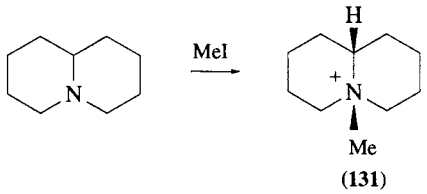
The quaternization of simple quinolizidines and related alkaloids has attracted much attention, directed primarily at the stereochemistry of the reaction. Methylation of *trans*-quinolizidine affords



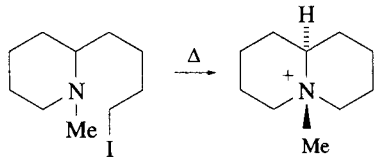
Scheme 17



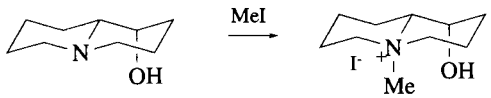
the *cis*-fused 5-methylquinolizidinium salt (**131**) (Equation (9)); its isomer (**132**) is available only from cyclization of piperidine derivatives (Equation (10)) ⟨51JA3681⟩. In the particular case of 1-hydroxyquinolizidines, compound (**133**) gave the *trans*-fused quinolizidine methiodide (**134**) (formerly assigned as a *cis* conformer) (Equation (11)), while (**135**) gave a 10 : 1 mixture of the *trans*- and *cis*-fused methiodides (**136**) and (**137**) ⟨83H(20)1239⟩, the latter of which exists as a mixture of conformers (**137a**) and (**137b**) (Scheme 18). Carbon substituents at C-1 exert a different influence, as shown by the fact that methylation of lupinine (**138**) gives a *cis*-fused quaternary salt (**139**) (Equation (12)).



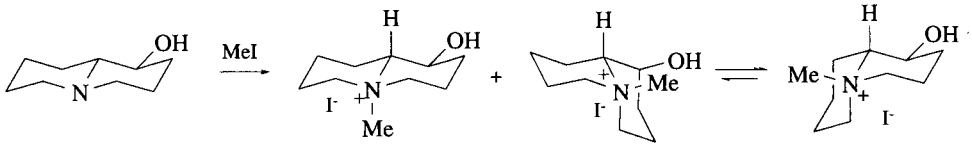
(9)



(132) (10)

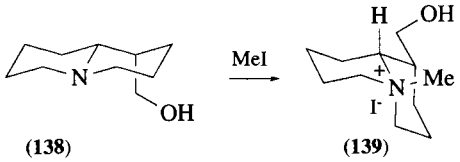


(133) (134) (11)



(135) (136) (137a) (137b)

Scheme 18



(138) (139) (12)

The stereochemistry of the *N*-oxidation of quinolizidines is similar to that of their alkylation ⟨76AQ917⟩.

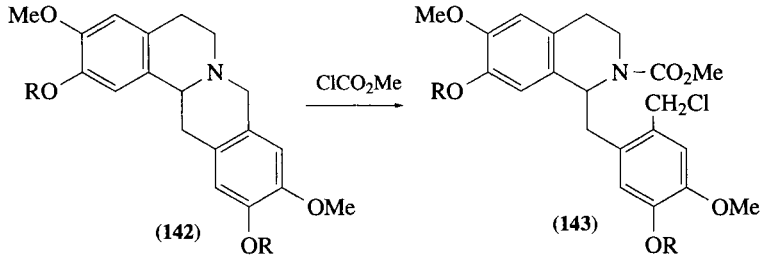
8.22.6.2.3 Reactions involving C—N bond fission

(i) Hofmann degradation

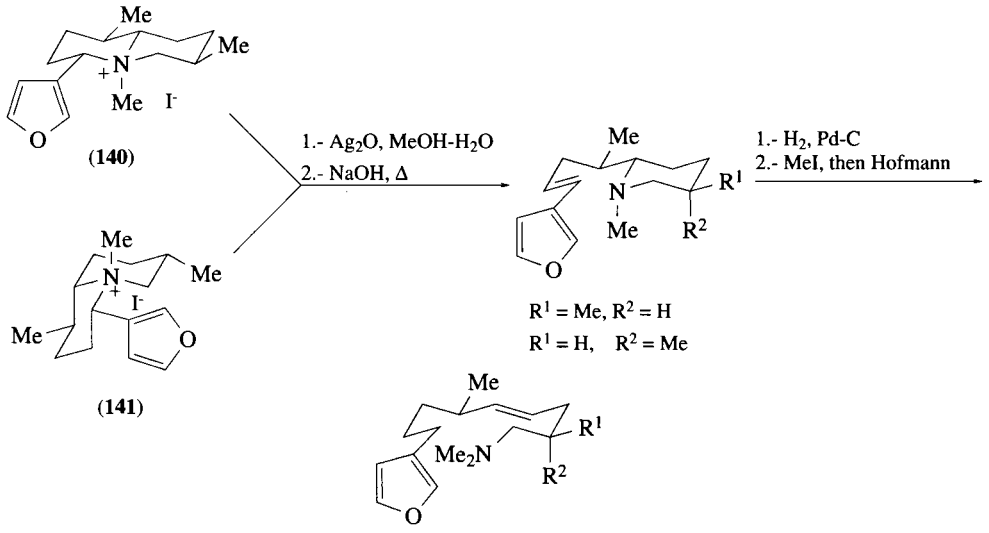
Quaternization of the nitrogen atom is the first step of the classical Hofmann degradation of quinolizidines, a reaction that is still widely practised ⟨82JOC5141, 82AP(315)273, 84TL5169⟩. As an example, the degradation of deoxynupharidine methiodide (**140**) and its 7-epi derivative (**141**) ⟨83H(20)1773, 84JST(116)1⟩ is summarized in Scheme 19.

(ii) Degradation by reaction with alkyl chloroformates

In a related reaction, treatment of protoberberines (**142**) with alkyl chloroformates afforded compound (**143**) (Equation (13)), arising from cleavage of the C_8—N bond and useful as a building block in alkaloid synthesis ⟨82H(19)1895, 83H(20)2417⟩. This regioselectivity is not always achieved, and the C_6—N bond can also cleave to give a mixture ⟨78T635, 79H(12)497, 81H(15)297⟩.

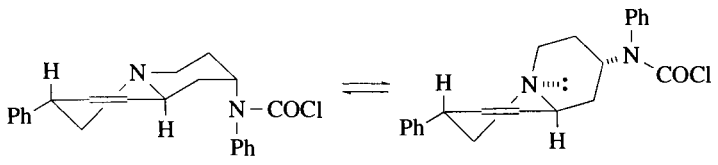


(142) (143) (13)



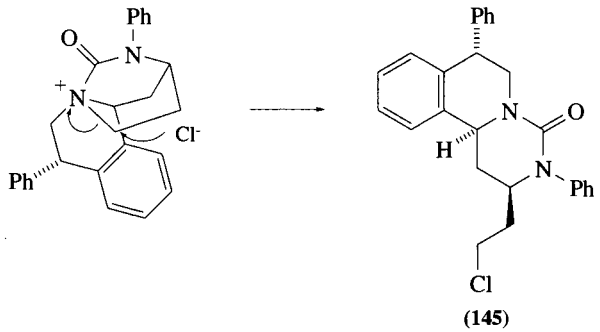
Scheme 19

A benzo[*a*]quinolizidine rearrangement involving an intramolecular version of this degradation has been described ⟨82TL2829, 83JOC5074⟩. The reaction consists of a remarkably stereoselective intramolecular carbamyl chloride-induced cleavage of the quinolizidine ring, and allows the transformation of (**144**) into the pyrimidino [4,3-*a*]isoquinoline (**145**). The mechanism of the rearrangement involves intramolecular acylation of the carbamyl chloride group in the *cis* conformer (**144b**) and regiospecific cleavage of a C—N bond (Equations (14) and (15)), and its facility must be attributed to the high population of the *cis* conformer in the starting material.



(14)

(**144a**) (*trans*) (**144b**) (*cis*)



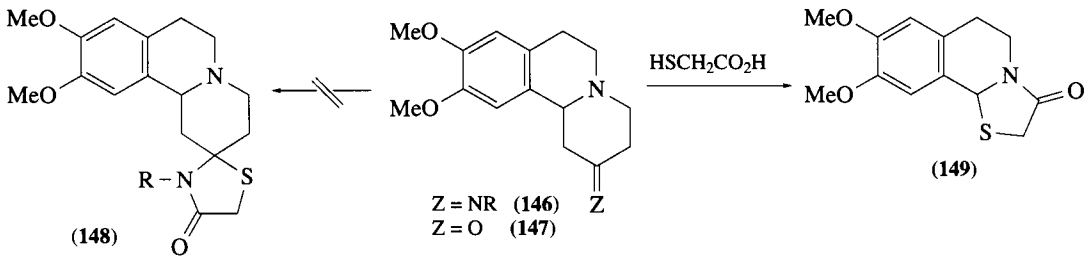
(15)

(**145**)

8.22.6.2.4 Degradation of benzo[a]quinolizidines

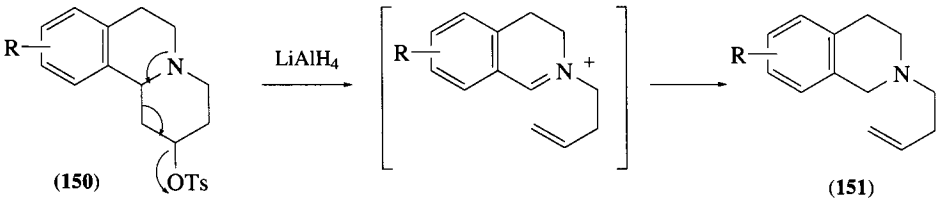
Benzo[*a*]quinolizidin-2-ones can be degraded in certain acidic media to 3,4-dihydroisoquinolines ⟨83JOC1075⟩. For example, treatment of 2-iminobenzo[*a*]quinolizidines (**146**) with thioglycolic acid under a variety of experimental conditions led to the thiazolo[2,3-*a*]isoquinoline (**149**) instead of the expected spiro compound (**148**), and the same result was obtained starting from ketone (**147**) (Scheme 20) ⟨90H(31)2065⟩. These results were explained according to the mechanism, which is a

reversal of the one that takes place during the synthesis of (**147**) from 6,7-dimethoxy-3,4-dihydroisoquinoline and methyl vinyl ketone or a synthetic equivalent (Section 8.22.8.5.1).



Scheme 20

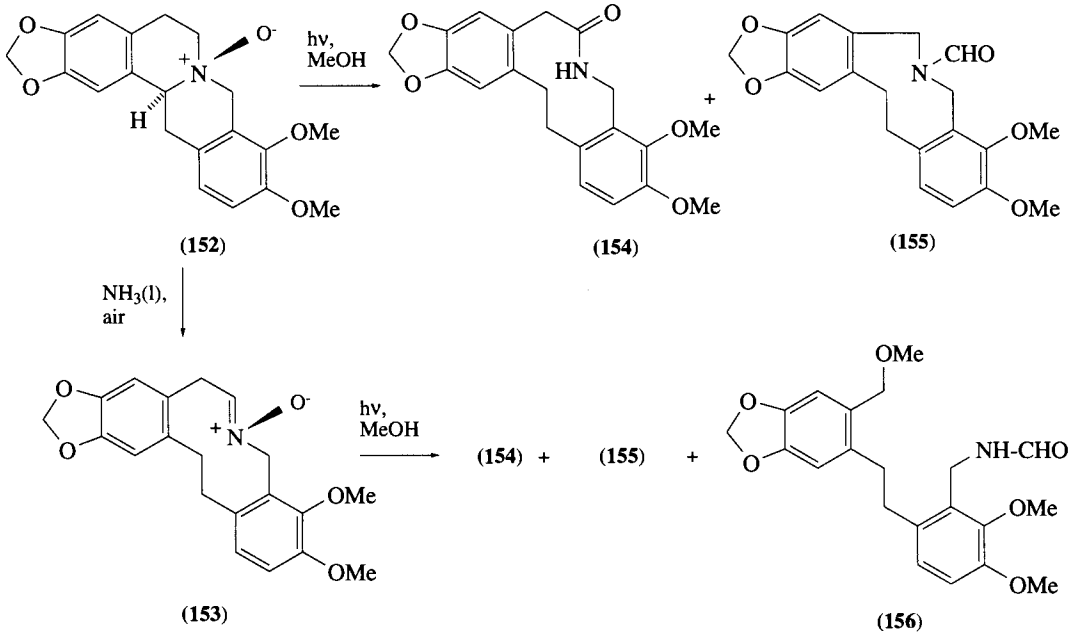
A reductive ring cleavage has been described for areno[*a*]quinolizidine tosylates (**150**) by treatment with lithium aluminum hydride, yielding compounds (**151**) ⟨87H(26)3059⟩ (Scheme 21).



Scheme 21

8.22.6.2.5 Photochemical reactions

N-Oxides of berbines, obtained by treatment of the parent compounds with *m*-chloroperbenzoic acid ⟨81JOC1378⟩, are interesting starting materials for the preparation of ring-cleaved berberines. For example, *trans*-canadine *N*-oxide (**152**) afforded nitrone (**153**) by treatment with aerated liquid ammonia. Photolysis of (**152**) gave two products ((**154**) and (**155**)), which were also obtained, together with (**156**), in the photolysis of the nitrone (**153**) (Scheme 22) ⟨80T1515⟩.



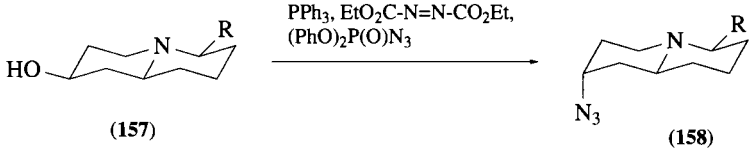
Scheme 22

8.22.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Attachment of functional groups to quinolizine carbon atoms does not normally alter their expected reactivity. This will be exemplified below with a few literature examples selected from the vast amount of references available. Many of these examples have been taken from benzo[*a*]quinolizidine chemistry.

8.22.7.1 Hydroxy and Amino Groups

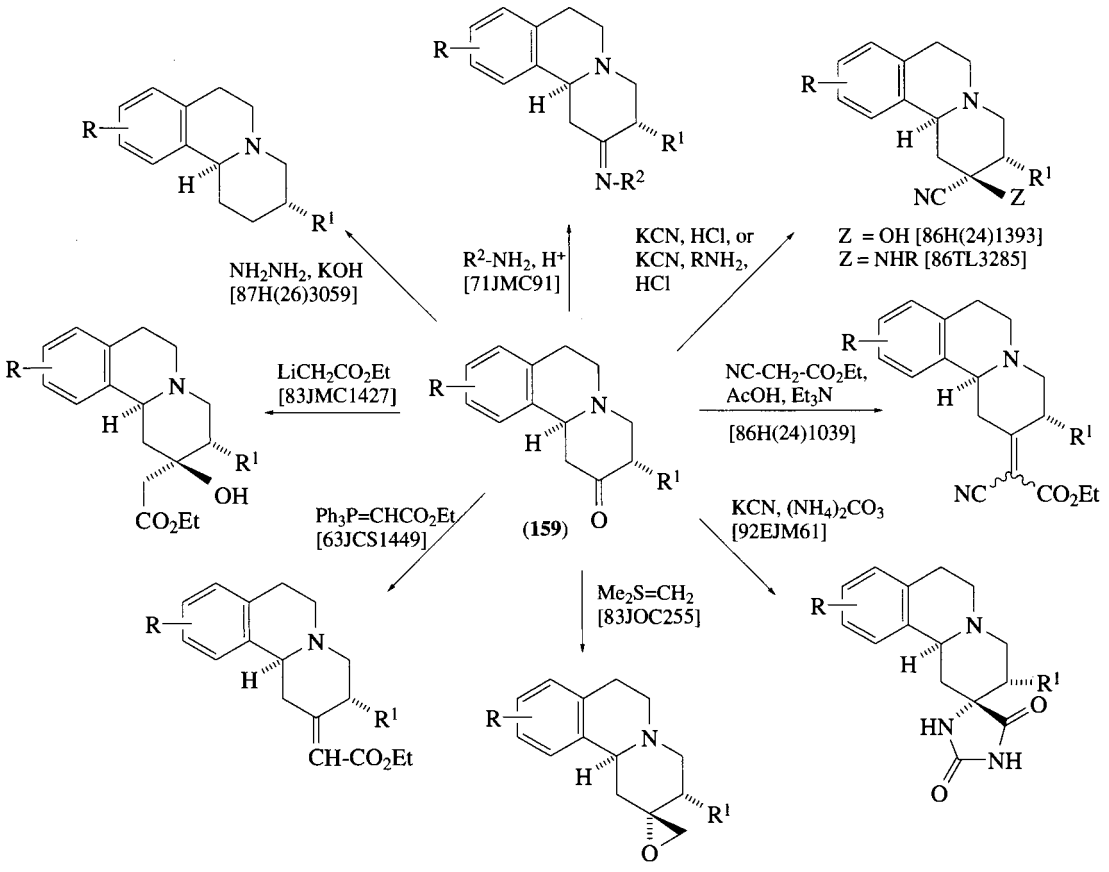
Quinolizidine alcohols and amines react as nucleophiles in the expected way, yielding amides and esters. They can also take part in Mitsunobu-type chemistry, and thus conversion of equatorial hydroxyquinolizidines (**157**) to axial azides (**158**) has been accomplished by treatment with triphenyl phosphine, diethyl azodicarboxylates, and diphenyl phosphoryl azide (Equation (16)) ⟨77TL1977⟩.



(157) (158) (16)

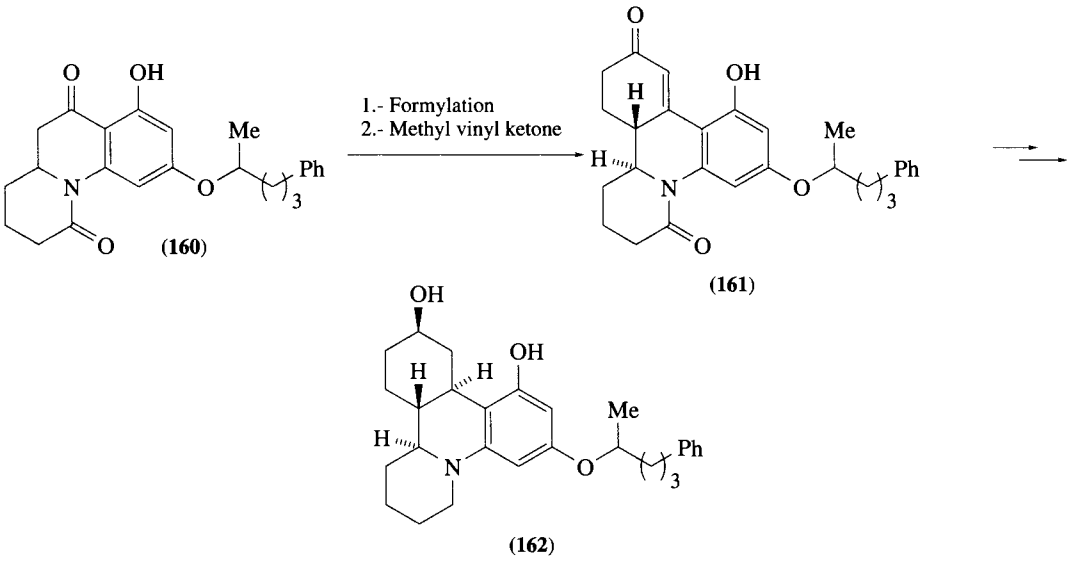
8.22.7.2 Ketones and their Derivatives

Ketone groups attached to quinolizidine systems also display the expected reactivity towards nucleophiles. This is illustrated in Scheme 23 with several reactions of benzo[*a*]quinolizidin-2-one systems (**159**).



Scheme 23

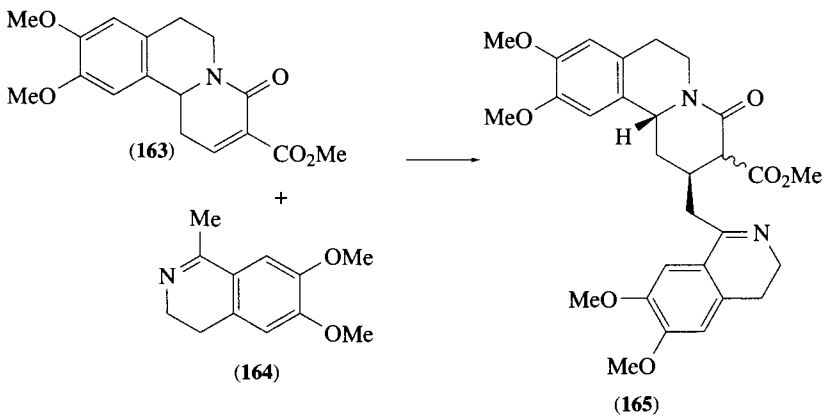
Quinolizidinones can also serve as substrates for Robinson annelation procedures. For example, benzo[*c*]quinolizidinedione derivative (**160**) was activated in the position α to the ketone group in C-6 by formylation and then treated with methyl vinyl ketone to yield the pyrido[1,2-*f*]phenanthridine (**161**), which was then functionalized to the CNS active agent (**162**) ⟨83EUP90526⟩ (Scheme 24).



(160) (161) (162)

Scheme 24

Quinolizidine-derived enones display also the expected reactivity. For example, treatment of benzo[*a*]quinolizidin-4-one (**163**) with a dihydroisoquinoline (**164**) gave the conjugate addition product (**165**), an emetine analogue (Equation (17)) ⟨82H(19)857⟩.

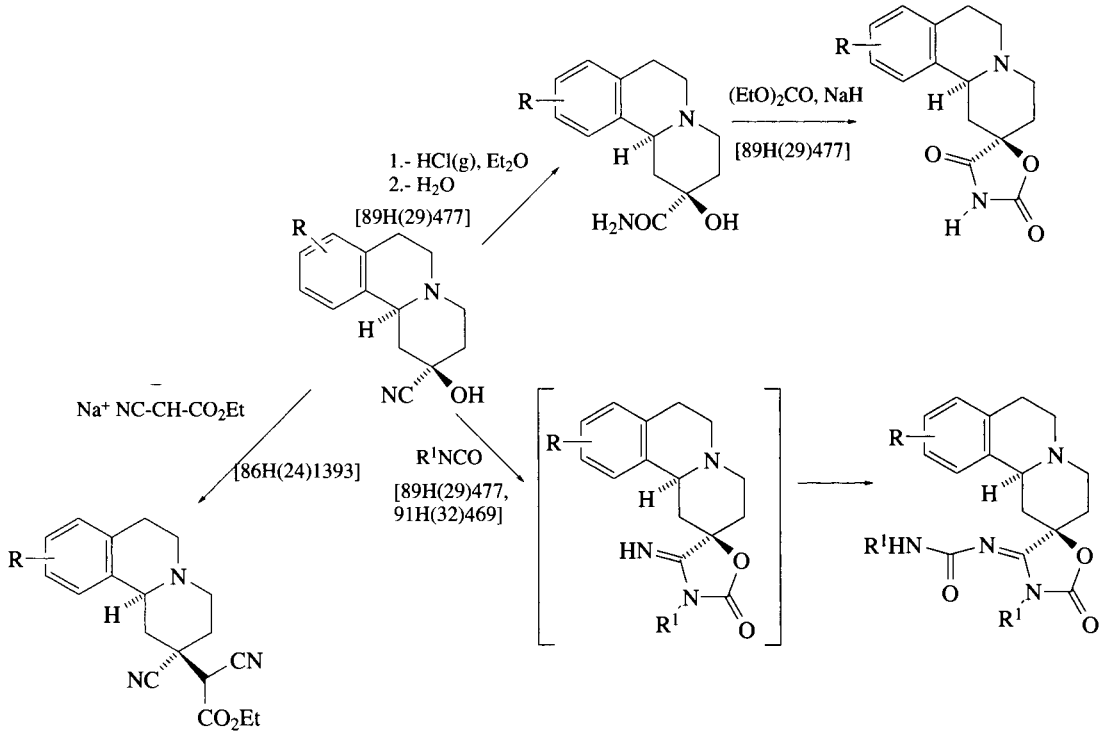


(163) (164) (165) (17)

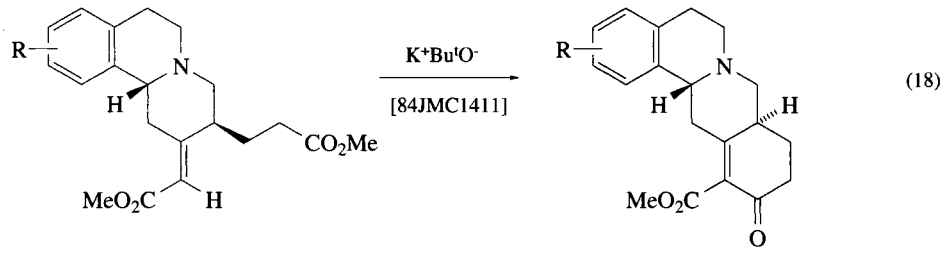
The stereochemistry of the reduction of quinolizidine oximes can be partially controlled through suitable choice of the reducing agent. The main reaction product is normally the one resulting from axial attack and therefore shows the amino group in an equatorial position ⟨83JMC416⟩. However, reagents with large steric requirements may afford considerable amounts of the thermodynamically less stable, but kinetically favored, axial amino derivatives ⟨71CRV109⟩.

8.22.7.3 Carboxylic Acids and their Derivatives

A few reactions of benzo[*a*]quinolizidine carboxylic acid derivatives are summarized in Scheme 25 and Equation (18); these functional groups also show the expected behavior.



Scheme 25



(18)

8.22.8 RING SYNTHESES

As already mentioned, most of the syntheses known for the quinolizinium system were suitably covered in CHEC-I and the field has shown little activity in the years following ⟨81AQ225, 85JHC681, 86JHC1151, 92T8459, 94JOC8294⟩. Therefore, this section will be devoted primarily to the synthesis of quinolizines and quinolizidines. The routes are classified according to the number and position of the new bonds.

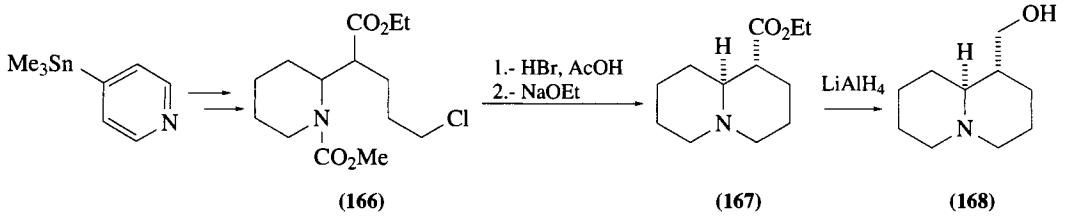
8.22.8.1 Formation of a New Bond α to the Heteroatom

Many syntheses of quinolizidine derivatives are based upon intramolecular nucleophilic attack of a piperidine nitrogen atom onto an electrophilic function placed in the ε position of a side chain. These reactions are systematized below on the basis of the nature of the electrophile.

8.22.8.1.1 From alkyl halides

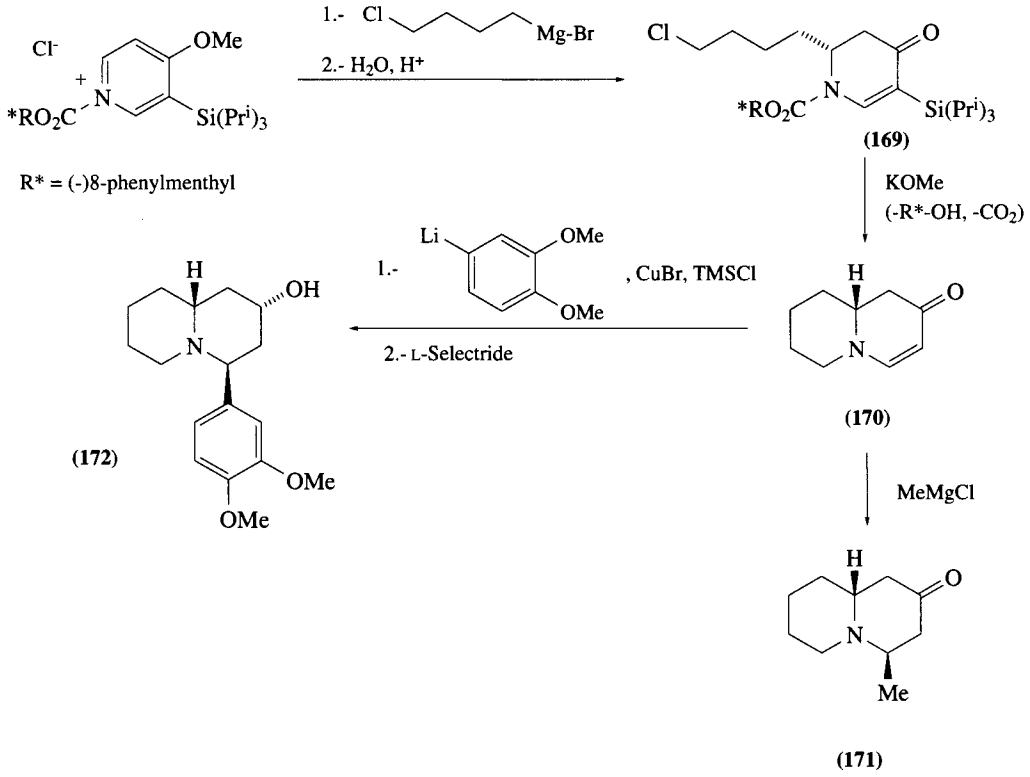
A conceptually very simple approach to epilupinine ⟨86TL2219⟩ involves the preparation of quinolizidine (**167**), readily available by deprotection of piperidine (**166**) by acid hydrolysis, sub-

sequent ring closure through intramolecular nucleophilic displacement of the halogen atom and equilibration in the presence of base to yield the stereochemistry shown for (**167**) (Scheme 26); a final reduction step yields (±)-epilupinine (**168**). The precursor (**166**) was available in two steps from 4-trimethyltinpyridine.



Scheme 26

The asymmetric total synthesis of the *Lytraceae* alkaloids (+)-myrtine (**171**) and (−)-lasubine I (**172**) from common precursors shown in Scheme 27 ⟨92JOC5807⟩ includes a cyclization step of the same type. Thus, the chiral dihydropyridone (**169**) was deprotected and cyclized to (**170**), which, after enantiospecific conjugate addition of the suitable organometallic reagent and, in the case of (−)-lasubine I, a final reductive step, afforded the desired alkaloids. Other auxiliary groups that have been employed for the asymmetric total synthesis of quinolizidine alkaloids in related strategies include chiral 4-isopropylthiazolidinethiones ⟨88JA289⟩.

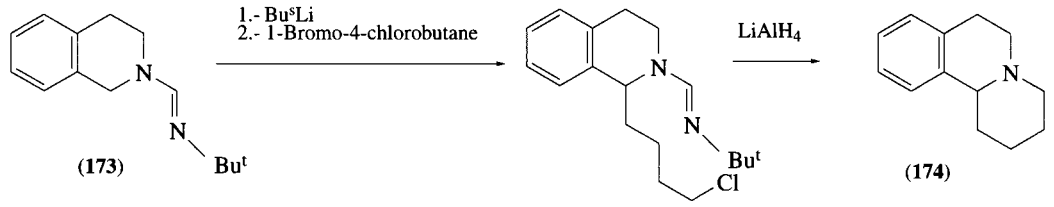


Scheme 27

Metallation and alkylation of *N*-formamidine derivatives of tetrahydroisoquinolines (**173**), followed by reductive regeneration of the amino group and intramolecular cyclization, affords benzo[*a*]quinolizidines (**174**) (Scheme 28) ⟨81TL515⟩.

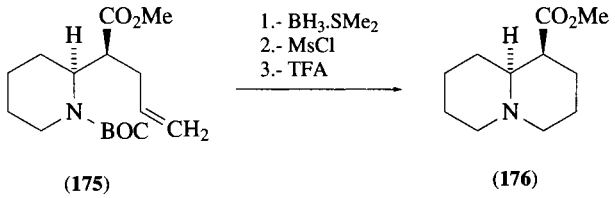
8.22.8.1.2 From mesylates

An approach to quinolizidines very similar to the one discussed in the previous section employs the intramolecular cyclization of a mesylate as the critical step. A simple example of this methodology



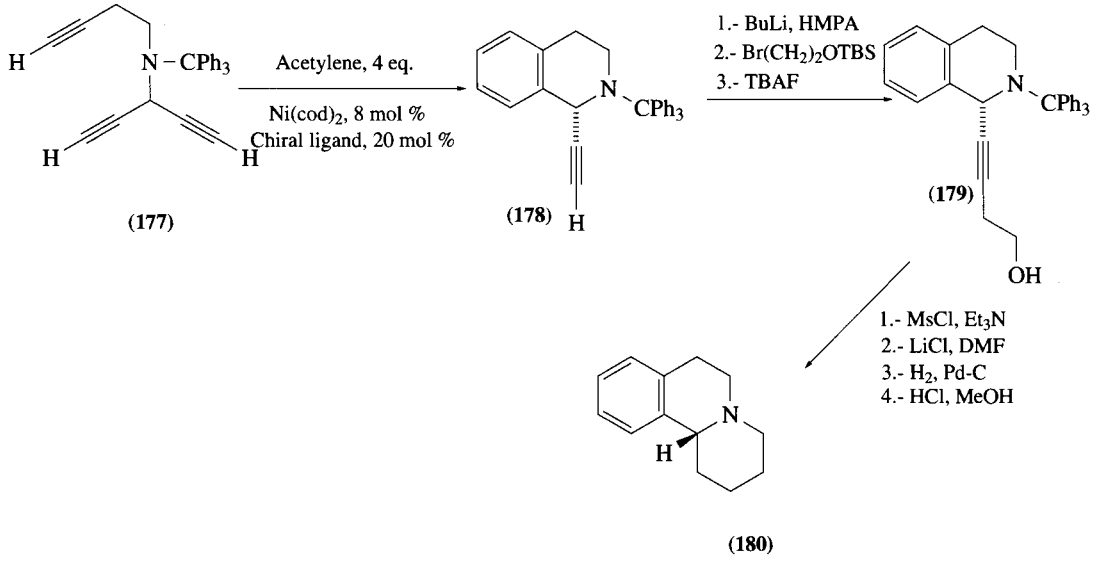
Scheme 28

is summarized in Equation (19) for the synthesis of (**176**), and involves the cyclization in trifluoroacetic acid of the mesylate of the alcohol obtained by hydroboration–oxidation of (**175**) ⟨90TA147⟩.



(19)

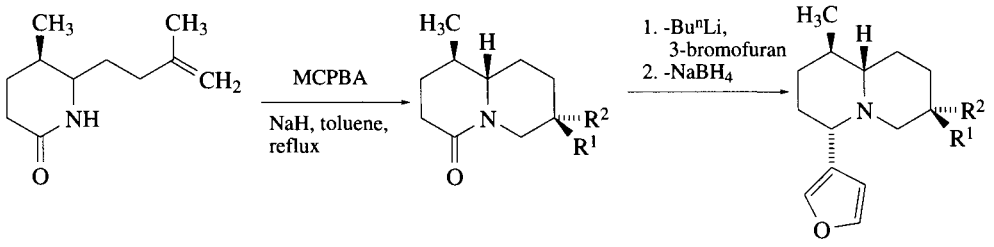
Nickel(0)-catalyzed [2 + 2 + 2] cocyclization of the precursor (**177**) in the presence of several chiral ligands afforded the chiral tetrahydroisoquinoline (**178**) in a novel asymmetric cycloaddition. Compound (**178**) could be transformed into the benzo[*a*]quinolizidine (**180**), albeit in modest enantiomeric excess, through a multistep route involving extension of the alkynic side chain at C-1 to yield (**179**), introduction of a ω halogen atom, reduction of the triple bond, *N*-deprotection and final cyclization (Scheme 29) ⟨94JOC6133⟩.



Scheme 29

8.22.8.1.3 From epoxides

The *Nuphar* quinolizidine alkaloid nupharotuline (**181**) and its 7-epi analogue (**182**) have been prepared in a sequence featuring as the key step the intramolecular, base-induced opening of an epoxide intermediate, in turn available from the Beckmann rearrangement product of a cyclopentane derivative (Scheme 30) ⟨80JOC3644⟩.

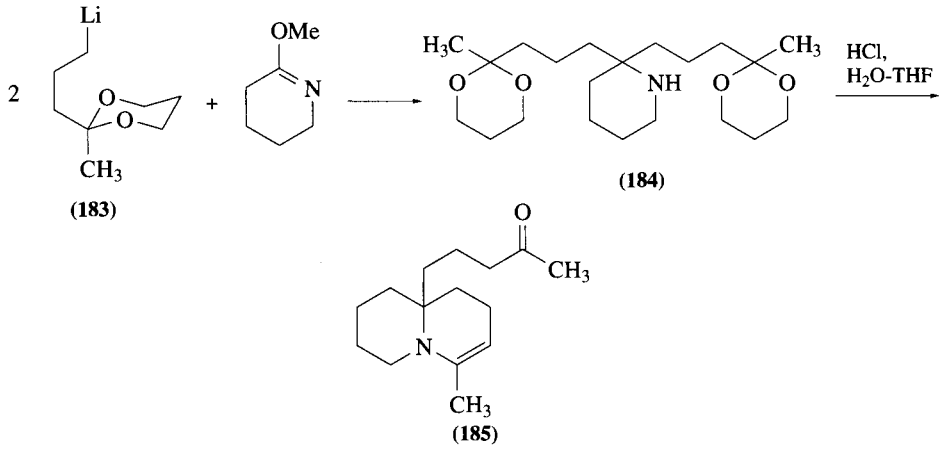


(**181**) R^1 = OH, R^2 = Me
(**182**) R^1 = Me, R^2 = OH

Scheme 30

8.22.8.1.4 From aldehydes and ketones

Intramolecular enamine formation between an aldehyde or ketone and the nitrogen atom of a piperidine ring can serve as the key step in the preparation of quinolizidine derivatives. For example, the ketal (**184**), prepared by double addition of the lithio derivative (**183**) to 6-methoxy-2,3,4,5-tetrahydropyridine, can be easily cyclized to the quinolizidine derivative (**185**) by double acid-catalyzed deprotection, cyclization, and dehydration (Scheme 31). These reactions constitute the first steps of a stereocontrolled total synthesis of the alkaloid (±)-porantherine ⟨87JA4940⟩.



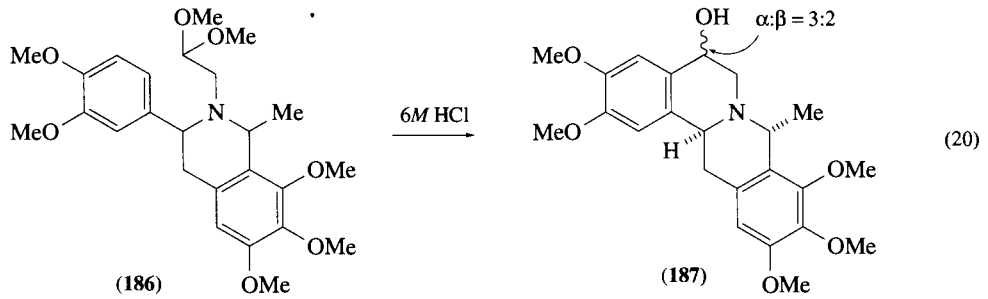
(**183**)

(**184**)

(**185**)

Scheme 31

Similarly, acid-catalyzed deprotection and cyclization of tetrahydroisoquinoline acetal (**186**) afforded protoberberines (**187**) (Equation (20)) ⟨88T203⟩.

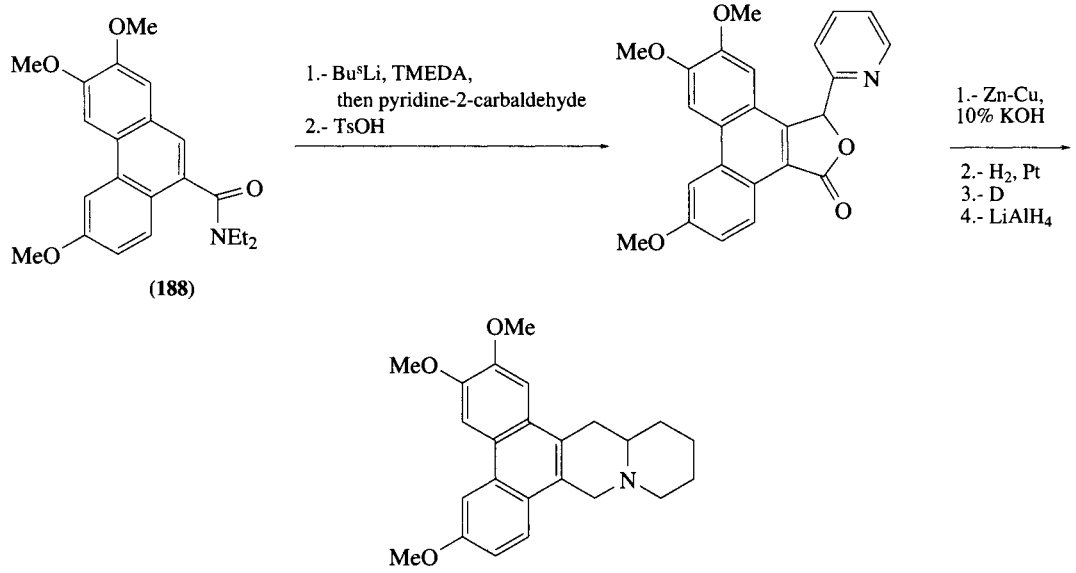


(**186**) (**187**) (20)

8.22.8.1.5 From carboxylic acids and their derivatives

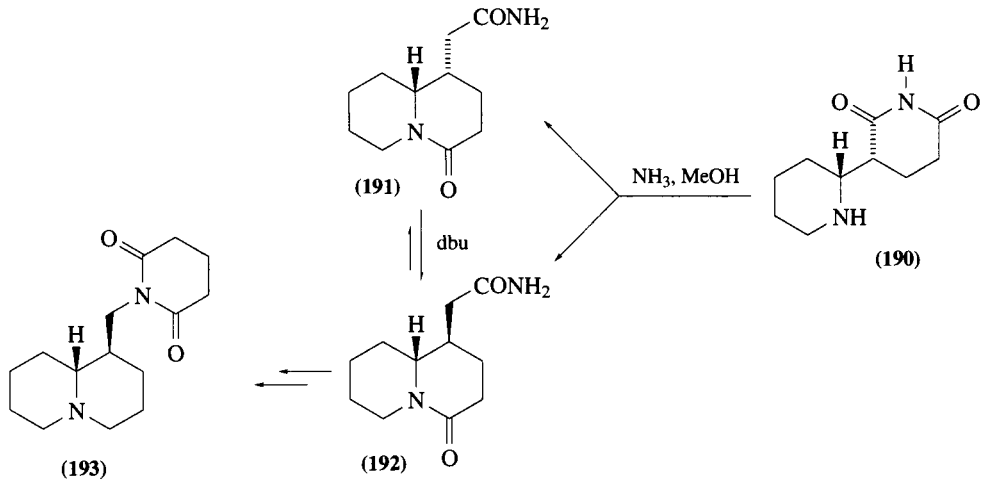
Intramolecular amide formation is also a useful route to quinolizines. Thus, a very efficient synthesis of the phenanthroquinolizidine alkaloid cryptopleurine (**189**) described by Snieckus and

co-workers ⟨81TL2349⟩ uses a benzamide-directed metallation reaction on (**188**) for the introduction of the pyridine ring, followed by phthalide reduction and intramolecular amide formation for the creation of the quinolizidine (Scheme 32). Many other examples of straightforward cyclizations of this type are known ⟨83EUP90526, 83JOC1621⟩.



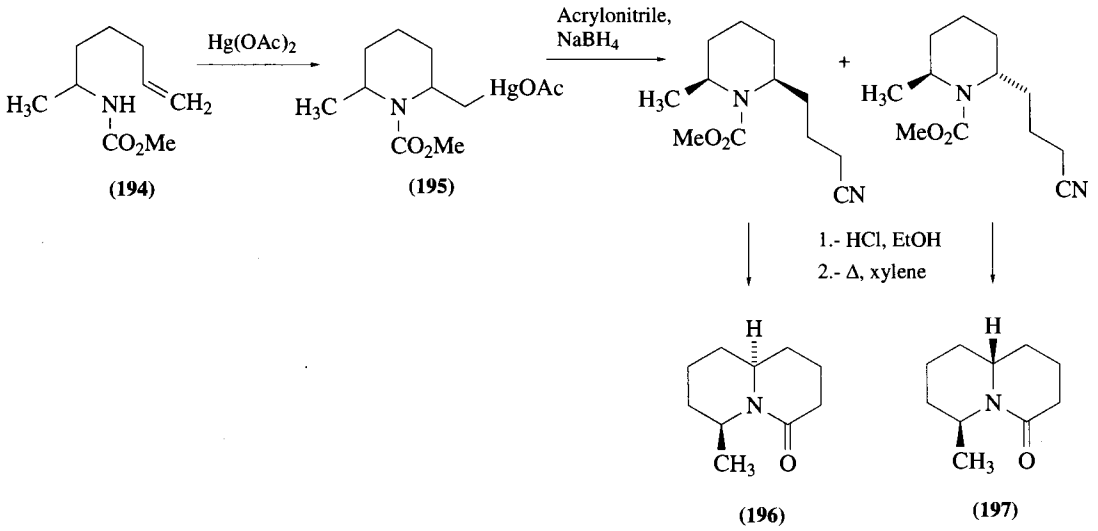
Scheme 32

A biomimetic approach to the quinolizidine alkaloid lamprolobine (**193**) ⟨91T8431⟩ exploits the cyclization of the bispiperidine system (**190**) by treatment with ammonia in methanol. This reaction affords a mixture of quinolizidines (**191**) and (**192**), whose ratio can be shifted in favor of the minor isomer (**192**) by equilibration in the presence of dbu. Compound (**192**) displays suitable stereochemistry to act as a precursor of lamprolobine (Scheme 33).



Scheme 33

A related cyclization step is employed in an approach to 4-quinolizidinones through intramolecular amidomercuriation of *N*-protected amines (**194**) followed by reaction of the organomercury compound (**195**) with acrylonitrile, deprotection, and cyclization to (**196**) and (**197**) (Scheme 34) ⟨84CC1235⟩.

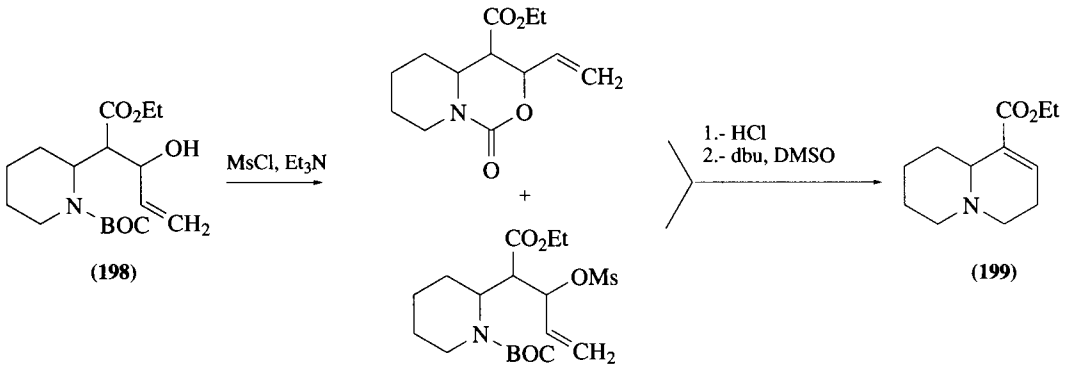


(194) (195) (196) (197)

Scheme 34

8.22.8.1.6 From activated double bonds

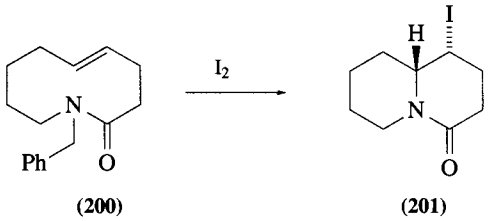
Michael acceptors and other activated alkenic double bonds can play the role of electrophilic components in the cyclization of piperidine derivatives to quinolizidines. For example, base-induced β-elimination of the mesylated alcohol (**198**) gave the epilupinine precursor (**199**) (Scheme 35) ⟨88CPB1597⟩.



(198) (199)

Scheme 35

Halogenation is an alternative procedure for double-bond activation. Thus, treatment of the ten-membered lactam (**200**) with iodine induced its stereoselective cyclization to the quinolizidine (**201**), as shown in Equation (21) ⟨91JA6690, 91TL5709⟩.

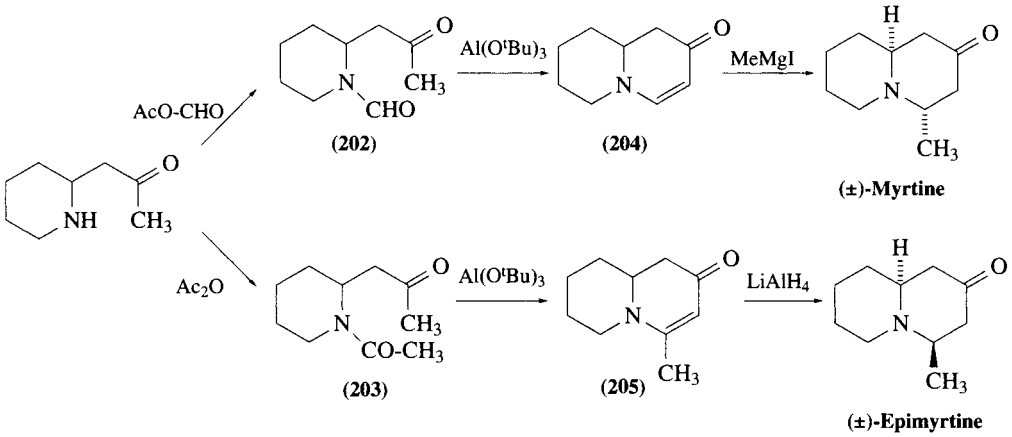


(200) (201) (21)

8.22.8.2 Formation of a New Bond β to the Heteroatom

8.22.8.2.1 Intramolecular aldol reactions

N-Acylpiperidines are good precursors for quinolizidine derivatives through intramolecular aldol condensations with suitable carbonylic side chains. For example, treatment of *N*-acylpelletierines (**202**) and (**203**) with base gives 3,4-dehydroquinolizidin-2-ones ((**204**) and (**205**) respectively). The conjugate addition of nucleophiles to these compounds is stereospecific, yielding products in which the entering nucleophile and the hydrogen atom at C-9a are *cis*. Scheme 36 shows the application of this chemistry to the total synthesis of (±)-myrtine and (±)-epimyrtine ⟨81T4287⟩.



Scheme 36

8.22.8.2.2 Intramolecular Friedel–Crafts cyclizations

This strategy is well represented by several syntheses of the alkaloid cryptopleurine ⟨58CJC581, 71T3465, 80JHC69⟩ (see also Scheme 32) and its analogues ⟨86JHC601, 86JHC929⟩ by intramolecular cyclization of *N*-(9-phenanthrylmethyl)piperidine-2-carboxylic acid derivatives (e.g. **206**) to ketones (**207**) followed by multistep reduction of the carbonyl group (Scheme 37).

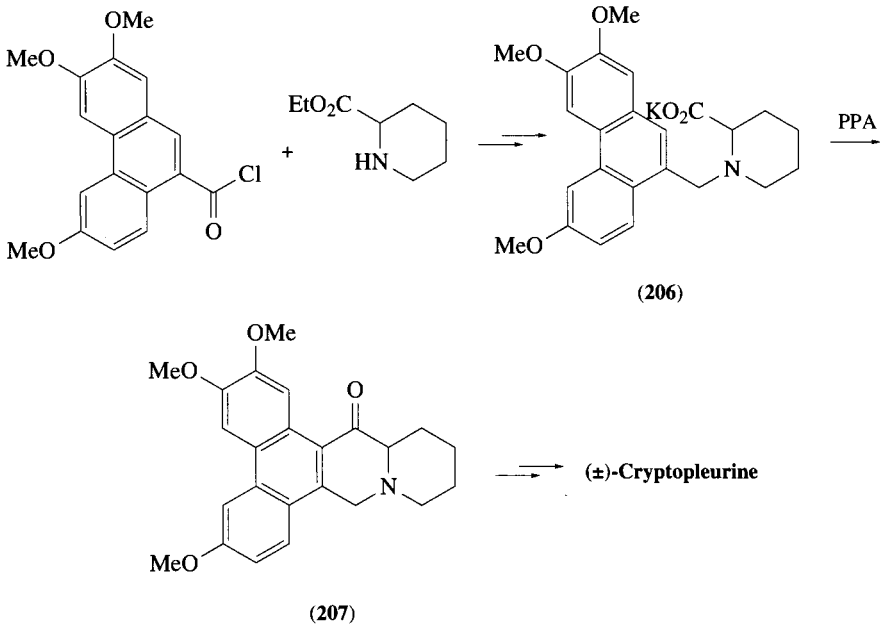
The preparation of berbines (Scheme 38) through treatment of 1-benzyl-1,2,3,4-tetrahydro-isoquinolines with phosgene gas to yield the *N*-chloroformyl derivatives (**208**) is another example of the use of intramolecular Friedel–Crafts reactions in the construction of quinolizidine systems. These intermediates gave berbin-8-ones (**209**) by intramolecular ring closure in the presence of several Lewis acid catalysts (Scheme 38) ⟨85T169⟩.

8.22.8.2.3 Bischler–Napieralsky reactions

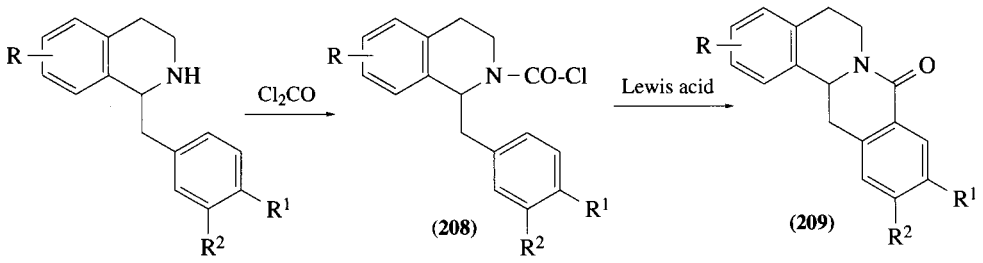
Cyclization of 1-arylethyl-2-piperidones by the Bischler–Napieralsky procedure is one of the main routes to benzo[*a*]quinolizidines, and has been extensively used by Fujii *et al.* ⟨81CPB2691⟩ in the synthesis of alkaloids containing this ring system, including emetine, emetamine, tubulosine, alangycine, psychrotrine, and others. As an example, part of their route to the *Alangium* alkaloid (±)-9-demethylpsichrotrine is depicted in Scheme 39 ⟨85CPB144⟩. Lactim ether (**210**) is the precursor of the arylethyl-2-piperidone (**211**), which generates the benzo[*a*]quinolizidine derivative after treatment with phosphorus oxychloride. Alternatively, the arylethylpiperidone may be prepared by oxidation of the corresponding piperidine derivative with mercury(II) acetate ⟨85CPB1023⟩.

Combination of the Pummerer ((**212**) → (**213**)) and Bischler–Napieralsky ((**214**) → (**215**)) reactions, with an intermediate reductive removal of both the halogen and the methylthio group has allowed the synthesis of protoberberine alkaloids from benzyl phenylethyl amines ⟨87TL2399⟩, as shown in Scheme 40.

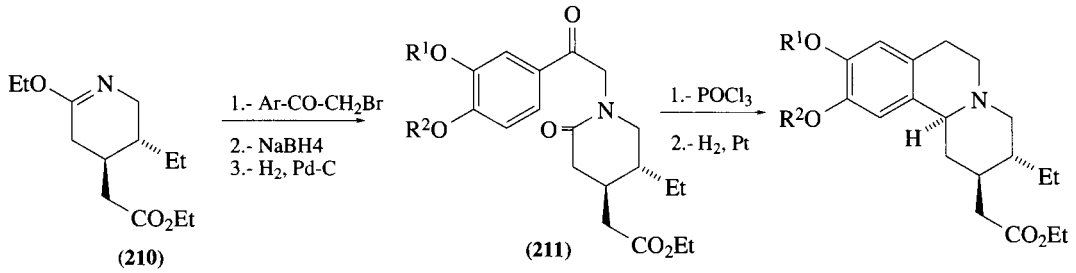
The cyclization step of the synthesis of benzo[*a*]quinolizin-4-ones developed by Burgstahler and Bithos ⟨60JA5466⟩ can be considered as a variant of a Bischler–Napieralsky reaction. These authors



Scheme 37

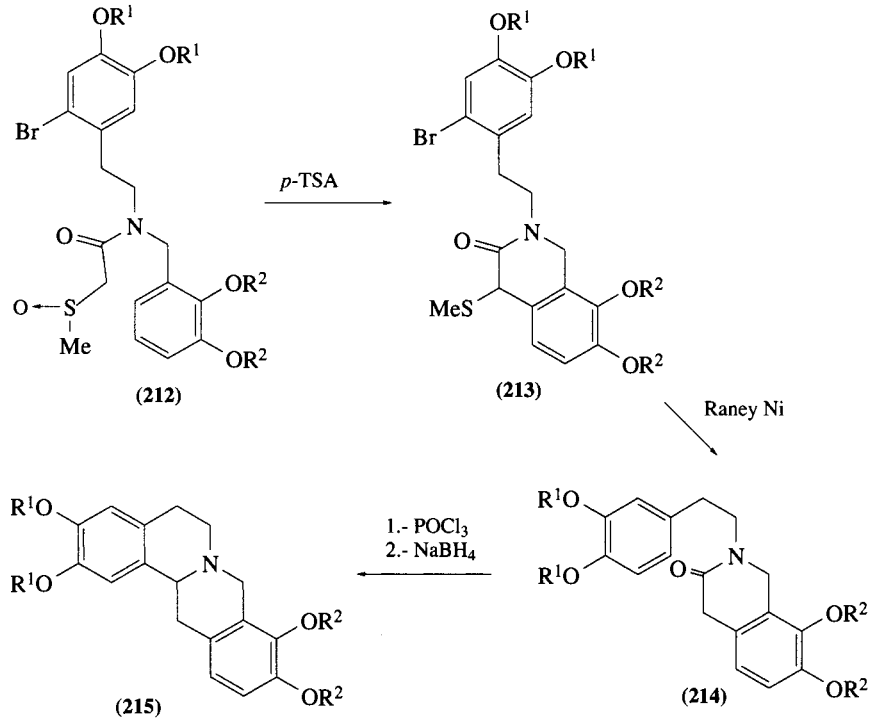


Scheme 38

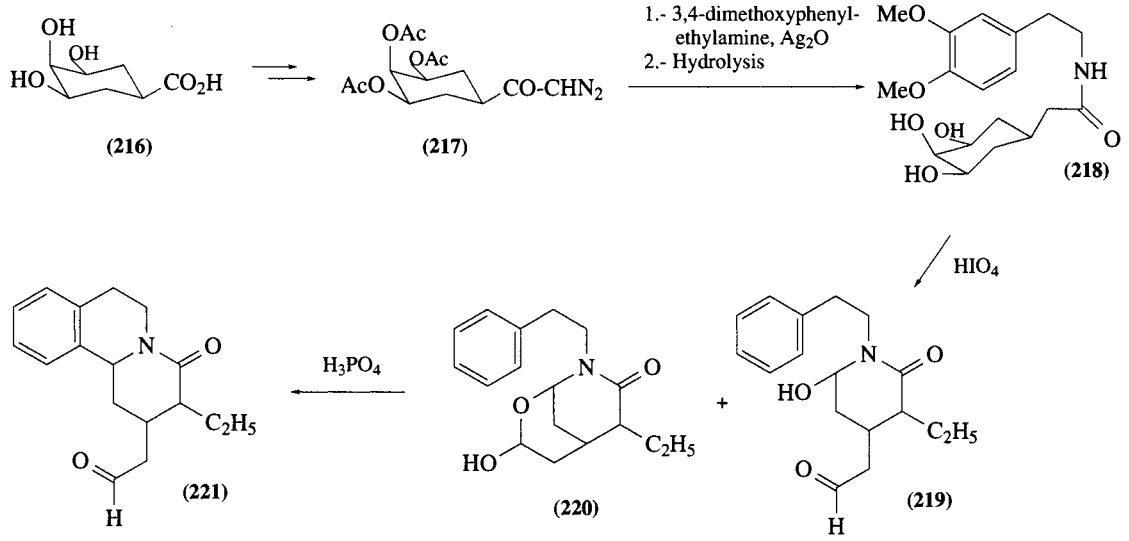


Scheme 39

prepared diazoketone (**217**) from the all-*cis* hexahydrogallic acid derivative (**216**) and decomposed it in the presence of silver oxide and 3,4-dimethoxyphenylethylamine to give the amide (**218**) via Wolff rearrangement and hydrolysis of the protecting groups. Treatment of (**218**) with periodic acid afforded a mixture of the hydroxy aldehyde (**219**) and its acetal (**220**), which cyclized to the benzo[*a*]quinolizidin-4-one (**221**) by treatment with dilute polyphosphoric acid (Scheme 41).



Scheme 40

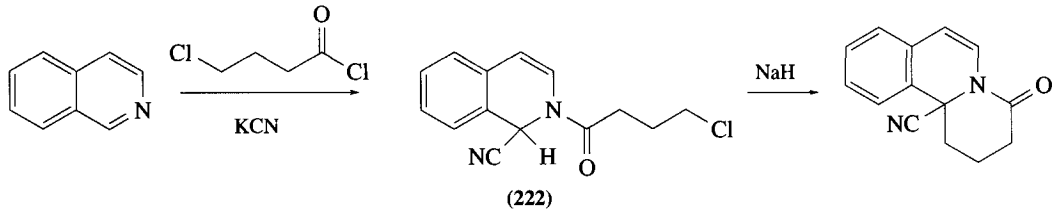


Scheme 41

8.22.8.2.4 *Intramolecular nucleophilic displacement reactions and iminium ion-mediated cyclizations*

A base-catalyzed intramolecular nucleophilic substitution reaction on isoquinoline Reissert compounds (**222**) is the basis of a benzo[*a*]quinolizidine synthesis developed by Popp *et al.* (Scheme 42) ⟨72JHC541⟩.

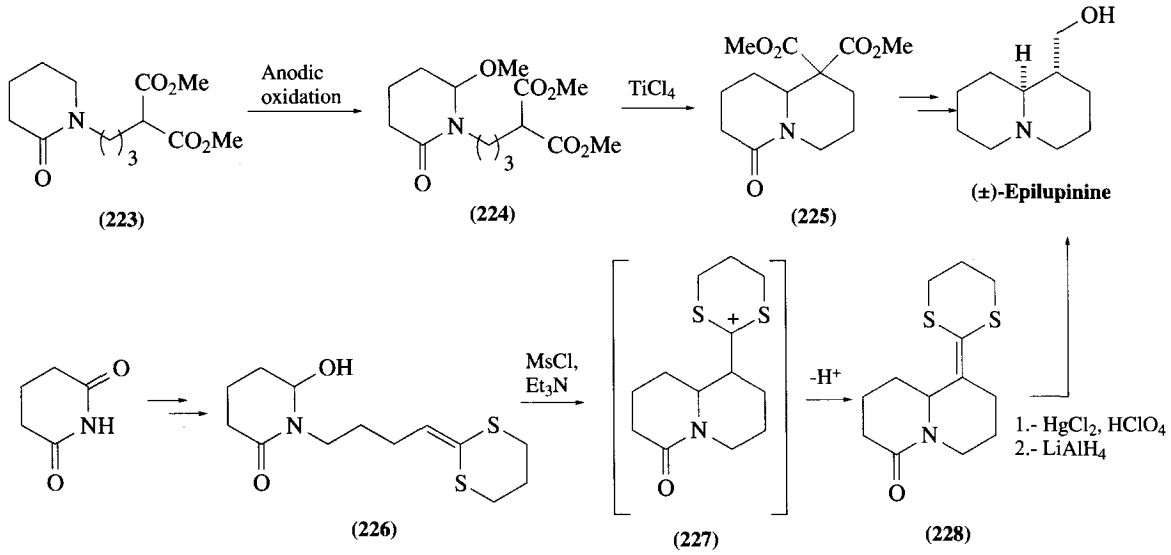
Similar cyclizations using piperidines with leaving groups at C-2 are probably mediated by iminium ions. For example, a total synthesis of epilupinine ⟨83H(20)401⟩ relies on the anodic oxidation of the lactam (**223**) to the methoxy derivative (**224**), which was subsequently converted into the quinolizidine (**225**) through a titanium tetrachloride-mediated cyclization, a reaction that has been



(222)

Scheme 42

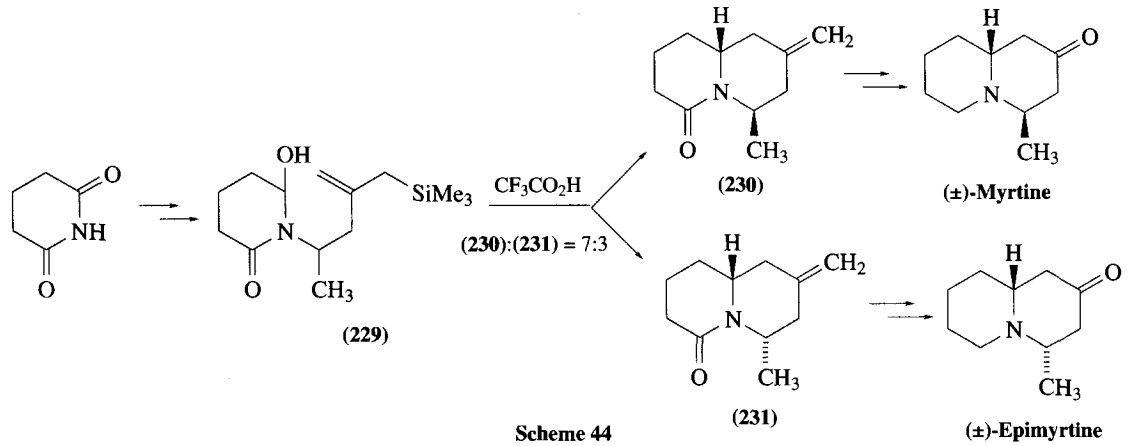
employed in other quinolizidine syntheses ⟨86JOC2202⟩. A related synthesis of epilupinine ⟨84JOC1642⟩ starts with the hydroxylactam dithioketal (**226**), which can be cyclized to quinolizidine (**228**) in the presence of mesyl chloride and triethylamine because of the formation of a sulfur-stabilized intermediate cation (**227**) (Scheme 43).



(223) (224) (225) (226) (227) (228)

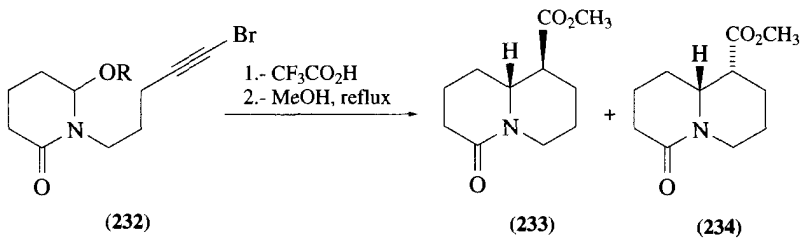
Scheme 43

In a reaction related to the transformation ((**226**) → (**228**)), acid-promoted cyclization of the hydroxylactam (**229**) afforded a 7 : 3 mixture of the quinolizidines (**230**) and (**231**), easily transformed into the alkaloids myrtine and epimyrtine (Scheme 44) ⟨92TL73⟩. Related hydroxylactams bearing bromoalkynyl substituents can also give similar cyclizations. For example, treatment of compound (**232**) with trifluoroacetic acid and methanol afforded a 45 : 55 mixture of the quinolizidines (**233**) and (**234**), precursors of lupinine and epilupinine (Equation (22)) ⟨92TL3633⟩.



(229) (230) (231)

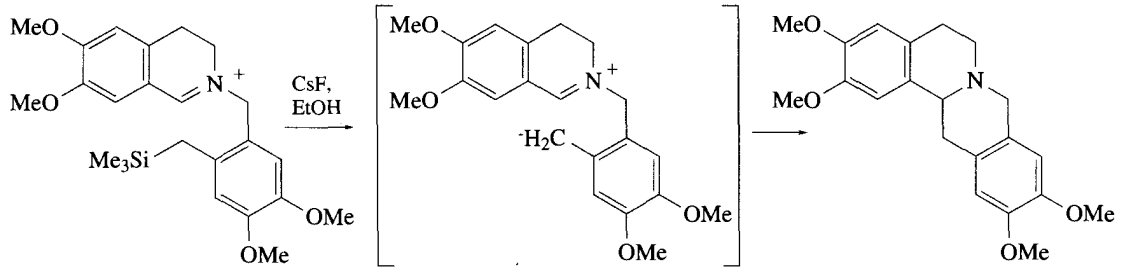
Scheme 44



(232) (233) (234)

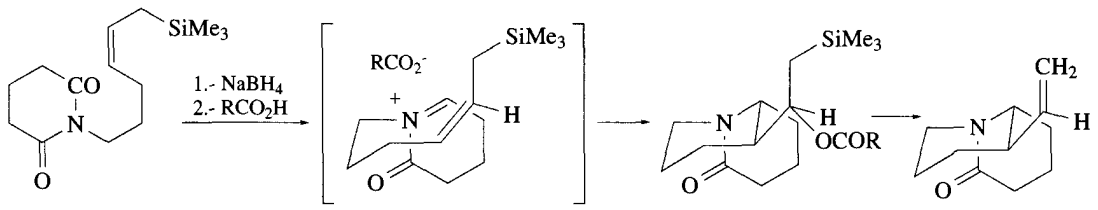
(233):(234) = 45:55 (22)

Nucleophilic intramolecular addition of a carbon–silicon bond onto a carbon–nitrogen iminium ion is the key step of a berbine synthesis ⟨82CC769, 83H(20)417⟩. Thus, treatment of the isoquinolinium salt (**235**) with caesium fluoride in ethanol afforded (±)-xylopinine (**237**), presumably via the betaine (**236**) (Scheme 45). A silicon-directed intramolecular cyclization of a *N*-acyliminium ion (**238**) was also the key step of Speckamp's synthesis of (±)-epilupinine as shown in Scheme 46 ⟨85JOC4014⟩.



(235) (236) (237) (±)-Xylopinine

Scheme 45

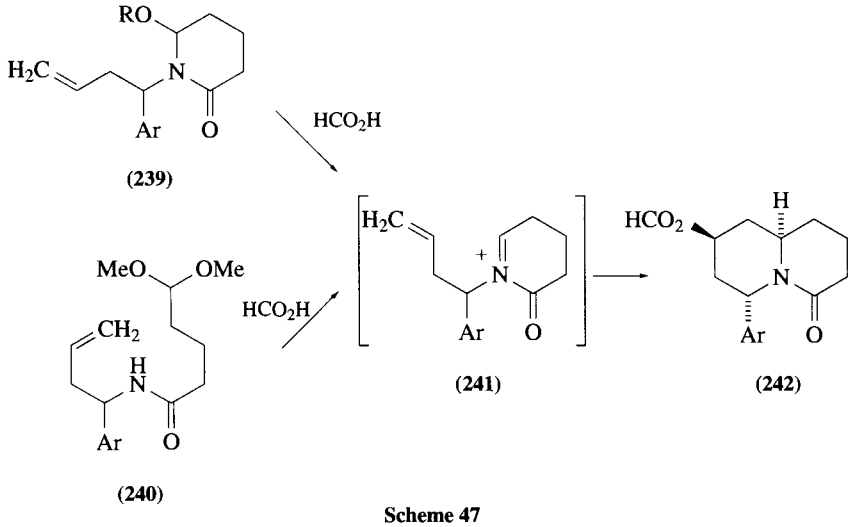


(238)

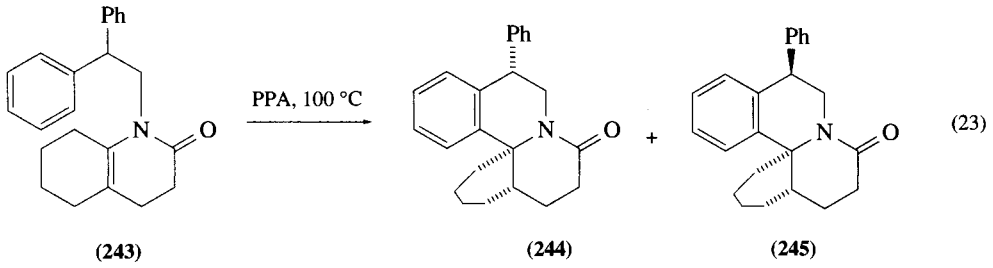
Scheme 46

An interesting electrophilic process occurs when *N*-acyliminium ions such as (**241**), derived from alkoxy lactams (**239**) ⟨85T4367⟩ or protected formylamides such as (**240**) ⟨82JOC1555, 85JOC3670, 87JOC4665⟩ cyclize in formic acid leading to quinolizidines (**242**). These are precursors of *Lythraceae* alkaloids such as (±)-vertaline ⟨82JOC1555⟩ or (±)-lythrancepine II ⟨87JOC4665⟩ (Scheme 47). The cyclization follows a concerted pathway, in which the conformation of the transition state, with the aromatic groups in an axial position ⟨80TL1991, 81RTC345⟩ determines the stereochemistry of the final product.

Cationic π cyclizations can achieve remarkably stereocontrolled syntheses of benzo[*a*]quinolizidines. For example, treatment of compound (**243**) with polyphosphoric acid leads to (**244**) and (**245**) ((**244**) : (**245**) > 95 : 5) (Equation (23)) ⟨83JOC5062⟩.



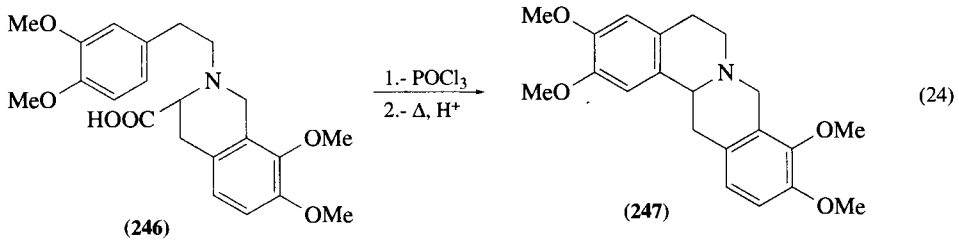
Scheme 47



(23)

(244) : (245) > 95:5

Other ways of generating nonisolable iminium species that can cyclize to quinolizine derivatives include decarbonylation of α-tertiary amino acids such as compound (**246**) by heating with phosphorus oxychloride, which was the key step of Rapoport's approach to the synthesis of protoberberine alkaloids bearing oxygen functions at the 9,10 positions (**247**) (Equation (24)) ⟨78JOC2115⟩.



(24)

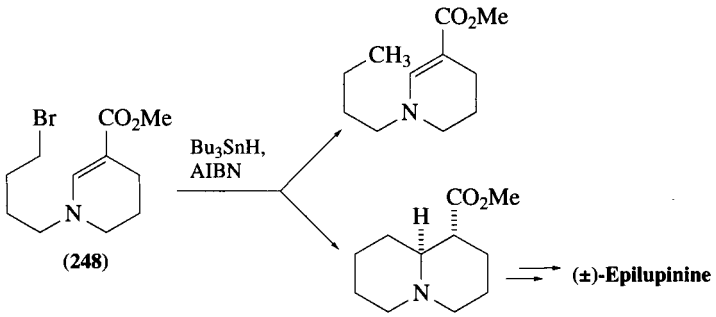
8.22.8.2.5 Radical reactions

Vinylogous urethane (**248**) was employed in a radical-mediated synthesis of epilupinine (Scheme 48), where its cyclization was induced by treatment with tributyltin hydride–AIBN ⟨89T5269⟩. In another radical process, a very efficient synthesis of berbine was achieved by photolysis of compound (**249**), which induced a diradical cyclization process promoted by an excited-state electron-transfer desilylation (Scheme 49) ⟨85TL5867⟩.

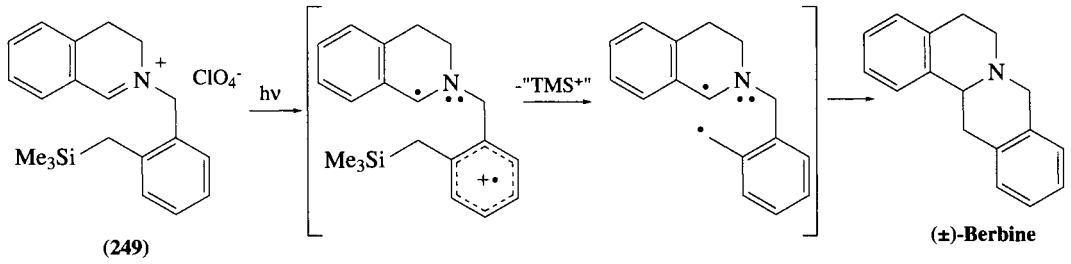
8.22.8.3 Formation of a New Bond γ to the Heteroatom

8.22.8.3.1 Intramolecular enamine cyclizations

Intramolecular nucleophilic addition reactions of enamines to suitable electrophiles placed γ to the enamine nitrogen atom afford quinolizine derivatives. Examples of this strategy (Schemes 50

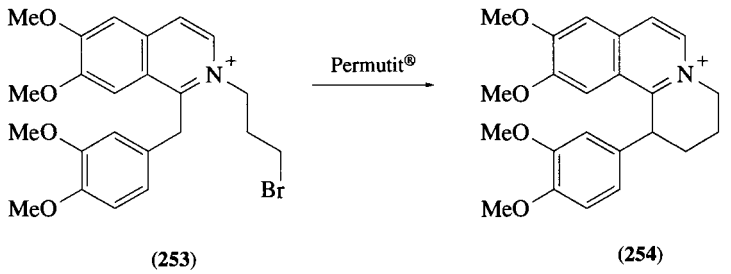


Scheme 48



Scheme 49

and 51, and Equation (25)) are the concise synthesis of (±)-cryptopleurine through cyclization of the nonisolated enamine (**250**) in the presence of titanium tetrachloride followed by thallium trifluoroacetate-promoted biaryl coupling ⟨78CC794, 82JCS(P1)2487⟩, the preparation of a precursor of lupinine (**252**) by halogen exchange-promoted cyclization of (**251**) ⟨87H(26)2335⟩ and the cyclization of the 2-(3-bromopropyl) derivative of papaverine (**253**) to the tetrahydroquinolizinium salt (**254**) in the presence of a basic ion-exchange resin ⟨85AP(318)531⟩.

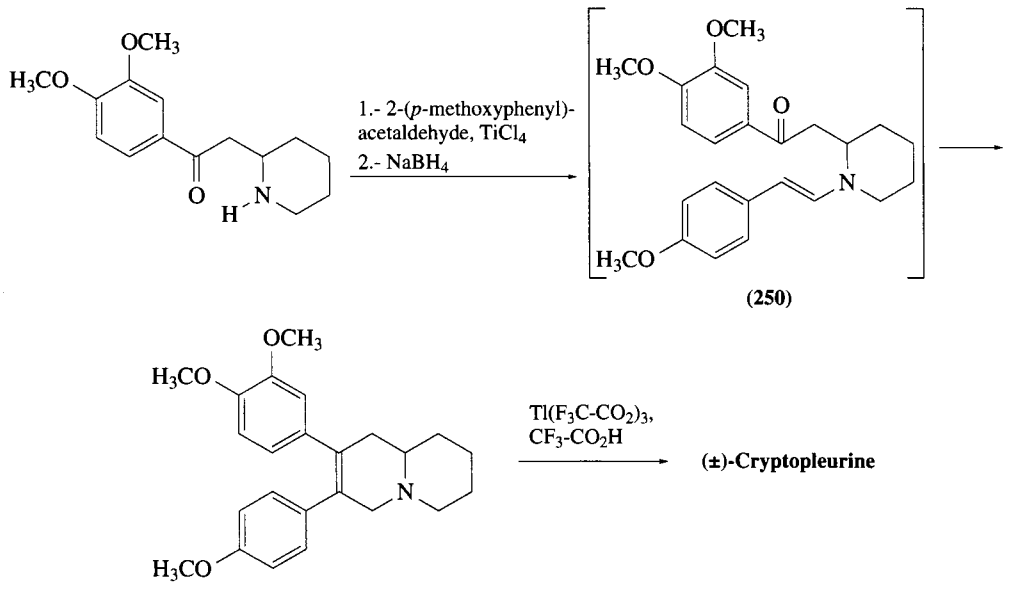


(25)

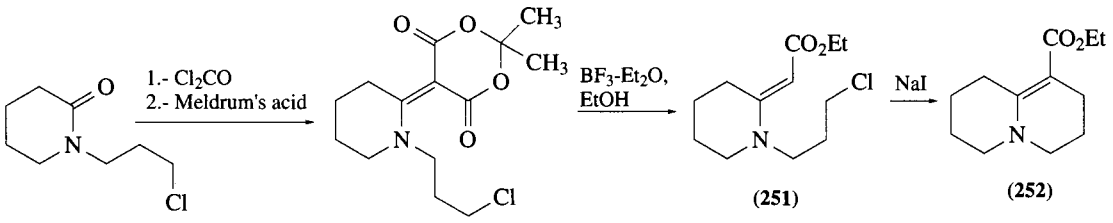
8.22.8.3.2 Dieckmann condensations

Intramolecular base-promoted cyclization of suitable diesters (Scheme 52) is one of the earliest routes to benzo[*a*]quinolizidines, which was exploited in the synthesis of racemic emetine developed by Oppenshaw ⟨53JCS2463⟩. Reaction of tetrahydroisoquinoline (**255**) with ethyl α-formylbutyrate followed by hydrogenation afforded (**256**), which was cyclized by base to yield (**257**), the benzo[*a*]-quinolizidine portion of the alkaloid. On this occasion only one of the two possible Dieckmann condensation products was observed, although this has not always been the case with related cyclizations ⟨73BSF3476⟩.

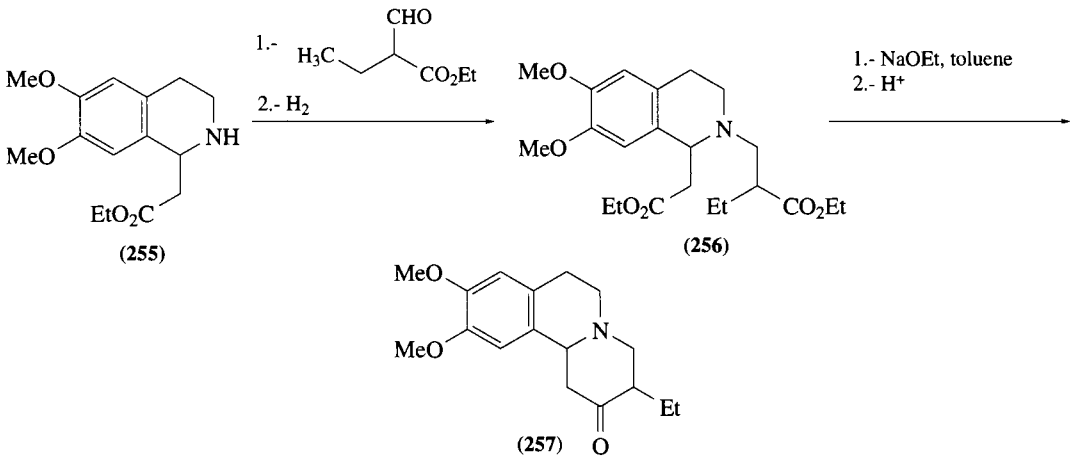
In a minor variation of this route, the diester system can be prepared prior to creation of the isoquinoline ring through Bischler–Napieralsky reaction ⟨62CPB185⟩.



Scheme 50



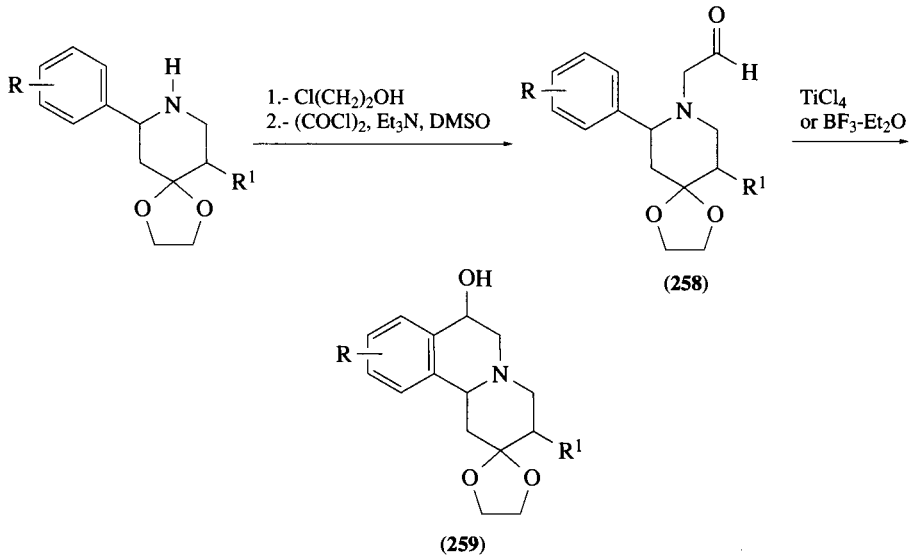
Scheme 51



Scheme 52

8.22.8.3.3 Intramolecular electrophilic aromatic substitutions

This is one of the simplest and most efficient strategies for the preparation of arenoquinolizidines. As an example, the preparation of benzo[*a*]quinolizidines (**259**) from 2-phenylpiperidines (**258**) is depicted in Scheme 53 ⟨87T3021⟩.



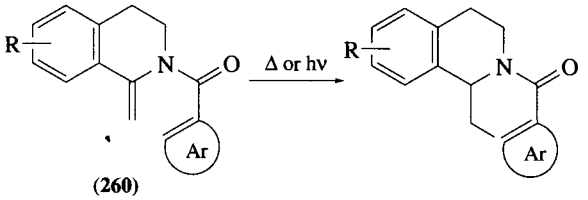
(258)

(259)

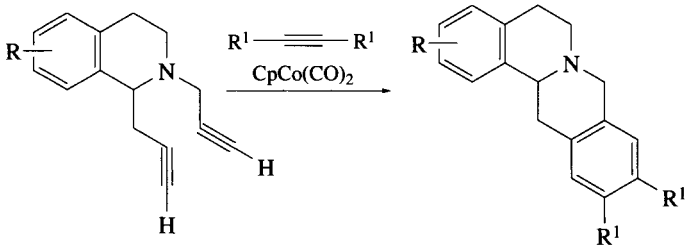
Scheme 53

8.22.8.3.4 Pericyclic reactions

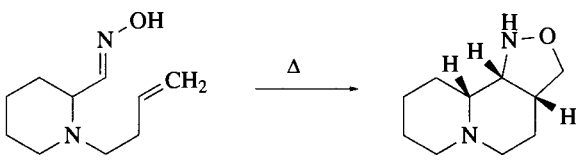
A few examples of this type of syntheses are summarized in Equations (26)–(28). Thus, thermal or photochemical electrocyclization reactions of 1-methylenetetrahydroisoquinolines (**260**) affords quinolizidine derivatives (Equation (26)); this reaction has been exploited for the preparation of a number of berbine alkaloids and their heteroanalogues ⟨81H(16)725, 81JCS(P1)2830, 83H(20)775, 83H(20)853, 83TL291⟩. Rings C and D of berbines were also generated by cobalt-promoted oligomerization of diyne (**261**) with simple alkynes (Equation (27)) ⟨83T905⟩. Finally, fused quinolizidine derivatives have been prepared with high stereoselectivity by thermally induced cycloaddition of oxime-alkenes (**262**) (Equation (28)) ⟨81T3615, 91JOC2775⟩.



(260) (26)



(261) (27)



(262) (28)

8.22.8.4 Formation of Two New Bonds

A number of syntheses of quinolizidines involve the formation of two bonds in the same reaction. These methods will be classified according to the size of the fragments leading to the quinolizidine nucleus and, in the case of intramolecular reactions where a single precursor is used, according to the position of the new bonds with respect to the heteroatom (Figure 1).

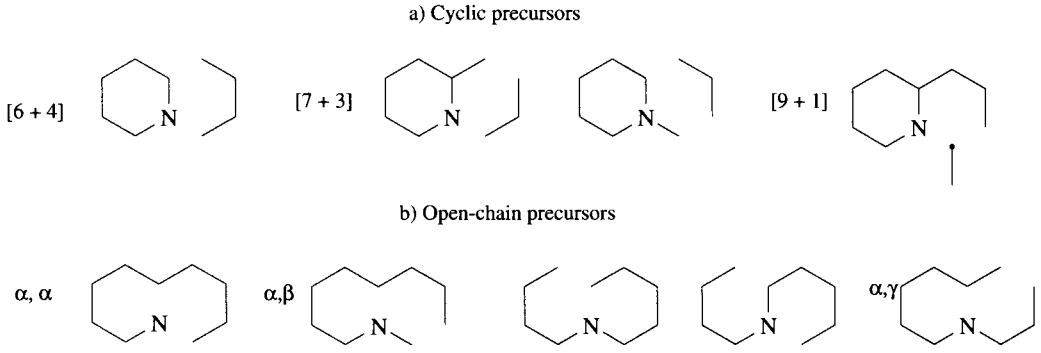
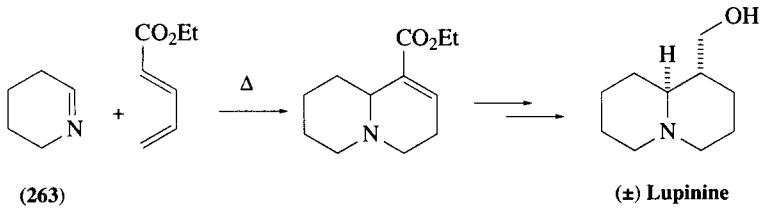


Figure 1 Types of precursors for quinolizidine synthesis through formation of two new bonds.

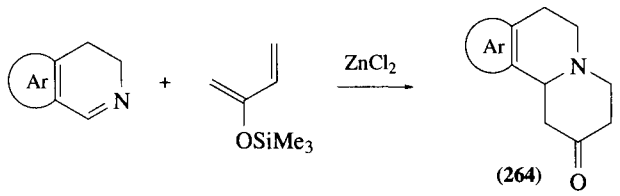
8.22.8.4.1 From [6 + 4] fragments

(i) Hetero Diels–Alder reactions

The use of imines as dienophilic components in [4 + 2] cycloaddition reactions is well known ⟨79H(12)949, 82T3087⟩. For example, a Diels–Alder reaction between the tetrahydropyridine (**263**) and ethyl 2,4-pentadienoate was the key step in Bohlmann's synthesis of lupinine (Scheme 54) ⟨67CB2742⟩. Similar methodology has been applied to the preparation of a variety of areno[*a*]quinolizidin-2-ones (**264**) ⟨85TL1277⟩ (Equation (29)).



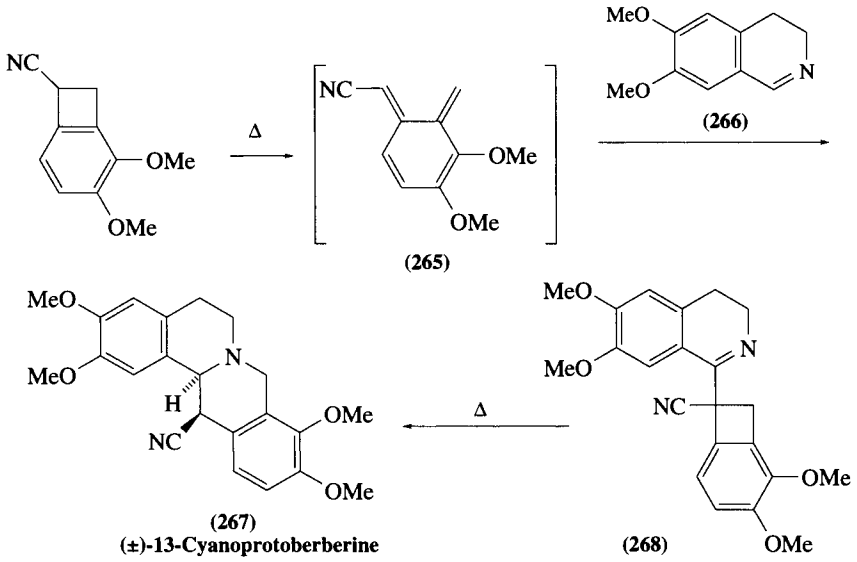
Scheme 54



(29)

Similarly, hetero Diels–Alder reactions between *o*-quinodimethanes (**265**) and 3,4-dihydroisoquinolines (**266**) ⟨87AHC(42)245⟩ have been extensively used by the Kametani group in the synthesis of berberine alkaloids ⟨75JCS(P1)737⟩, as an application of their "retro-mass spectral" synthetic design ⟨76ACR319⟩. This approach is exemplified (Scheme 55) by the total synthesis of (±)-13-cyano-protoberberine (**267**) ⟨81JCS(P1)2830, 85JCS(P1)2125⟩. Thermal electrocyclic reactions leading to the same results are known ⟨75H(3)29, 84H(22)1067⟩, e.g. the transformation (**268**) → (**267**). Intra-

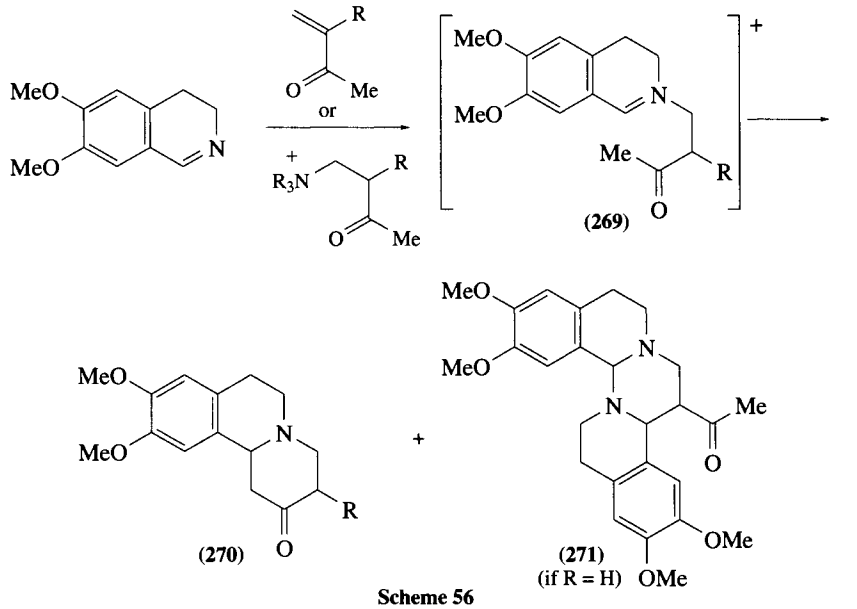
molecular hetero Diels–Alder reactions of the same type have also been employed for the construction of indole alkaloids containing a quinolizidine fused system, such as eburnamonine ⟨94JOC7197⟩.



Scheme 55

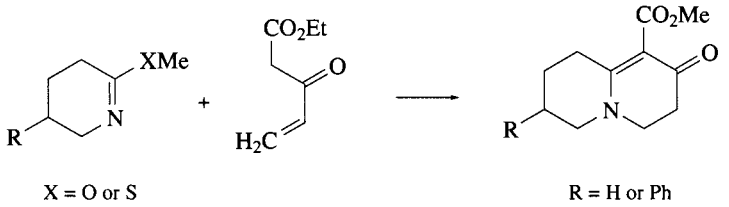
(ii) Robinson-like annelation reactions

The most widely used procedure for the preparation of benzo[*a*]quinolizidin-2-ones and their 3-alkyl derivatives (**270**) consists of the reaction between 3,4-dihydroisoquinolines and α,β-unsaturated ketones, with iminium salt (**269**) as an intermediate ⟨62CB2135⟩. 4-Dimethylamino-2-butanone derivatives can play the same role as unsaturated ketones, and have the advantage of allowing the reaction to be conducted in aqueous solutions, which facilitates the isolation of the product ⟨69JCS(C)85⟩ (Scheme 56). The yields obtained in the latter case are usually quantitative for 3-substituted benzo[*a*]quinolizidin-2-ones, but are considerably lower for the unsubstituted system because of the formation of a secondary product (**271**). Fortunately, this problem may be overcome by modifying the pH and temperature of the reaction medium ⟨88TH822-01⟩.



Scheme 56

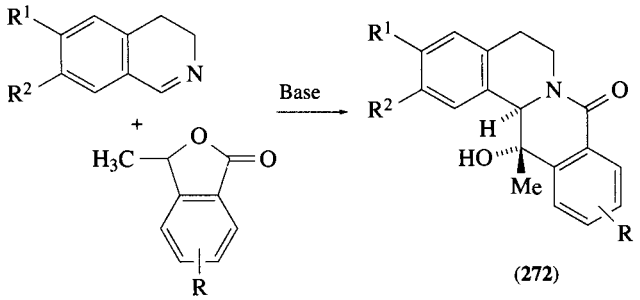
Similar reactions can be employed for the preparation of quinolizines, usually from tetrahydropyridines bearing a donor group on the C=N bond. Equation (30) summarizes two such syntheses, both employing ethyl 3-oxo-4-pentenoate (Nazarov's reagent) as the Michael acceptor ⟨82USP4339582, 84JMC165, 86H(25)37⟩.



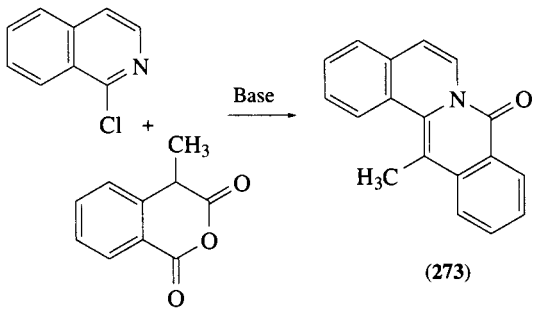
(30)

(iii) Other reactions starting from dihydroisoquinolines

Nucleophilic species derived from treatment of lactones and anhydrides with base can also react with 3,4-dihydroisoquinolines or with 1-chloroquinolines to give quinolizidines. Two examples of the application of this methodology to the preparation of berberine derivatives (**272**) and (**273**) ⟨84LA389⟩ are shown in Equations (31) and (32).



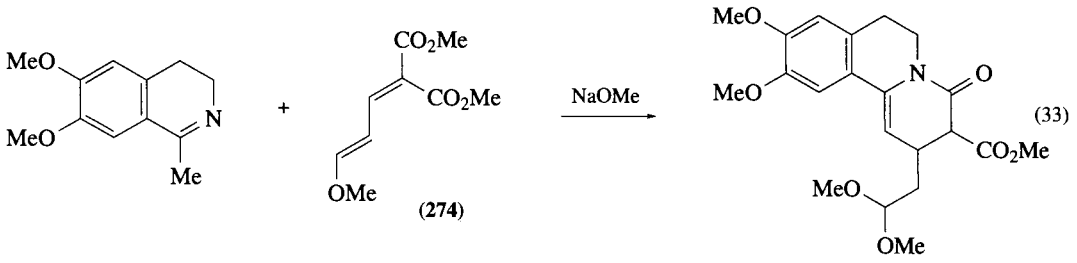
(31)



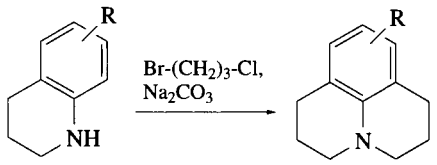
(32)

8.22.8.4.2 From [7 + 3] fragments

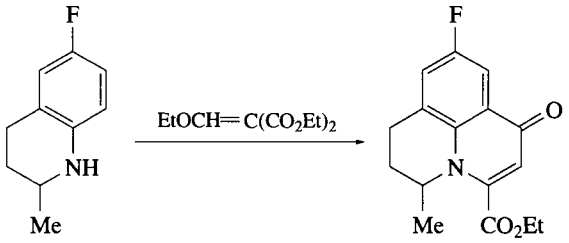
Some examples of quinolizidine preparations following this pattern are summarized in Equations (33)–(36). Kametani *et al.* ⟨77H(8)119, 79JCS(P1)1211⟩ have reported a quinolizine synthesis based on a tandem conjugate addition–amide formation process between 1-methyl-3,4-dihydroisoquinolines and the unsaturated malonate (**274**) or a saturated δ-lactone (Equation (33)) ⟨82H(19)1829⟩. 1,3-Dihalides can also be employed as dielectrophiles in similar reactions, a strategy often used for the preparation of benzo[*i,j*]quinolizidines (julolidines), e.g. (**275**) from anilines, presumably via the unisolated tetrahydroisoquinolines (Equation (34)) ⟨82JHC925⟩; see also the antibacterial flumequine from (**276**) and diethyl ethoxymethylenemalonate (Equation (35)) ⟨81FRP2476079⟩. Use of the chiral β-sulfinyl enamine methodology developed by Hua *et al.* ⟨90JOC2128⟩ has allowed a chiral version of this type of synthesis. For example, enamine (**277**) was transformed into sulfoxide (**278**), a precursor of lupinine and epilupinine (Equation (36)) ⟨91S970⟩.



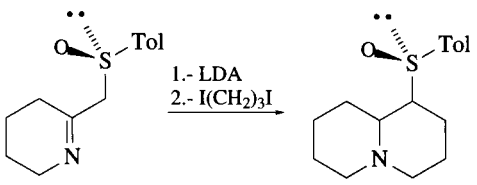
(33)



(275) (34)



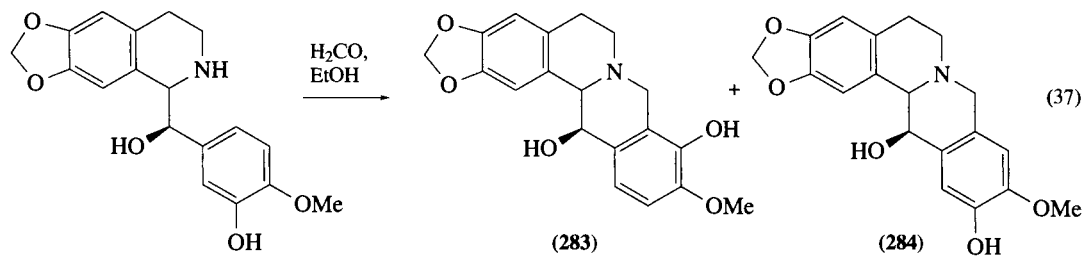
(35)



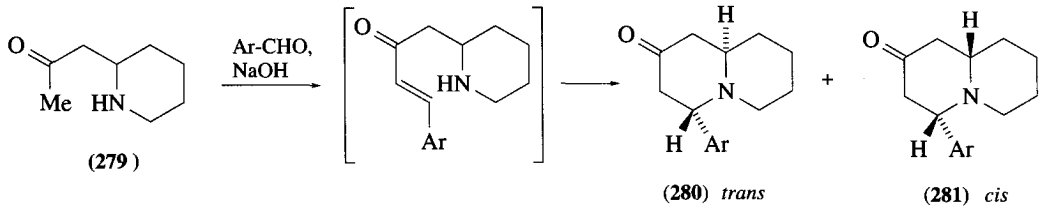
(277) (278) (36)

8.22.8.4.3 *From [9 + 1] fragments*

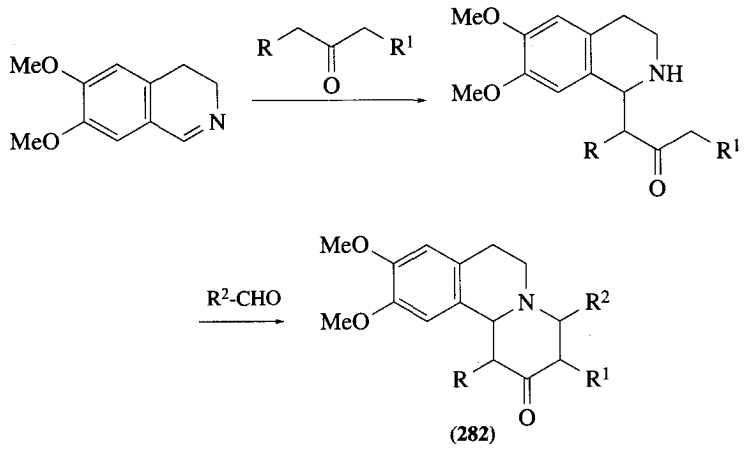
Most of the quinolizine syntheses that can be included under this heading have intramolecular Mannich reactions as their key steps. Pelletierine derivatives (**279**) are good starting materials for the preparation of 2-quinolizidinones by reaction with aldehydes in basic media (Scheme 57) ⟨77H(6)391, 81H(15)237, 82TL1439⟩. Although the cyclization is not stereoselective, under thermodynamic conditions the main products are the *trans* quinolizidines (**280**), while kinetic conditions give primarily the *cis* stereochemistry (**281**), defined by the relative position of the C-4 and C-10 hydrogens. The method has been particularly useful for the synthesis of precursors of lactonic *Lythraceae* alkaloids ⟨76CPB1045⟩. Benzo[*a*]quinolizidines (**282**) ⟨66PHA26⟩ and berberines (**283**) and (**284**) ⟨77JCS(P1)376, 83IJC(B)5, 84JOC947, 85IJC(B)596⟩ have also been prepared through intramolecular Mannich reactions (Scheme 58 and Equation (37)).



(37)



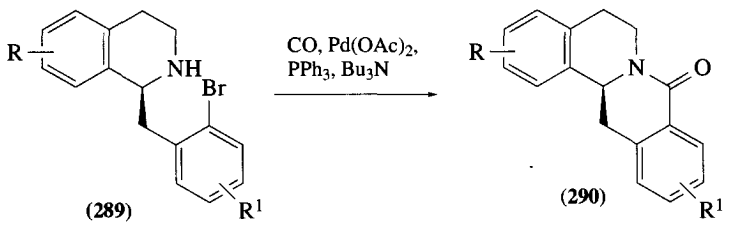
Scheme 57



Scheme 58

On the basis of the ability of chiral formamidines to generate stereocenters α to nitrogen in an optically pure form ⟨85MI 822-01⟩, Meyers and co-workers have developed highly efficient syntheses of chiral tetrahydroisoquinoline derivatives (e.g. (**285**) and (**286**)) from chiral formamidine precursors. These tetrahydroisoquinolines could be cyclized to benzo[*a*]quinolizidines (**288**) ⟨81TL515, 91JOC6873⟩ or dibenzo[*a*,*g*]quinolizidines (**287**) ⟨84AC448, 91JOC6873⟩ through the use of previously established ⟨88JOC686⟩ Mannich-type chemistry (Scheme 59).

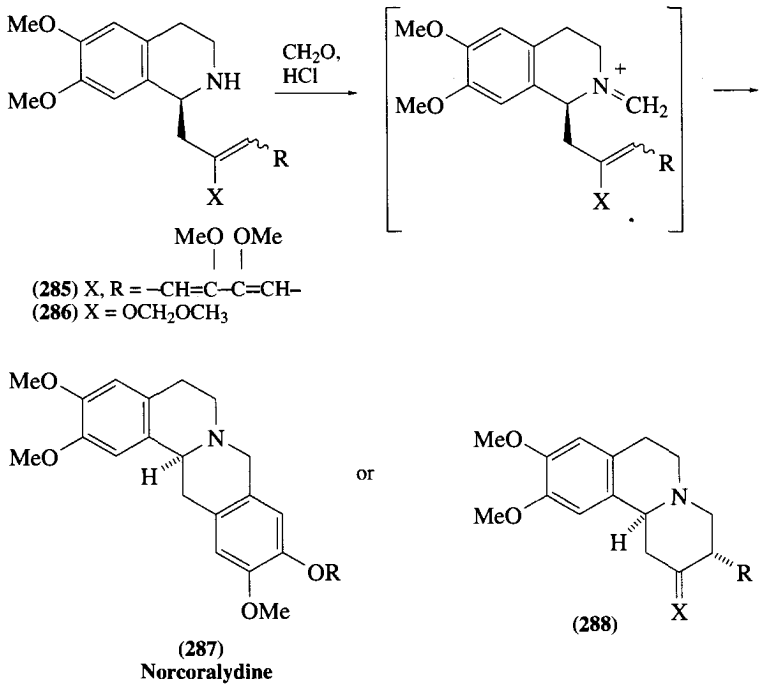
Another route to chiral berbine alkaloids from the same type of precursors is based upon palladium-catalyzed carbonylation of 1-(*o*-bromobenzyltetrahydroisoquinolines (**289**), leading to 8-oxoberbines (**290**) in a single step (Equation (38)) ⟨78JOC1684⟩. A number of alkaloids have been synthesized by means of this reaction ⟨79SC895, 81T1213⟩.



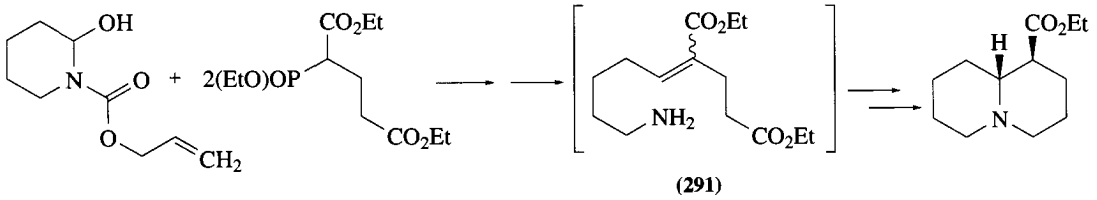
(38)

8.22.8.4.4 Formation of two α bonds

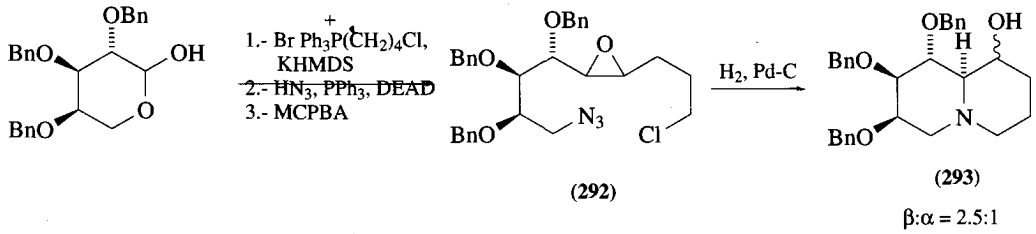
Intramolecular tandem Michael addition–amide formation in the intermediate (**291**) afforded an epilupinine precursor (Scheme 60) ⟨89H(29)1209⟩. Another quinolizidine synthesis forming two α bonds in its key step is the reductive double alkylation of azido epoxides with an ω leaving group (**292**). This strategy has been applied to the synthesis of ring-expanded analogues of indolizidine alkaloids (e.g. (**293**)) from D-arabinose (Scheme 61) ⟨93TL8221⟩.



Scheme 59



Scheme 60



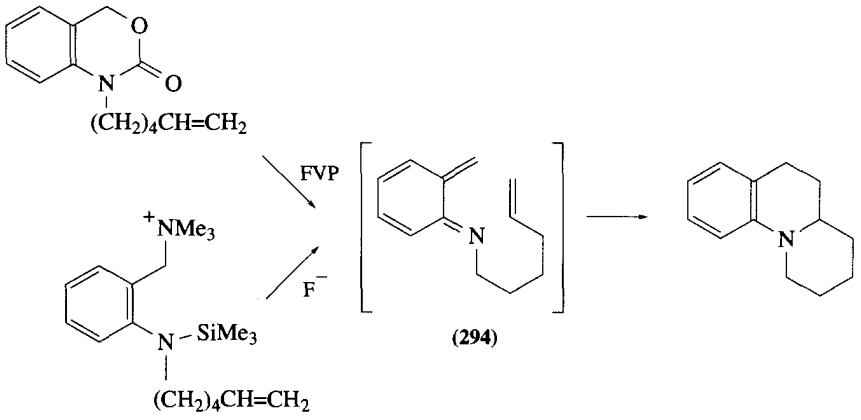
Scheme 61

8.22.8.4.5 Formation of α,β bonds

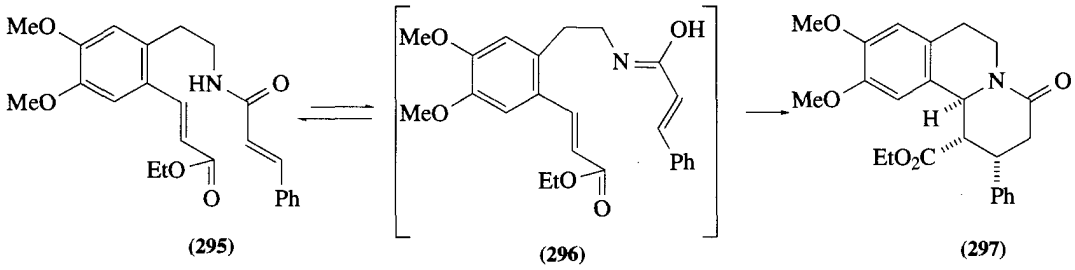
(i) Intramolecular hetero Diels–Alder reactions

Hetero Diels–Alder reactions of 1-azadienes have attracted much attention in recent years ⟨83T2869, 85MI 822-02, B-87MI 822-01, 87AHC(42)245, 89CRV1525, 89PHC(1)31, 90BSB599, 93AHC(57)1⟩, and intramolecular versions of these reactions can be adapted to the synthesis of quinolizines. Simple 1-azadienes are not stable enough to be handled but can be generated *in situ*, as in the case of the azaxylylene (**294**) ⟨81JA5250, 82TL4501⟩, a precursor of benzo[*c*]quinolizidine (Scheme 62).

Enamides such as compound (**295**) can also give intramolecular cycloadditions through their enol tautomer (**296**) ⟨84TL4541, 85H(23)1097⟩, again to yield benzo[*a*]quinolizidines (**297**) (Scheme 63).

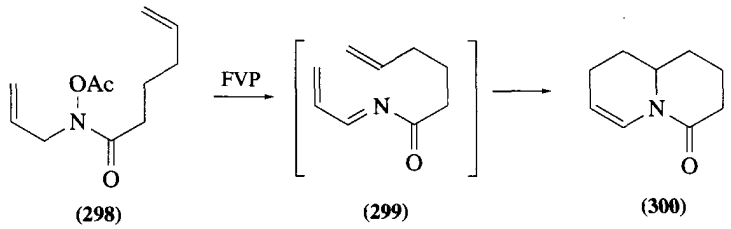


Scheme 62



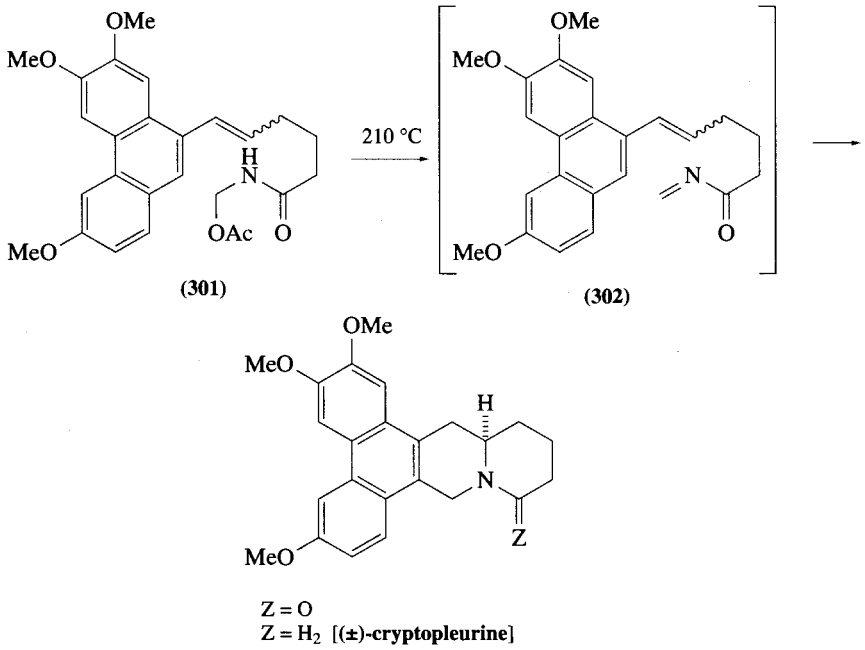
Scheme 63

Fowler and co-workers have studied the participation of 1-acyl-1-azadienes in hetero Diels–Alder reactions, finding that vacuum pyrolysis of the *O*-acylhydroxamic acid (**298**) leads to a quinolizine system (**300**) through an intermediate *N*-acyl-1-azadiene (**299**) (Scheme 64), a method that was later applied to the synthesis of several quinolizine alkaloids ⟨83JA7696, 85JOC2719⟩. A similar result can be achieved by flash-vacuum pyrolysis of 1-acyl-2-azetines ⟨91JOC6729⟩.



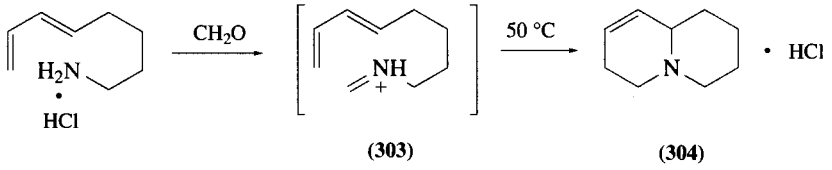
Scheme 64

Intramolecular hetero Diels–Alder reactions can also be planned in such a way that nitrogen is placed in the "dienophilic" component of the cycloaddition, and thus *N*-acylimines are precursors of quinolizines. For example, compound (**301**) can be transformed into (±)-cryptopleurine through pyrolytic elimination to (**302**) followed by hetero Diels–Alder reaction and reduction (Scheme 65) ⟨83JOC3661, 83TL261⟩. Other aspects of the cycloaddition chemistry of *N*-acylimines have been studied by Weinreb et al. ⟨89CRV1525⟩. The conditions for intramolecular cycloadditions of imines such as the intermediate (**302**) are normally pyrolytic, and a significant advance came from the observation by Larsen and Grieco ⟨85JA1768⟩ that iminium salts, usually generated *in situ*, react with dienes under very mild conditions. This reaction can be easily adapted to quinolizine synthesis (e.g. **303** → **304**) Scheme 66 ⟨85JA1768, 88JOC3325⟩.



(301) (302)

Scheme 65

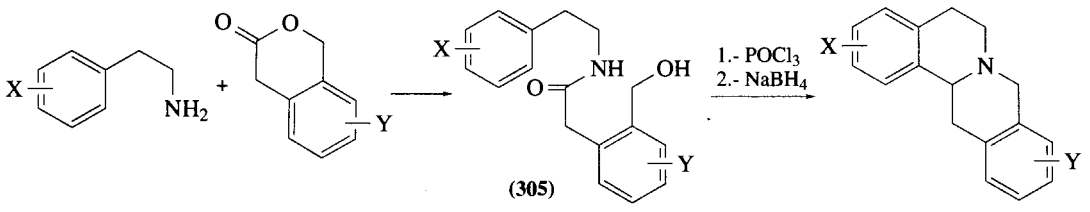


(303) (304)

Scheme 66

(ii) Tandem Bischler–Napieralsky/nucleophilic displacement reactions

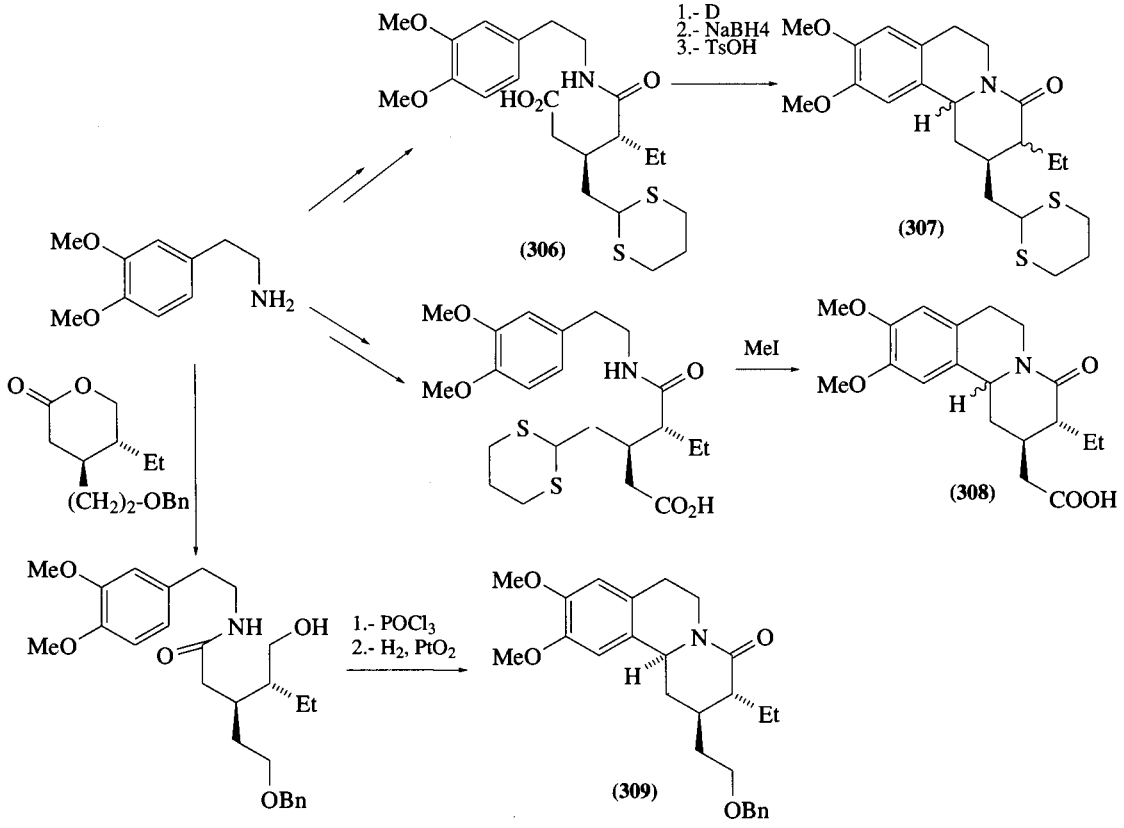
A very common method for the synthesis of berbine alkaloids is based on the one-pot double cyclization of *N*-(phenylethyl)benzeneacetamide derivatives (e.g. **305**) in the presence of phosphorus pentachloride or phosphorus oxychloride (Scheme 67) ⟨81H(16)449, 81S818, 85AP(318)168, 85IJC(B)360⟩.



(305)

Scheme 67

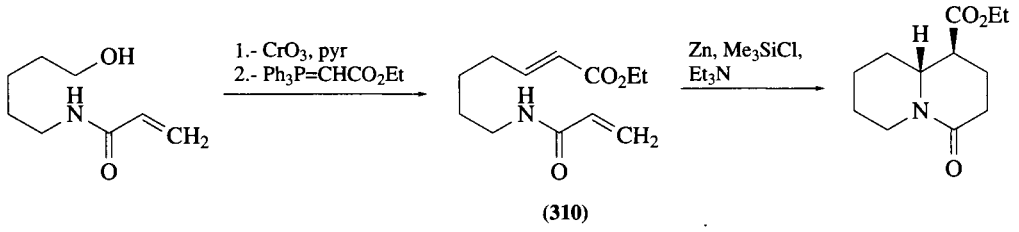
In a related procedure, thermal cyclization of *N*-(phenylethyl)glutaric acid monoamide (**306**) affords benzo[*a*]quinolizidines (**307**). An isomer of (**306**), in the presence of methyl iodide, gave compounds (**308**) through two successive alkylations ⟨82H(17)263⟩. Related emetine precursors (**309**) were similarly obtained (Scheme 68) ⟨90JCS(P1)1469⟩.



Scheme 68

8.22.8.4.6 Formation of α,γ bonds

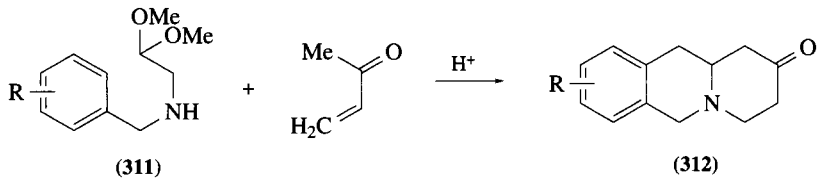
An intramolecular double Michael reaction of intermediate (**310**) (Scheme 69) was the key step in one of the syntheses of racemic epilupinine developed by Kametani and co-workers ⟨87JCS(P1)1719⟩.



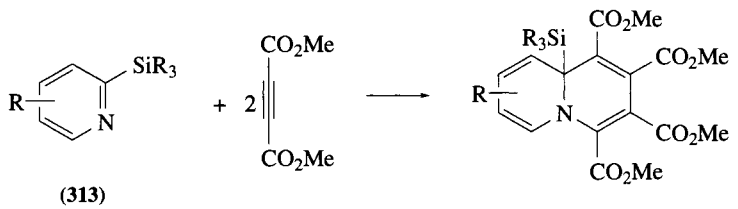
Scheme 69

8.22.8.5 Formation of Three New Bonds

In a Robinson-type annelation, benzo[*b*]quinolizidinones (**312**) have been obtained by treatment of benzylamino derivatives (**311**) with methyl vinyl ketone in acid solution (Equation (39)) ⟨83AJC149⟩. Three quinolizine bonds are also formed in the reaction between 2-silylated pyridines (**313**) and two equiv. of DMAD (Equation (40)) ⟨83CB2564⟩.



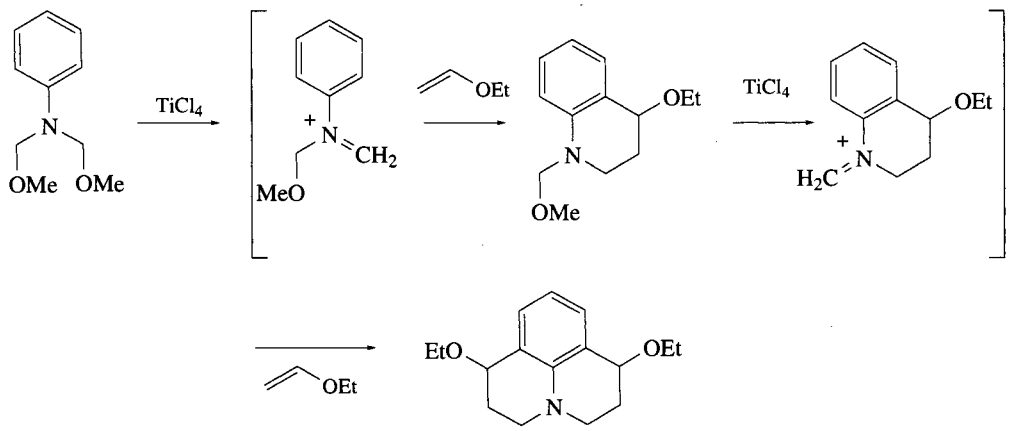
(311) (312) (39)



(313) (40)

8.22.8.6 Formation of Four New Bonds

A versatile route to julolidines involves the anodic oxidation of *N,N*-dimethylaniline in methanol yielding the julodinine skeleton through the generation of two successive iminium ions by treatment with ethyl vinyl ether and titanium tetrachloride (Scheme 70) ⟨82JA5753⟩.



Scheme 70

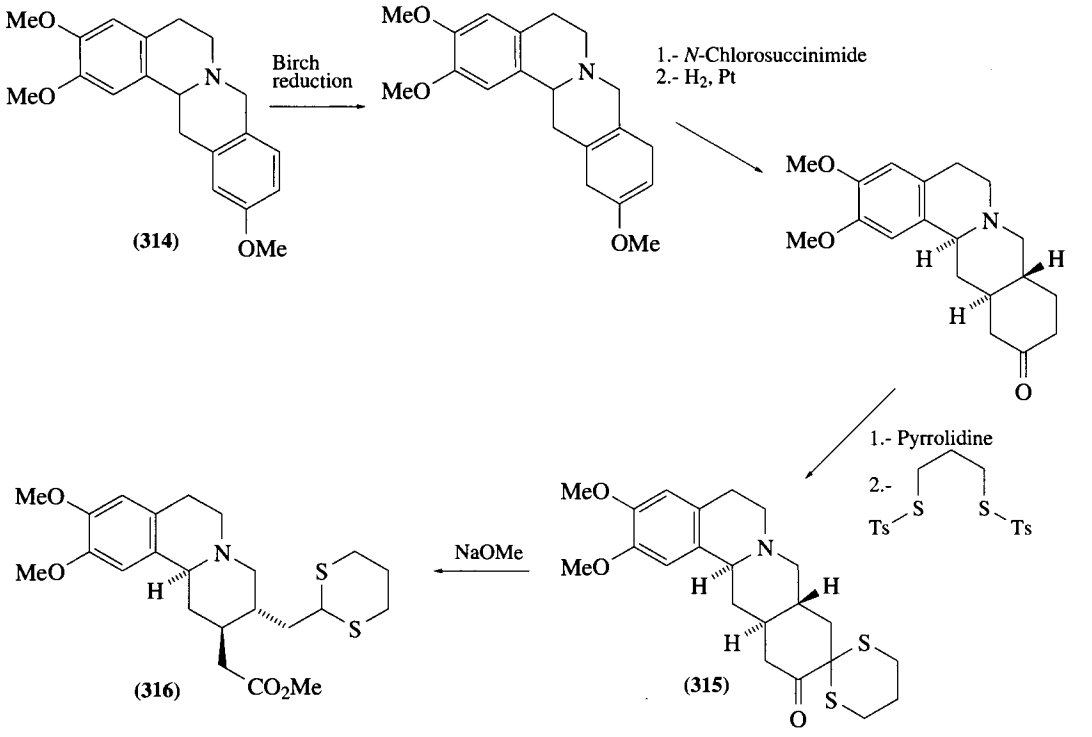
8.22.9 RING SYNTHESIS BY TRANSFORMATION OF OTHER RINGS

8.22.9.1 Degradation of Benzo[*b*]quinolizines

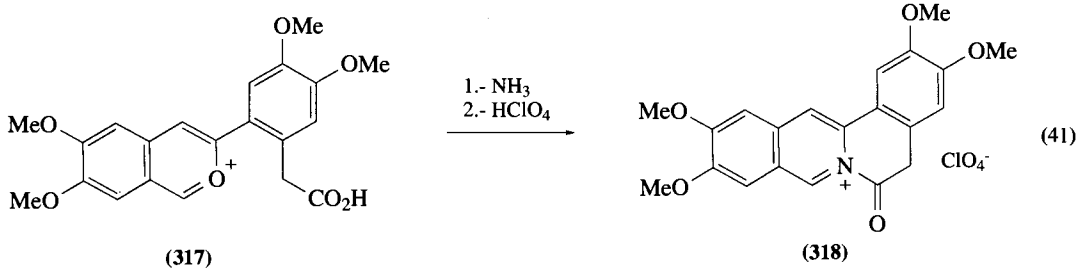
Takano *et al.* ⟨78JOC4169⟩ prepared an emetine precursor (**316**) through cleavage with base of the α-diketone monothioketal derivative (**315**), obtained by Birch reduction of the tetrahydroprotoberberine system (**314**) followed by functionalization as shown in Scheme 71.

8.22.9.2 Ammonolysis of Pyrylium Salts

Treatment of benzopyrylium salt (**317**) with ammonia followed by cyclization with perchloric acid afforded the 6-oxo-dibenzo[*a,g*]quinolizinium compound (**318**) (Equation (41)) ⟨82KGS1381⟩.



Scheme 71

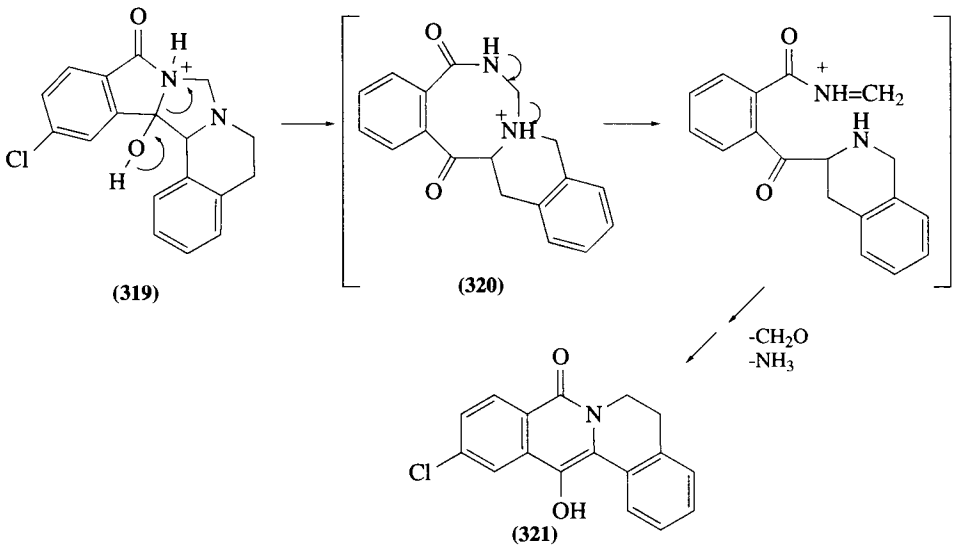


8.22.9.3 Degradation of 9b-Hydroxyimidazo[4,3-*a*]isoindol-5-ones

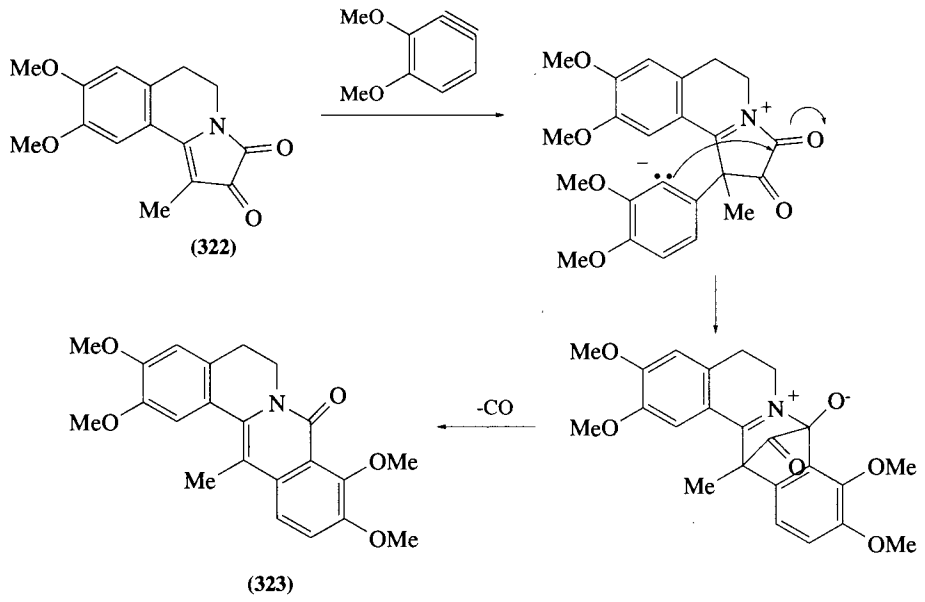
13-Hydroxy-5,6-dihydrodibenzo[*a*,*g*]quinolizin-8-ones (**321**) were obtained from protonated 9b-hydroxyimidazo[4,3-*a*]isoindol-5-ones (**319**) ⟨85JCR(S)351⟩. The mechanism proposed for this reaction comprises an acid-promoted ring opening of the imidazolidine unit, followed by opening of the diazocine (**320**) and final cyclization with loss of ammonia and formaldehyde (Scheme 72).

8.22.9.4 Aryne Addition to 2,3-Indolizidinediones

The indolizidinedione derivatives (**322**), easily available from 1-alkyl-3,4-dihydroisoquinolines and oxalyl chloride, react with arynes to give 13-substituted 8-oxo-protoberberines (**323**), probably through the mechanism outlined in Scheme 73. This chemistry has been exploited in the total synthesis of the alkaloid (±)-corydaline ⟨86JOC2781⟩.



Scheme 72



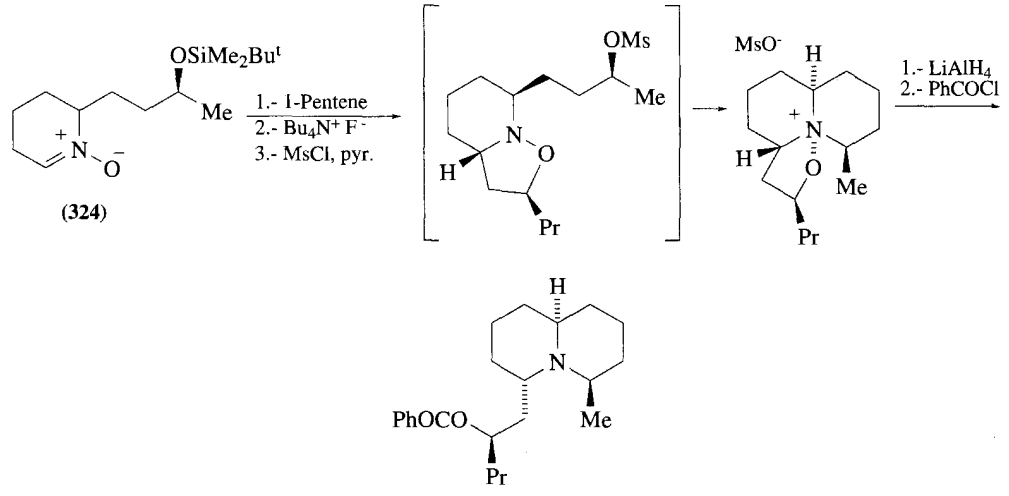
Scheme 73

8.22.9.5 Intramolecular *N*-Alkylation/Reduction in Isoxazolo[2,3-*a*]pyridines

exo-1,3-Dipolar cycloaddition of nitrones derived from 2,3,4,5-tetrahydropyridine with alkenes leads to perhydro isoxazolo[2,3-*a*]pyridines. Subsequent ring closure through intramolecular nucleophilic attack onto a leaving group initially contained either in the nitrone or the alkene molecules, followed by reductive opening of the isoxazolidine ring, affords quinolizidine derivatives. For example, nitrone (**324**) was transformed into the alkaloid porantheridine (**325**) ⟨80MC143⟩, as shown in Scheme 74. A number of other alkaloids have been synthesized using this method ⟨81CC940, 81T3615, 82JOC230, 82JOC4137, 83CC1143, 83TL2783, 84CPB3892, 85CPB532⟩.

8.22.9.6 Autooxidation/Rearrangement of Bicyclic Imines

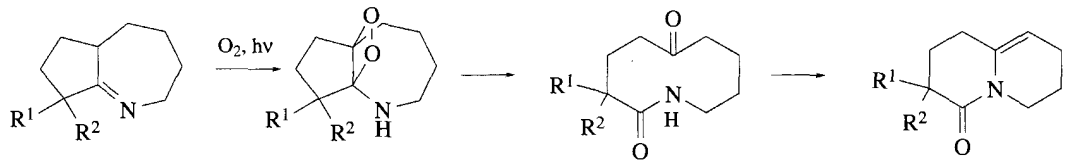
2-Azabicyclo[5,3,0]-1-decene derivatives (**326**) can be oxidized to the corresponding cyclic endoperoxides (**327**), which rearrange to compounds (**328**), precursors of quinolizine derivatives (**329**) (Scheme 75) ⟨82CB1626⟩.



(324)

(325)
(±)-Porantheridine

Scheme 74



(326) (327) (328) (329)

Scheme 75

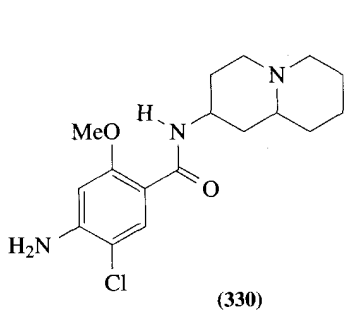
8.22.10 IMPORTANT COMPOUNDS AND APPLICATIONS

8.22.10.1 Biological Activity

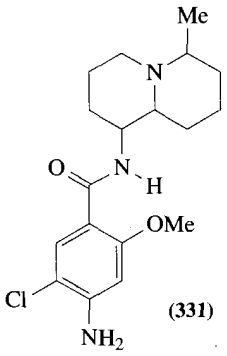
Many quinolizidine derivatives have interesting pharmacological (neuroleptic, analgesic, antiemetic, etc.) properties, and very often the quinolizidine system behaves in these compounds as a bulky aminoethyl-like structure. This is the case, for example, of orthopramides (**330**) ⟨85JMC339⟩ and (**331**) ⟨86MI 822-04⟩, which can be considered as analogues of metoclopramide and have shown good gastric prokinetic activities. Similarly, the antiarrhythmic agent and local anaesthetic (**332**) ⟨86JAP(K)6115882⟩ can be considered as an analogue of lidocaine and the anticholinesterase properties of some ethyl *O*-lupinyl alkylphosphonates (**333**) can be explained on the basis of their phosphonate and tertiary amino groups ⟨85DOK(6)36⟩. Benzo[*a*]quinolizines (**334**) and (**335**) inhibit neuronal gamma-aminobutyric acid (GABA) uptake and can be considered as analogues (similar nitrogen-carbonyl distances) of conformationally restricted GABA analogues such as guvacine (**336**) ⟨86EJM151⟩.

Many quinolizines show interesting affinity towards a variety of receptors. Compounds (**337**) and (**338**), which contain a partial dopamine structure, behave as antagonist and agonist, respectively, of brain dopamine receptors ⟨87JMC142⟩. The same type of affinity has been observed in tetrahydroberberines. (+)-Butaclamol (**339**) and a number of simplified analogues such as (**340**) are very potent neuroleptic agents that also act on dopaminergic receptors ⟨84JMC165⟩. Tetrabenazine (**341**) is an antipsychotic benzo[*a*]quinolizidine, but its mechanism of action is similar to that of reserpine and depends on neurotransmitter depletion ⟨84MI 822-02, 84MI 822-05⟩. 2-Benzamide- and 2-sulfonamidobenzo[*a*]quinolizidines (e.g. (**342**)) have been extensively studied as selective antagonists of adrenergic α_2-receptors ⟨83JMC416, 84BP1566, 86MI 822-03, 88JMC641⟩.

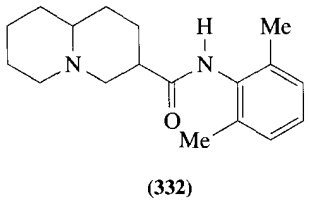
Other useful biological properties found in quinolizidine derivatives include the inhibition of angiotensin-converting enzyme (ACE) by compound (**343**) ⟨85JAN1003⟩, which shares some structural features with the lead compound in this area, i.e. captopril (**344**), the antibacterial activity of some benzo[*i,j*]quinolizidines (**345**) that belong to the quinolone group of chemotherapeutic agents



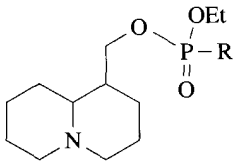
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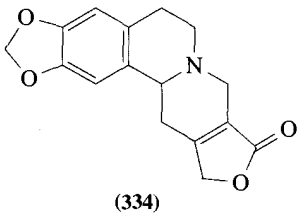
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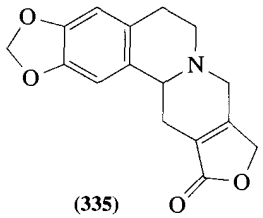
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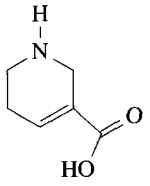
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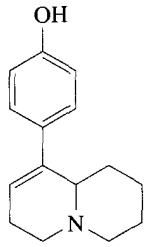
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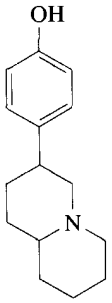
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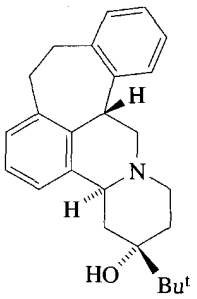
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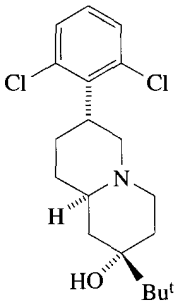
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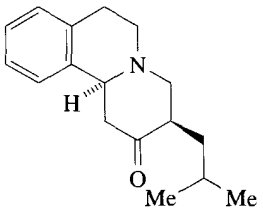
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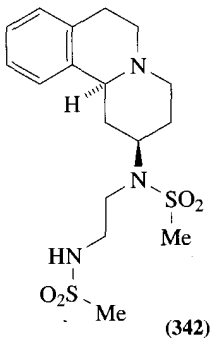
(339)



(340)



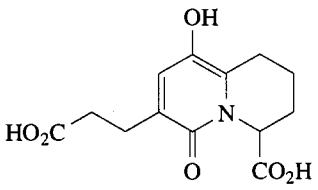
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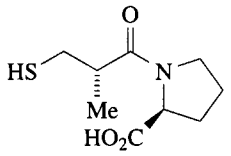
(342)

and act as DNA girase inhibitors ⟨82BEP891046⟩, the use of perfluoroquinolizidines (e.g. **346**) as artificial blood substitutes ⟨83MI 822-04⟩ and the chemotherapeutic (antitumor, amoebicidal) properties of cryptopleurine (**347**) and emetine (**348**) ⟨B-83MI 822-02⟩ and berberine compounds (**349**) ⟨82MI 822-02⟩. The alkaloids of the berberine group form complexes with biologically important macromolecules, such as alcohol dehydrogenase, reverse transcriptase, and nucleic acids ⟨59MI 822-01, 83JPS538, 84MI 822-03⟩.

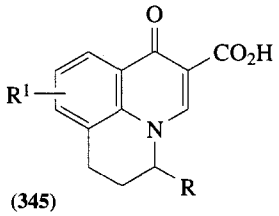
Some quinolizinium derivatives have also interesting pharmacological properties. Coralyne (**350**) is well known as an antitumor compound ⟨72JPS969, 74JMC347⟩, and coralyne analogues interact with template primers, inhibiting reverse transcriptase ⟨85JPS889⟩.



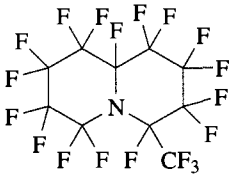
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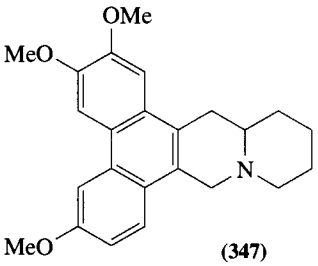
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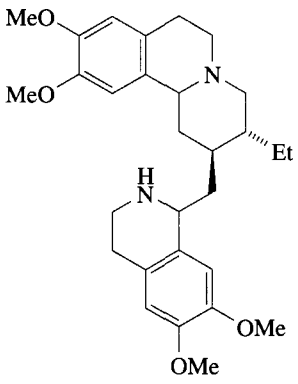
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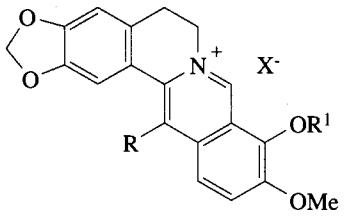
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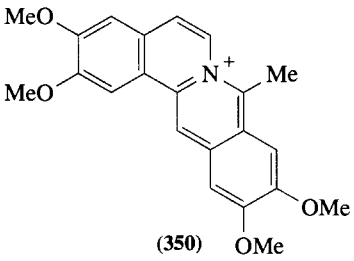
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(348)

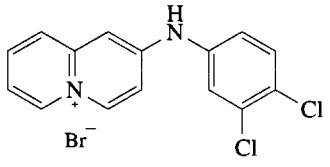


(349)



(350)

Nolinium bromide (**351**) blocks the entry of K^+ in the gastric H^+–K^+-dependent ATPase, interfering with the enzyme turnover, and is thus potentially useful as an antiulcer agent ⟨87BJ(241)175⟩.

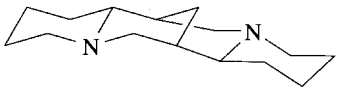


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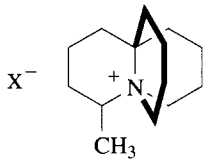
8.22.10.2 Quinolizidines as Inductors of Chirality

Some quinolizidine alkaloids can be employed as chiral catalysts in a variety of reactions. For example, Refortmasky reactions carried out in the presence of (−)-sparteine (**352**) proceed with

asymmetric inductions varying from moderate to high ⟨73T3659⟩, yielding β-hydroxyesters with an (*S*) configuration as major products. Similarly, sparteine causes some asymmetric induction in electrolytic reductions of ketones ⟨73MI 822-04⟩. Substituted 1-azonia[4.4.4]propellane cations (**353**), obtained by intramolecular cyclization, are rigid structures, with the substituted ring frozen in a chair form with an equatorial substituent. Ring inversion is very slow, and therefore these compounds exist as enantiomeric pairs. Hence, it has been proposed that these ions, after resolution, may be useful as chiral phase-transfer catalysts ⟨82JOC3777⟩.



(352)
Sparteine



(353)

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8.23
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: One Extra Heteroatom 1 : 0

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and

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Institute for Drug Research, Budapest, Hungary

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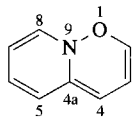
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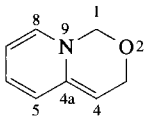
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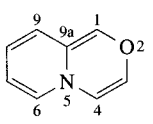
8.23.1 INTRODUCTION

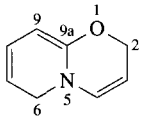
This chapter deals with bicyclic ring systems containing one ring junction nitrogen and one extra heteroatom, and with their benzo derivatives.

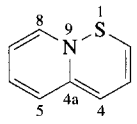
All 12 of the nitrogen ring junction bicyclic systems containing one oxygen, sulfur or nitrogen as extra heteroatom are known, comprising pyrido[1,2-*b*][1,2]oxazine (**1**), 1*H*,3*H*-pyrido[1,2-*c*]-[1,3]oxazine (**2**), pyrido[2,1-*c*][1,4]oxazine (**3**), 2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (**4**), pyrido[1,2-*b*]-[1,2]thiazine (**5**), 1*H*,3*H*-pyrido[1,2-*c*][1,3]thiazine (**6**), pyrido-[2,1-*c*][1,4]thiazine (**7**), 2*H*,6*H*-pyrido-[2,1-*b*][1,3]thiazine (**8**), 1*H*-pyrido[1,2-*b*]pyridazine (**9**), 1*H*-pyrido[1,2-*c*]pyrimidine (**10**), 2*H*-pyrido-[1,2-*a*]pyrazine (**11**), and 2*H*-pyrido[1,2-*a*]pyrimidine (**12**); the ring numbering is as shown on the structures. Of these, only the aromatic azaquinolizinium ions of (**9**), (**11**), and (**12**) are systematically discussed as primary subjects in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(2)572⟩, while some derivatives of (**4**) ⟨84CHEC-I(3)1005⟩ and (**8**) ⟨84CHEC-I(3)1005, 84CHEC-I(4)483⟩ are also mentioned in CHEC-I. Besides the above ring systems, only the aromatic form of 1*H*-pyrido[2,1-*f*][1,2]-azaborine has been the subject of a semiempirical quantum chemical calculation ⟨71CCC1248⟩.

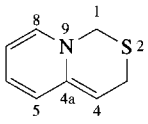

(**1**)

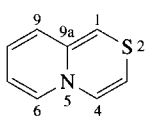

(**2**)

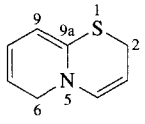

(**3**)

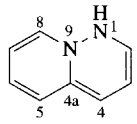

(**4**)

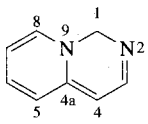

(**5**)

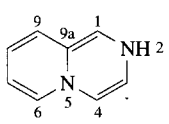

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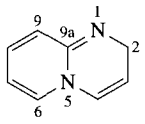

(**7**)


(**8**)


(**9**)


(**10**)

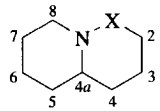

(**11**)

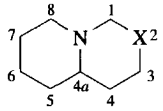

(**12**)

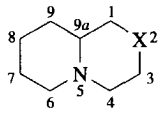
The known benzo derivatives of the above nitrogen bridgehead bicyclic systems are indicated with their *Chemical Abstracts* names in Table 1. No benzo derivative of pyrido[1,2-*b*]-[1,2]thiazine (**5**) is known.

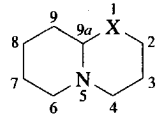
The early publications on (**1**) ⟨61HC(39)1211⟩, (**2**) ⟨61HC(39)1201⟩, 1,9*a*,9-benzologue of (**3**) ⟨61HC(39)1180⟩, (**7**) ⟨61HC(39)1182⟩, (**10**) ⟨61HC(39)1203⟩, its 2,3-benzologue ⟨61HC(39)1207⟩ (**11**) ⟨61HC(39)1188⟩, (**12**) ⟨61HC(39)1141⟩, and its 2,3-benzologue ⟨61HC(39)1153⟩ were treated in Mosby's review in 1961. Further reviews are available for (**12**), which cover its chemistry ⟨83AHC(33)241, 94KGS579, 95AHC(63)103⟩ and pharmacological properties ⟨88MI 823-01⟩, and for the 3,4-benzologue of (**10**), and the 2,3- and 3,4-benzologues of (**12**) ⟨86AHC(39)281⟩.

Table 1 Benzofused systems (arbitrary numbering).









O = *X* FUSION 2,3 Pyrido[1,2-*b*][1,2]benzoxazine FUSION 4,4*a*,5 Pyrido[3,2,1-*ij*][2,1]benzoxazine FUSION 7,8 [1,2]Oxazino[2,3-*a*]quinoline	FUSION 3,4 Pyrido[1,2-*c*][1,3]benzoxazine FUSION 4,4*a*,5 Pyrido[3,2,1-*ij*][3,1]benzoxazine FUSION 5,6 [1,3]Oxazino[4,3-*a*]isoquinoline FUSION 6,7 [1,3]Oxazino[3,4-*b*]isoquinoline FUSION 7,8 [1,3]Oxazino[3,4-*a*]quinoline	FUSION 3,4 Pyrido[2,1-*c*][1,4]benzoxazine FUSION 6,7 [1,4]Oxazino[4,3-*a*]quinoline FUSION 7,8 [1,4]Oxazino[4,3-*b*]isoquinoline FUSION 8,9 [1,4]Oxazino[3,4-*a*]isoquinoline FUSION 1,9*a*,9 Pyrido[1,2,3-*de*]-1,4-benzoxazine	FUSION 2,3 Pyrido[2,1-*b*][1,3]benzoxazine FUSION 3,4 Pyrido[1,2-*a*][3,1]benzoxazine FUSION 6,7 [1,3]Oxazino[3,2-*a*]quinoline FUSION 7,8 [1,3]Oxazino[3,2-*b*]isoquinoline FUSION 8,9 [1,3]Oxazino[2,3-*a*]isoquinoline FUSION 9,9*a* [1,3]Oxazino[2,3-*j*]quinoline
S = *X*	FUSION 3,4 Pyrido[1,2-*c*][1,3]benzothiazine FUSION 4,4*a*,5 Pyrido[3,2,1-*ij*][3,1]benzothiazine FUSION 5,6 [1,3]Thiazino[4,3-*a*]isoquinoline FUSION 6,7 [1,3]Thiazino[3,4-*b*]isoquinoline	FUSION 3,4 Pyrido[2,1-*c*][1,4]benzothiazine FUSION 6,7 [1,4]Thiazino[4,3-*a*]quinoline FUSION 7,8 [1,4]Thiazino[4,3-*b*]isoquinoline FUSION 8,9 [1,4]Thiazino[3,4-*a*]isoquinoline FUSION 1,9*a*,9 Pyrido[1,2,3-*de*]-1,4-benzothiazine	FUSION 2,3 Pyrido[2,1-*b*][1,3]benzothiazine FUSION 6,7 [1,3]Thiazino[3,2-*a*]quinoline FUSION 7,8 [1,3]Thiazino[3,2-*b*]isoquinoline FUSION 8,9 [1,3]Thiazino[2,3-*a*]isoquinoline
N = *X* FUSION 2,3 Pyrido[1,2-*b*]cinnoline FUSION 3,4 Pyrido[2,1-*a*]phthalazine FUSION 4,4*a*,5 Pyrido[3,2,1-*ij*]cinnoline FUSION 5,6 Pyridazino[6,1-*a*]isoquinoline FUSION 6,7 Pyridazino[1,6-*b*]isoquinoline FUSION 7,8 Pyridazino[1,6-*a*]quinoline	FUSION 3,4 Pyrido[1,2-*c*]quinazoline FUSION 4,4*a*,5 Pyrido[3,2,1-*ij*]quinazoline FUSION 5,6 Pyrimido[6,1-*a*]isoquinoline FUSION 6,7 Pyrimido[1,6-*b*]isoquinoline FUSION 7,8 Pyrimido[1,6-*a*]quinoline	FUSION 3,4 Pyrido[1,2-*a*]quinoxaline FUSION 6,7 Pyrazino[1,2-*a*]quinoline FUSION 7,8 Pyrazino[1,2-*b*]isoquinoline FUSION 8,9 Pyrazino[2,1-*a*]isoquinoline FUSION 1,9*a*,9 Pyrido[1,2,3-*de*]quinoxaline	FUSION 2,3 Pyrido[2,1-*b*]quinazoline FUSION 3,4 Pyrido[1,2-*a*]quinazoline FUSION 6,7 Pyrimido[1,2-*a*]quinoline FUSION 7,8 Pyrimido[1,2-*b*]isoquinoline FUSION 8,9 Pyrimido[2,1-*a*]isoquinoline

Within each of the subsections 8.23.2 "Structure," 8.23.3 "Reactivity," 8.23.4 "Synthesis" and 8.23.5 "Applications and Important Compounds," the bicyclic systems together with their structurally related benzologues are treated.

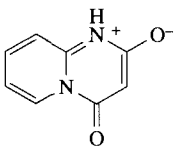
8.23.2 STRUCTURE

8.23.2.1 Thermodynamic Aspects

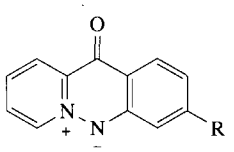
2-Oxo-2*H* derivatives of (**12**) and their 6,7,8,9-tetrahydro derivatives, 6-oxo-1,2,3,4-tetrahydro-6*H* derivatives of the 3,4-benzologue of (**12**), 2-oxo-2*H* derivatives of the 8,9-benzologue of (**12**), and 3-oxo-3*H* derivatives of the 6,7-benzologue of (**12**), have higher melting points than the isomeric 4-oxo-4*H* derivatives of (**12**) ⟨52JA5491⟩ and their 6,7,8,9-tetrahydro derivatives ⟨82JHC909⟩, 11-oxo-6,7,8,9-tetrahydro-11*H* derivatives of the 2,3-benzologue of (**12**) ⟨73CB1595⟩, 4-oxo-4*H* derivatives of the 8,9-benzologue of (**12**) ⟨95EJM27⟩, and 1-oxo-1*H* derivatives of the 6,7-benzologue of (**12**) ⟨79CPB2927⟩ because of the higher contribution of a zwitterionic mesomeric form to their structures. The solubilities of different (**12**) ⟨86MI 823-01⟩ and their 2,3-benzo derivatives ⟨83MI 823-01⟩ have been determined in H_2O, EtOH and *n*-octanol.

Protonation constants of derivatives of (**9**) ⟨71CPB159, 72KGS220⟩, (**11**) ⟨81BAP423⟩, (**12**) ⟨85C269, 74ACH15, 83MI 823-01, 85MI 823-01, 86MI 823-02, 87MI 823-01, 92JC223, 92MI 823-01⟩, and those of the 9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro derivative of the 8,9-benzologue of (**4**) ⟨66AP(299)817⟩, aromatic 2-amino-6,7-dihydro derivatives of the 5,6-benzologue of (**10**) ⟨82KGS1095⟩, and 11-oxo-11*H* derivatives of the 2,3-benzologue of (**12**) ⟨83MI 823-01, 84MI 823-01, 84MI 823-01, 86MI 823-02⟩ were measured.

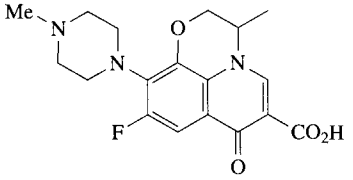
The pK_a values of (**13**) ⟨62JCS1544⟩ and (**14**, R = H) ⟨74JHC125⟩ were determined to be 0.07 and −0.25, respectively. Both the protonation macroconstants and microconstants of ofloxacin (**15**) have been determined ⟨92JPS592, 92MI 823-02, 93MI 823-01⟩. The 9-formyl-4-oxo-1,6,7,8-tetrahydro-4*H* derivatives of (**12**) ⟨86JCS(P2)1911⟩ and their 2,3-benzo derivatives ⟨84JHC219⟩ underwent protonation on the oxygen atom of the formyl group. The stability constants of metal complexes of (**15**) ⟨92CPB692⟩, 9-hydroxy-4-oxo-4*H* derivatives of (**12**) ⟨93JCC283⟩, and different 3-carboxyl-4-oxo-4*H* derivatives of (**12**) ⟨87ICA61⟩ have been determined.



(**13**)



(**14**)



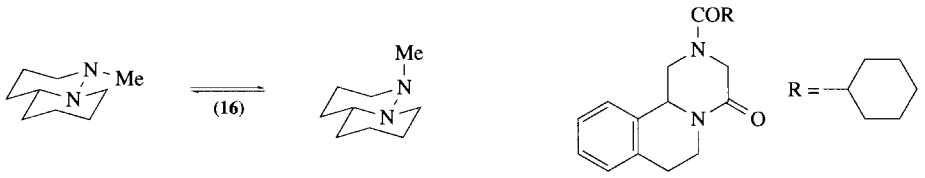
(**15**)

The octanol–water partition coefficients of (**15**), its (*S*)-(-)enantiomer (levofloxacin) ⟨85MI 823-02, 91MI 823-01, 92AF70, 92MI 823-03, 92MI 823-04⟩, 3-substituted 2,3,4,4*a*,5,6-hexahydro-1*H* derivatives of the 6,7-benzologue of (**11**) ⟨80IJC(B)879⟩, various saturated 4-oxo-4*H* derivatives of (**12**) ⟨81MI 823-01, 82JC67, 83JC91, 88MI 823-02, 92JC223, 92MI 823-01⟩, and its 2,3-benzologue ⟨83MI 823-03, 83MI 823-04, 83JC91⟩ were determined. In the case of derivatives of (**12**), the Hansch π values of the substituents were also calculated.

The polarographic behavior of 5*a*-hydroxy-11-oxo-5*a*,6,7,8,9,11*a*-hexahydro derivatives of the 2,3-benzologue of (**4**) ⟨67IZV1952⟩, and partly saturated 11-oxo-11*H* derivatives of the 2,3-benzologue of (**12**) ⟨84PHA106, 88MI 823-03, 90PHA740, 91PHA846⟩ have been investigated. For (**16**) the lone-pair peak separation of 1.04 eV, measured by means of photoelectron spectroscopy, was indicative of the presence of the *trans*-fused conformation (**16a**) with an axial methyl group ⟨79JA1874⟩. Ionization potentials and the oxidation potential of (**16**) have been determined ⟨79IJ45, 79JA1874, 84JOC1891⟩. The molar refractions of five 4-oxo-4*H* derivatives of (**12**) were determined in dioxane ⟨87JC11⟩. The purity of (**17**) ⟨88MI 823-04⟩, and its physicochemical interactions with oxamnique and tablet excipients ⟨92JPP259⟩ were investigated with the aid of DSC.

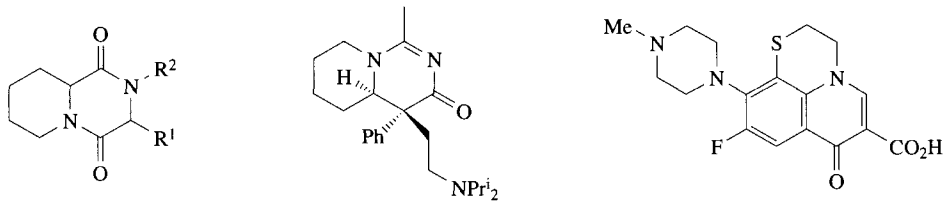
8.23.2.1.1 Chromatographic investigations

4-Oxo-4*H* derivatives of (**12**) ⟨81MI 823-02, 82JC67, 83JC91, 88MI 823-05, 88MI 823-06, 88MI 823-07, 89MI 823-01, 90MI 823-01⟩, and 11-oxo-tetrahydro- and octahydro-11*H* derivatives of the 2,3-benzologue of



(16e) (16a) (17)

(**12**) ⟨83JC91, 91JC365⟩, and (**17**) ⟨92JLC1639⟩, were investigated by TLC and OPTLC. The 4-oxo-4*H* derivatives of (**12**) ⟨80JC245, 80JC122, 81MI 823-03, 83JC91, 91JC365⟩, the 11-oxo-11*H* derivatives of the 2,3-benzologue of (**12**) ⟨83JC91, 91JC365, 91JC371, 91JC377⟩, and (**17**) ⟨92MI 823-05⟩ were also investigated by GC. Pyrolysis–gas chromatography was used to determine the degradation of peptides to diketopiperazines [such as (**18**)] for sequence determination in actinomycins ⟨71CC39⟩.



(18) (19) (20)

The chromatographic behavior of (**15**) ⟨91JLC3411, 93MI 823-01⟩, actisomide (**19**) ⟨87JLC3427⟩, 4-oxo-4*H* derivatives of (**12**) ⟨75MI 823-01, 76JC345, 79MI 823-01, 84MI 823-03, 84JLC1133, 84JLC1151, 85JLC1071, 85JLC1093, 86MI 823-03, 86MI 823-04, 87JPS918, 92JC223, 93JC333, 93JPS447⟩, and its 2,3-benzologue ⟨79JC311, 80AC1554, 83JC91, 84MI 823-03, 84JLC1133, 84JLC1151, 85MI 823-03, 85JLC381, 85JLC1071, 85JLC1093, 86MI 823-05⟩ were studied by different HPLC methods. HPLC was also applied to determine (**15**) and its (*S*)-enantiomer ⟨86JLC2539, 88JC153, 88JC257, 88JC192, 88JC135, 88JC461, 88JC320, 88JC439, 89MI 823-02, 91JC313, 91MI 823-02, 91JLC3411, 92JC289⟩, rufloxacin (**20**) ⟨90MI 823-02, 91JC346, 92JC168, 92JC129, 92MI 823-06⟩, (**17**) ⟨83JC127, 92JC265, 93JC174⟩, and derivatives of the benzologue of (**12**) ⟨79JC311, 84JC151, 84JC301, 84MI 823-04⟩ in biological fluids. The microbial sidephore pseudolactins (containing a pyrido[1,2-*a*]quinoline moiety) and its iron(III) complex were analyzed by means of HPLC with amperometric detection ⟨93MI 823-02⟩.

Enantiomers of the 6-oxo-11,11*a*-dihydro-6*H*,10*H* derivative of the 3,4-benzologue of (**2**) were quantitatively separated by chiral HPLC ⟨91ACS716⟩. The optical purity of levo-floxacin [the (S)-enantiomer of (**15**)] was determined by HPLC ⟨89MI 823-03⟩. Enantiomers of (**17**) were resolved by HPLC ⟨86JLC341, 93JC215, 93MI 823-03, 93MI 823-04⟩.

Good correlations were found between the partition coefficients and the TLC R^+ values ⟨82JC67⟩, the GC ΔI values ⟨81MI 823-03, 82JC347, 82JC67, 83MI 823-05⟩, difference HPLC retention indices (k′) ⟨84MI 823-03, 84JLC1133, 84JLC1151, 85MI 823-03, 86MI 823-03⟩ and molecular connectivity indices ⟨83JC91, 83MI 823-03⟩ of various 4-oxo-4*H* derivatives of (**12**), and the molar refractions and GC retention data of 11-oxo-11*H* derivatives of 2,3-benzologues of (**12**) ⟨87JC11⟩.

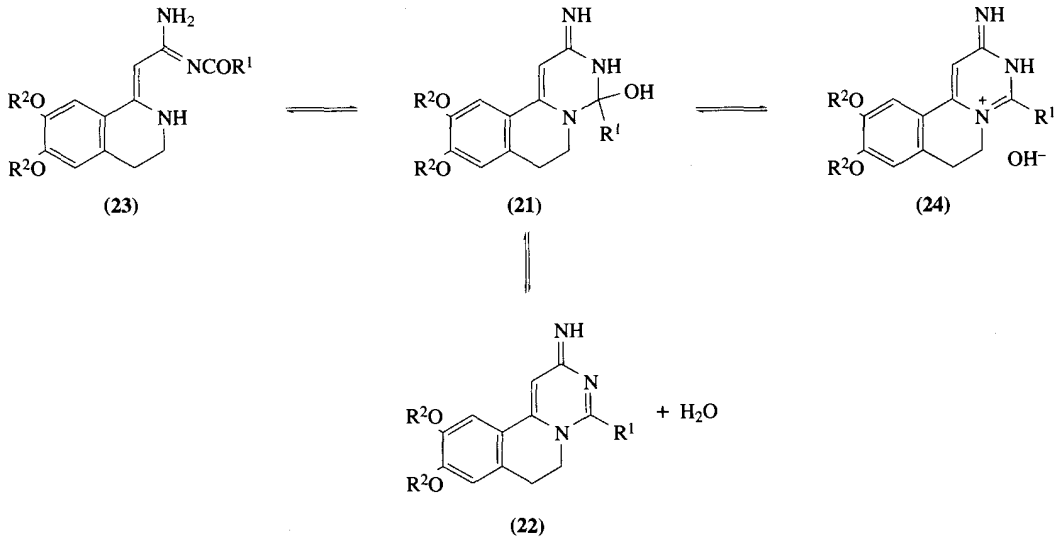
8.23.2.1.2 Tautomerism

Ring-chain tautomerism involving the hetero rings must be considered in the reactions of perhydro derivatives of (**4**) ⟨92T6325, 92TL507⟩, and its 2,3- ⟨89TL7321⟩, 8,9-benzologues ⟨66AP(299)817, 86AJC893⟩, and (**12**) ⟨68YZ212, 92AP(325)177⟩, and its 6,7- ⟨63YZ682⟩, 7,8- ⟨51JCS551, 73JOC437⟩, and 8,9-benzologue ⟨59YZ1014, 69YZ649⟩,

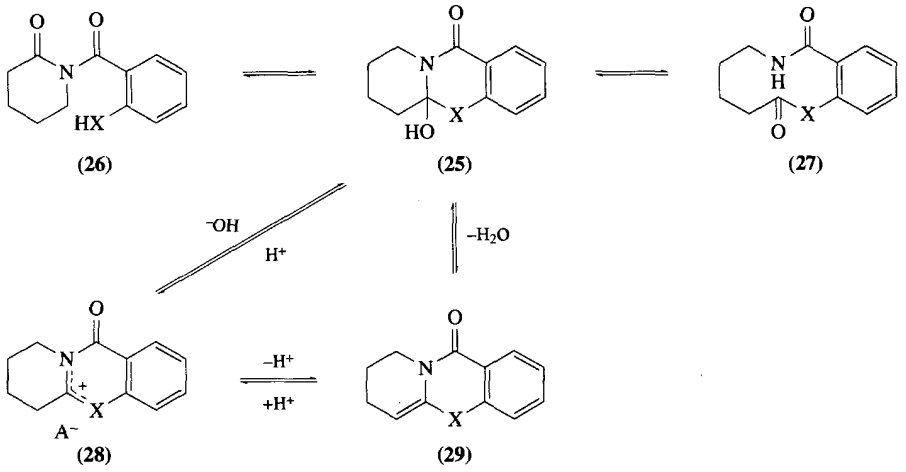
3-Cyano-4-imino-4*H* derivatives of (**12**) and its 6,7-, 7,8-, and 8,9-benzologues exhibit solvent-, temperature-, and substituent-dependent ring-chain tautomerism ⟨86JOC2988⟩. On protonation, the ring-chain equilibrium is shifted towards the ring form in consequence of the formation of a 4-amino-3-cyanopyrido[1,2-*a*]pyrimidinium cation. Ring-chain tautomerism was also detected for the 3-ethoxycarbonyl-4-imino-7-cyano-9-methylthio-6-oxo-1,6-dihydro-4*H* derivative of (**12**) ⟨86T3537⟩.

2-Imino-6,7-dihydro derivatives of the 5,6-benzologue of (**10**) yield an equilibrium system involving the tautomeric forms of pseudo bases (**21**), (**22**), (**23**), and anhydro base (**24**) ⟨90CB493, 91CB111, 94H(37)2051⟩. Different tautomers (**26**), (**27**) and forms (**28**), (**29**) of pseudo bases (**25**, X = O

⟨65ZOB1389, 68ZOB2030⟩, and X = S ⟨68AG909, 70TL649, 70TL2467⟩) could be detected or separated. Compounds (**30**) exhibit a pH- and substituent-dependent tautomerism involving 1,6,7,8-tetrahydro (**32**) and ring-opened tautomeric forms (**33**) via the pseudo basic amino-carbinol tautomers (**31**) ⟨72AF815, 86ACH135⟩.



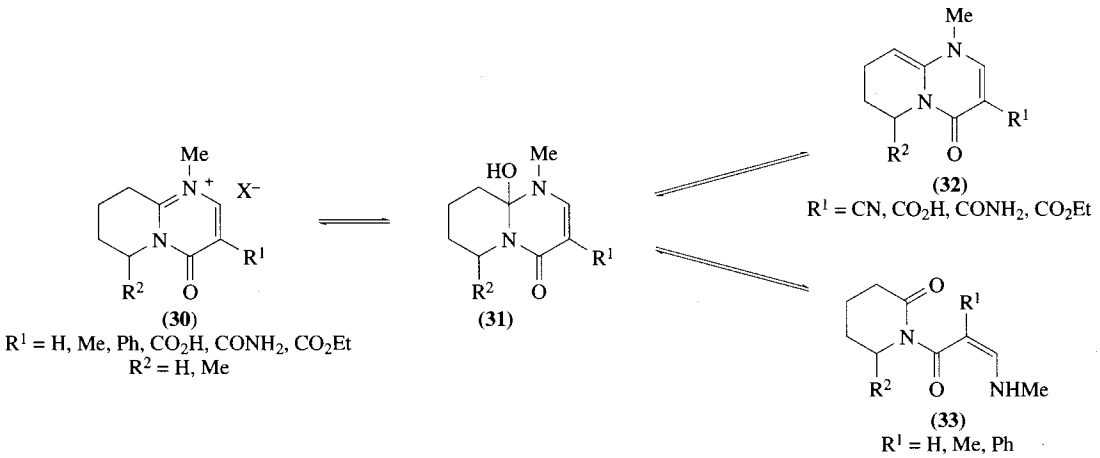
Scheme 1



Scheme 2

9-Substituted 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) exhibit a *cis-trans* isomerism through the 1,6,7,8-tetrahydro tautomeric form ⟨75S426, 76JHC797, 78CB2813, 79TL5039, 82OMR(20)229, 85JCS(P1)1015, 87H(26)869⟩. The 9-cyano, 9-nitro ⟨87H(26)869, 90JOC6198⟩, and 9-acyl derivatives ⟨79TL2557, 83JCS(P1)369, 83JCS(P2)1153, 85JCS(P2)1873, 85JCS(P2)1881, 85JHC593, 86JCS(P2)1911, 89JCS(P2)1613⟩ exist predominantly in the 1,6,7,8-tetrahydro tautomeric form. Similar phenomena were observed for 9-formyl-2-oxo-1,6,7,8-tetrahydro-2*H* derivatives of (**12**) ⟨85JCS(P2)1873⟩ and 6-formyl-11-oxo-5,7,8,9-tetrahydro- and -1,2,3,4,5,7,8,9-octahydro-11*H* derivatives of the 2,3-benzologue of (**12**) ⟨84JHC219, 87JHC1045⟩.

4,9-Dioxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) exhibit a solvent- and substituent-dependent oxo-enol tautomerism ⟨85JHC1253⟩. 9-Amino-4-oxo-6,7-dihydro-4*H* derivatives of (**12**) exist predominantly as the enamine tautomer and not as the 9-imino-6,7,8,9-tetrahydro tautomer. The latter tautomeric form predominates for 9-hydroxyimino-, 9-hydrazino-, and 9-aminomethylene-4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) ⟨83JCR(S)161, 83JCS(P2)165, 83JCS(P2)1409, 83OMR(21)687⟩, with a solvent-dependent *E–Z* geometric isomerism. 9-(Arylmethylenehydrazono)-4-oxo-6,7,8,9-tetra-



Scheme 3

hydro-4*H* derivatives of (**12**) exist as an equilibrium mixture of the 9-hydrazono-6,7,8,9-tetrahydro form and enehydrazine (6,7-dihydro form) tautomers, which can be separated ⟨91JHC781⟩. The 6-methyl-3-(*N*-methylaminomethylene)-2,4-dioxo-3,4,6,7,8,9-hexahydro-2*H* derivative of (**12**) exhibits a solvent-dependent imino-enamine-type tautomerism involving the 1,3,4,6,7,8-hexahydro form ⟨79TL1337⟩. Epimerization of 3-phenyl-4-oxoperhydro derivatives of (**12**) at position 3 proceeds via oxo-enol tautomerism ⟨82JOC4780⟩.

8.23.2.2 Theoretical Calculations

Different quantum chemical calculations were carried out to predict the most stable conformation(s) or tautomer of perhydro derivatives of (**2**) ⟨91JST(245)53⟩ and its cyclohexano derivatives ⟨92JST(274)259⟩; (**4**) ⟨90TL4281, 92T6325, 92TL507, 94JOC6904⟩; the 4′-hydroxy derivative of (**17**) ⟨91AP(324)479⟩; hydrogenated derivatives of (**12**) ⟨78T53⟩, and 3-ethoxycarbonyl-2-hydroxy-4-oxo-4*H* derivatives of the 8,9-benzologue of (**12**) ⟨89AJC2161⟩.

Structural, spectral properties and reactivities of a 6-oxo-6*H*,10*H* derivative of the 3,4-benzologue of (**2**) ⟨91ACS716⟩, 6-carboxyl-7-oxo-7*H* derivatives of the 1,9*a*,9-benzologue of (**3**) ⟨91JHC1067⟩, mesoionic derivatives of (**4**) ⟨85JOC5050, 88CB951⟩, 7,9-di(ethoxycarbonyl)-10-oxo-6,10-dihydro derivatives of the 3,4-benzologue of (**7**) ⟨93EJM13⟩, 6-carboxyl-7-oxo-7*H* derivatives of the 1,9*a*,9-benzologue of (**7**) ⟨91JHC1067⟩, derivatives of 2,3- and 3,4-benzologues of (**9**) ⟨92CB929⟩, (**17**) and its analogues ⟨90MI 823-03, 92MI 823-07⟩, the aromatic cation of (**12**) ⟨71JOC2457⟩, and 4-oxo-4*H* derivatives of (**12**) ⟨71MI 823-01, 72ACH281, 73ACH253, 73JHC479, 74JCS(P1)1753, 80MI 823-01, 83JCS(P2)1413, 85ACH321, 85JHC481, 85JOC2918, 87JST(153)59⟩ were also calculated by different quantum chemical programs.

8.23.2.3 Dipole Moment Investigations

Dipole moments of perhydro derivatives of (**2**) and (**6**) and 2-alkyl-3-oxoperhydro derivatives of (**10**) were determined in benzene and were used to estimate the conformation preferences of these bicyclic systems ⟨76JCS(P2)418⟩.

8.23.2.4 UV Spectroscopy

The UV spectrum of the 6-oxo-11,11*a*-dihydro-6*H*,10*H* derivative of the 3,4-benzologue of (**2**) is a superposition of the *N*-vinylcarbamate and phenyl chromophores ⟨91ACS716⟩. The UV spectra of 2,3,4,6,7,11*b*-hexahydro derivatives of the 8,9-benzologue of (**4**) indicated that only the cyclic form was present in cyclohexane, while both cyclic and ring-opened forms could be detected in water and ethanol ⟨66AP(299)817⟩. UV spectra of a 2*H* derivative of (**8**) ⟨73ACS1059⟩, 2,3-diaryl-3,5,6,7-tetrahydro derivatives of 1,9*a*,9-benzologues of (**11**) ⟨65JOC2589⟩, miscellaneous (**12**) ⟨58JA3066,

59JOC779, 62JCS1544, 62JOC1371, 70HCA905, 74ACH15, 74JPR875, 82JHC909, 83JCS(P2)1413, 85ACH305, 85JCS(P1)1015, 85JHC481, 85JHC1253, 85JOC2918, 87JHC393, 90MI 823-04〉 and their 8,9-benzo derivatives 〈70JCS(C)881〉 were investigated.

Spectroscopic methods (direct UV, difference UV, fourth derivative UV) were developed for quantitative determination of (**19**) and its sulfoxide impurity 〈91FES979〉 and (**17**) 〈88KFZ1140〉. UV data of pseudobactins 〈81B6446, 81B6457〉 and pyoverdine II metal complexes 〈87T2261〉 (containing a pyrimido[1,2-*a*]quinoline chromophore) were measured at different pH. The x-ray and photoelectron spectra of derivatives of (**13**) have been investigated 〈82MI 823-01〉.

8.23.2.5 CD Spectroscopy

Chiroptical properties of optically active perhydro derivatives of (**2**) 〈68CJC1105, 85T2891〉, the 6-oxo-11,11*a*-dihydro-6*H*,10*H* derivative of the 3,4-benzologue of (**2**) 〈91ACS716〉, the (*S*)-9-hydroxy-4-ethoxycarbonyl-6-methyl-3,4-dihydro-2*H* derivative of (**8**) 〈73ACS1059〉, 1,2,3,4,6,7-hexahydro-11*bH*- derivatives of 8,9-benzologues of (**11**) 〈67CB1383, 69T725, 71JPR825〉, enantiomers of (**17**) 〈85CB4620〉, and cyclodipeptides such as (**18**) 〈72TL1437, 73CCC3307〉 were studied by CD and/or ORD investigations. The homochiral 6-methyl- and 1,6-dimethyl-4-oxo-1,6,7,8,9,9*a*-hexahydro-4*H* derivatives of (**12**) exhibit enantiomeric CD spectra, because the 1-desmethyl-4oxohexahydro derivatives of (**12**) contain a transoid ring junction, while the 1-methyl derivatives adopt a cisoid one, in which the geometry of the inherently chiral chromophore, the pyrimidinone ring, is almost the reverse of that of the former 〈85JOC2918〉. CD spectra of pseudobactins (containing a pyrimido[1,2-*a*]quinoline moiety) and their Fe^{III} and Cr^{III} complexes were measured 〈81B6446, 81B6457〉.

8.23.2.6 Fluoroscence Spectroscopy

A fluorometric method was developed for determination of the level of (**20**) in biological fluids 〈89MI 823-04〉. The 8-carboxy-2-methoxy-11-oxo-11*H* derivative of the 2,3-benzologue of (**12**) was analyzed by laser induced spectrofluorimetry 〈80AC1554〉. Fluoroscence data of pyoverdine II metal complexes (containing a pyrimido[1,2-*a*]quinoline moiety) were measured at different pH 〈87T2261〉.

8.23.2.7 IR Spectroscopy

The appearance of the Bohlmann band in the IR spectra is frequently used to identify the *trans*-fused conformation of perhydro derivatives of (**2**) 〈68T4423, 70T3941, 85T2891, 87T935〉, and its 3,4- and 4,4*a*,5-cyclohexano, and 5,6-benzo derivatives 〈70T1217, 71TL3361, 80JCS(P2)1778, 84OMR(22)424〉; (**3**) 〈72JCS(P2)1374, 72OMR(4)509, 78JMC460, 92CPB652〉, and its 1,9*a*,9-cyclohexano and 7,8- and 8,9-benzologues 〈72OMR(4)509〉; (**4**) 〈84TL3227, 89CPB1676, 92TL507〉, and its 8,9-benzologue 〈61AP(294)645, 66AP(299)817〉; (**6**) 〈70T3941, 82OMR(20)239〉; (**10**) 〈69JHC181, 72JCS(P2)1920〉, and its 7,8-benzologue 〈79JCS(P2)581〉; (**11**) 〈69JHC181, 72JCS(P2)1374, 73CPB1248, 85BAP39, 93JOC690〉 and its 7,8- 〈75IJC230〉, 8,9-benzologue 〈84JMC995〉; (**12**) and its 7,8-benzologue 〈68CC1423, 69JHC181〉; also for the heterorings of a hexahydro derivative of the 8,9-benzologue of (**7**) 〈80JHC449〉, and a hexahydro-4*aH* derivative of the 6,7-benzologue of (**9**) 〈73JHC999〉.

The Bohlmann bands are not suitable for recognition of a *trans*-fused conformer of 1,3,4,4*a*,5,6-hexahydro derivatives of the 7,8-benzologue of (**2**) due to the flattening of the ring junction nitrogen pyramid, as a consequence of (p-p)π conjugation of the lone pair of the nitrogen atom and the aromatic π-orbitals of the benzene moiety 〈71TL3361〉. The application of Bohlmann's IR criterion to 2-alkylperhydro derivatives of (**10**) is greatly complicated by the presence of the two nitrogen atoms and in some cases the α-H atoms of the 2-alkyl group 〈70T701〉. The structures of (**18**) derived from pipecolic acid and other amino acids were studied by IR spectroscopy 〈72CCC4060, 72TL1437, 73CCC1957〉. An infrared spectrophotometric determination of (**17**) in CCl_4 was reported 〈91MI 823-03〉.

The aromatic 2,4-dimethyl-9-hydroxy salt of (**12**) and its metal complexes 〈90MI 823-04〉, 4-oxo-4*H* derivatives of (**12**) 〈77T2293, 79CPB2927, 85ACH305, 85JHC481, 85JHC1253, 87ACH819, 92MI 823-08〉 and the isomeric 2-oxo-2*H* derivatives 〈72CPB142, 73JHC821, 82FES747, 82JHC909, 87JHC329, 88FES705, 92HCA1262〉 were characterized by IR.

8.23.2.8 Proton NMR Spectroscopy

8.23.2.8.1 Fully saturated ring systems

Proton NMR spectra have been used to study conformation in perhydro derivatives of (**1**) ⟨85JA5534, 89JOC4088, 91CC1237, 92JOC2876⟩; (**2**) ⟨68T4423, 70T1217, 70T3941, 71TL3361, 76JCS(P2)418, 76OMR(8)258, 80JCS(P2)1778, 80OMR(13)159, 85T2891, 87T935, 88MRC748, 92MRC129⟩ and its 3,4- ⟨70T1217, 71TL3361⟩, 6,7- ⟨80HCA1158⟩, and 4,4*a*,5-cyclohexano derivatives ⟨80JCS(P2)1778, 80OMR(13)159, 84OMR(22)424⟩; (**3**) ⟨71OMR(3)263, 72JCS(P2)1374, 72OMR(4)283, 72OMR(4)509, 78JMC460, 92CPB652⟩, and its 1,9*a*,9-cyclohexano derivatives ⟨72OMR(4)509⟩; (**4**) ⟨90TL4281, 92TL507, 94JA2617, 94JOC6904, 94TL1715⟩; (**6**) ⟨70T3941, 82OMR(20)239⟩; (**7**) ⟨72OMR(4)283⟩; (**10**) ⟨70T701, 72JCS(P2)1920, 73OMR(5)397, 76JCS(P2)418, 79JCS(P2)504⟩; (**11**) ⟨72JCS(P2)1374, 73CCC1940, 73CPB1248, 76JCS(P2)187, 80BSB615, 85BSB413, 93JOC690⟩; and (**12**) ⟨82JOC4780⟩ and its 2,3-cyclohexano derivatives ⟨83JCS(P2)237⟩.

8.23.2.8.2 Partly saturated ring systems

Proton NMR spectra have been used to study conformation in partly saturated derivatives of 5,6- ⟨71TL3361, 76OMR(8)258, 77JCS(P2)370, 90CB803, 92T4937⟩, 6,7- ⟨71TL3361, 77JCS(P2)370⟩, and 7,8-benzologues ⟨71TL3361, 77JCS(P2)370, 77JCS(P2)1592, 93JCR(S)170⟩ of (**2**); 7,8- ⟨72OMR(4)283, 72OMR(4)509⟩; 8,9- ⟨72OMR(4)509, 78JMC785⟩, and 1,9,9*a*-benzologues ⟨72AJC1283, 73T2571⟩ of (**3**); the 5,6- benzologue of (**6**) ⟨76OMR(8)258, 77JCS(P2)370, 90CB803⟩; the 8,9-benzologue of (**7**) ⟨72AJC1283, 80JHC449⟩; (**9**) ⟨87JCS(P1)2511⟩ and its 6,7-benzologue ⟨73JHC999⟩, 5,6- ⟨77JCS(P2)370, 84JHC149, 91MRC1040⟩ and 7,8-benzologues ⟨79JCS(P2)581⟩ of (**10**); 6,7- ⟨85JMC945⟩ and 8,9-benzologues ⟨91KFZ85⟩ of (**11**); (**12**) ⟨85JOC2918, 86JOC394⟩, and its 2,3- ⟨66TL1091, 67CB3385, 83JHC93⟩ and 7,8-benzologues ⟨68CC1423⟩. The structures of different (**12**) ⟨61JOC4157, 70C418, 71JOC2457, 72CPB142, 73CJC2650, 73JCS(P1)1138, 73JHC821, 73KGS242, 75UKZ186, 78JHC801, 82OMR(20)229, 83JCR(S)161, 83JCS(P1)369, 83JCS(P2)165, 83JCS(P2)1153, 83JCS(P2)1409, 83OMR(21)687, 85JCS(P2)1873, 85JCS(P2)1881, 85JHC593, 85JHC1253, 86JCS(P2)1911, 89JCS(P2)1613, 91JHC781⟩, and their 2,3-benzo derivatives ⟨78CB2813, 83MI 823-06, 84JHC219, 84JHC1301⟩ were investigated and characterized by ^{1}H NMR investigations. Proton NMR and optical rotation measurement demonstrated that deuterium incorporation on the chiral C(4) in the 4-ethoxycarbonyl-9-hydroxy-6-methyl-3,4-dihydro-2*H* derivative of (**8**) in 0.4 *N* NaOH at 40 °C occurred without racemization ⟨73ACS1059⟩. Proton NMR investigations were also used to investigate and determine the structures of different siderophores containing a pyrimido[1,2-*a*]quinoline moiety ⟨81B6457, 83TL4877, 84B3534, 87T2261, 89LA375, 90TL7611, 92TL1737, 92TL1889, 93JPR83, 93JPR157⟩.

8.23.2.9 Carbon-13 NMR Spectroscopy

Carbon-13 NMR spectroscopy was also used to study conformation in perhydro derivatives of (**1**) ⟨85JA5534, 89JOC4088⟩, (**2**) ⟨85T2891, 88MRC748, 92MRC129⟩ and its 3,4-⟨93MRC505⟩, 4,4*a*,5-⟨92MRC129⟩, and 6,7-cyclohexano derivatives ⟨80HCA1158⟩, (**4**) ⟨93T4315⟩, (**6**) ⟨82OMR(20)239⟩, (**9**) ⟨78JA4012⟩, (**11**) ⟨85BAP39, 88PJC709⟩, (**12**) ⟨82JOC4780⟩ and their 2,3-cyclohexano derivatives ⟨83JCS(P2)237⟩.

The structure of the 2-oxo-3,4,5,6-tetrahydro-2*H* derivative of (**3**) ⟨78HCA607⟩, 5,6-benzo derivatives of (**6**) ⟨76OMR(8)258, 77JCS(P2)370, 90CB803⟩, 5,6-benzo derivatives of (**10**) ⟨90JHC957, 91MRC1040⟩, 8,9-benzo derivatives of (**11**) ⟨89AP(322)795, 91KFZ85⟩, different 4-oxo-4*H* derivatives of (**12**) ⟨79JHC1181, 82OMR(20)229, 83JCR(S)161, 83JCS(P2)165, 83JCS(P2)1153, 83JCS(P2)1409, 83JHC619, 83OMR(21)687, 85JCS(P1)1015, 85JCS(P2)1873, 85JCS(P2)1881, 85JHC593, 85JHC1253, 85JOC2918, 86JCS(P2)1911, 86JOC394, 89JCS(P2)1613, 89JHC1061, 90JHC247⟩, their 2,3-benzo derivatives ⟨83JHC93⟩, and different siderephores, containing a pyrimido[1,2-*a*]quinoline moiety ⟨81B6457, 83TL4877, 84B3534, 87T2261, 89LA375, 90TL7611, 92TL1737, 92TL1889, 93JPR83, 93JPR157⟩ were characterized by ^{13}C NMR spectroscopy.

8.23.2.10 Nitrogen-15 NMR Spectroscopy

In some cases ^{15}N NMR spectroscopy was also used to characterize the structure of perhydro (**2**) and (**6**) ⟨83OMR(21)203⟩, and 4-oxo-4*H* derivatives of (**12**) ⟨82JOC4780, 82OMR(20)229, 83JCS(P2)1153, 83JCS(P2)1409, 83OMR(21)687, 85JCS(P1)1015, 85JCS(P2)1881, 85JOC2918, 86JCS(P2)1911⟩.

8.23.2.11 Mass Spectroscopy

The fragmention pattern of (**15**) and its defluoro derivative ⟨91OMS(26)669⟩, 5,6-⟨85OMS(20)483⟩ and 6,7-benzo derivatives ⟨73JHC999⟩ of (**9**), 8,9-benzo derivatives of (**11**) ⟨91OMS(26)503⟩, derivatives of (**12**) ⟨72CPB142, 72MI 823-01, 76MI 823-01, 84AP(317)873, 89ACH333⟩, and its 2,3- ⟨78KPS414, 79KPS180, 83MI 823-07⟩ and 6,7- benzologues ⟨76MI 823-01, 79KPS180, 83TL4877, 87T2261, 89LA375, 90TL7611, 91OMS(26)899, 92TL1737, 92TL1889, 93JPR83, 93JPR157⟩ were investigated. Metabolites of (**15**) ⟨86MI 823-06⟩, (**17**) ⟨90MI 823-05, 90MI 823-06⟩, 2-methyl-4-oxo-4*H* derivatives of (**12**) ⟨88MI 823-08⟩, and a 2*H*-pyrazino[1,2-*b*]isoquinoline metabolite of quinapril ⟨86MI 823-06⟩ were identified by mass spectrometry.

8.23.2.12 X-ray Investigations

Absolute configurations of the *cis*-1,3,4*a*-H-1-(4-nitrophenyl)-3-methylperhydro derivative of (**2**) ⟨72AX(B)37⟩, the *cis*-7,11*b*-H-2-methyl-7-phenyl-1,3,4,6,7,11*b*-hexahydro-2*H* derivative of the 8,9-benzologue of (**11**) ⟨84AX(C)1103, 84JMC995⟩, and the 3-carboxy-9-(4-bromophenylamino)-6-methyl-4-oxo-6,7-dihydro-4*H* derivative of (**12**) ⟨83JCS(P2)1413⟩ were determined by x-ray diffraction. The solid-state structures of derivatives of (**2**) ⟨81JA7573⟩, its 5,6- ⟨90CB803, 90T4039⟩, and 6,7-benzologues ⟨80HCA1158⟩, 1-(*p*-bromophenyl)perhydro derivatives of (**2**) ⟨73MI 823-01⟩ and (**6**) ⟨73MI 823-02⟩, the perchlorate salt of (**15**) ⟨91MI 823-04⟩, an 11-oxohexahydro derivative of the 2,3-benzologue of (**4**) ⟨89TL7321⟩, a tetrahydro derivative of the 8,9-benzologue of (**8**) ⟨79AX(B)1285⟩, (**14**, R = Br) ⟨74JHC125⟩, some derivatives of (**10**) ⟨85JMC1285, 91KGS1556⟩ and its 5,6-benzologue ⟨82TL2829, 83JOC5074, 90CB493⟩, derivatives of (**18**) ⟨82BSB213, 83AX(C)905, 87AX(C)1603, 91AX(B)92, 93AX(C)1113⟩ and (**17**) ⟨91KFZ78⟩, derivatives of the 8,9-benzologue of (**11**) ⟨91AP(324)479, 91AX(C)2492, 92AX(C)1868⟩, different 2-oxo-2*H* ⟨88JCS(P1)2993, 95MI 823-01⟩, and 4-oxo-4*H* derivatives of (**12**) ⟨72AF815, 72AX(B)2405, 72CSC419, 73AX(B)1245, 73JHC123, 75AX(B)1695, 75AX(B)1702, 76CSC611, 83JCS(P1)369, 85AX(C)472, 85JOC2918, 86AX(C)573, 88JCS(P2)1287, 90DOK(312)619, 91T675, 92AX(C)1827, 93AX(C)1698, 93JHC33⟩, and its 2,3-⟨74JPR(316)496, 75JOC2201, 89JHC1229⟩, 6,7- ⟨81B6446⟩, and 8,9-benzologues ⟨89AJC2161⟩ were determined by x-ray crystallography.

8.23.3 REACTIVITY

8.23.3.1 Ring Opening

Ring junction nitrogen systems often suffer ring opening under acidic and alkaline conditions for example, derivatives of 2,3-benzologue of (**1**) ⟨81AG(E)481⟩, (**2**) ⟨57CLY927, 60JOC2028, 70LA(737)24, 84JA3240, 91TL4371⟩, and its 4,4*a*,5- ⟨64M59, 90CPB1575⟩, 5,6- ⟨67JCS(C)1569⟩, and 6,7-benzologues ⟨80HCA1158⟩, the 8,9-benzologue of (**3**) ⟨79T2345⟩; (**4**) ⟨77JCS(P2)759⟩, and its 3,4- ⟨70KGS879, 89IJC(B)126⟩, 7,8- ⟨75CJC3029⟩, and 8,9-benzologues ⟨67CB1094, 73IZV456⟩; (**8**) ⟨94H(37)441⟩; (**10**) ⟨56CB1642, 84JHC149, 87JOC2455⟩, and its 5,6-benzologue ⟨60YZ1414, 81KFZ44, 82KGS1095⟩; and (**12**) ⟨24CB1168, 48JA3348, 49JA3258, 52JA4906, 58JOC1358, 61JOC2350, 70HCA905, 73JCS(P1)1138, 73JOC437, 74JCS(P1)1753, 76AP(309)471, 77JCS(P1)789⟩.

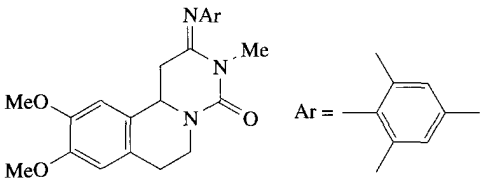
The rate of alkaline hydrolysis of 3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium perchlorates to the thermodynamic 1-(3-hydroxypropyl)-2-piperidones ⟨75CJC2791⟩ decreased with increasing substitution ⟨70CC900⟩.

Ring-opened products were also obtained in other reactions. Reductive N—O bond cleavage of perhydro and 2,4*a*,5,6,7,8-hexahydro derivatives of (**1**) occurred with zinc dust in aqueous AcOH ⟨85JA5534, 86TL5513, 89JOC4088, 91CC1237, 91TL4325, 92JOC2876⟩ or by hydrogenation over 5% Pd/C ⟨89JOC4088⟩, or with sodium amalgam ⟨94JOC1358⟩. Desulfurization of sulfur containing heterocycles over Raney nickel gave ring-opened products, for example derivatives of (**6**) ⟨85T2861⟩, (**7**) ⟨82TL3811, 85T2861⟩.

Ring-opened products were obtained from derivatives of (**2**) ⟨54JA2431, 57CLY927, 87T935, 93JOC5035⟩, and its 5,6-benzologue ⟨90T4039, 91ACH375⟩; (**3**) ⟨66JMC311, 76JMC334, 78JMC460, 88SC823, 91JMC19⟩; (**4**) ⟨61AP(294)65⟩, and its 8,9-benzologue ⟨67AP(300)308, 71MI 823-02⟩; the 3,4-benzologue of (**7**) ⟨73IJC1051⟩; (**9**) ⟨66KGS91⟩, and its 7,8-benzologue ⟨66YZ608⟩; and (**11**) ⟨73CPB1248⟩ during catalytic hydrogenation over Pt, Pd/C, and Raney nickel, and reduction with LAH and $NaBH_4$.

Sometimes reaction with Grignard reagents led to ring-opened products, for example from perhydro derivatives of (**2**) ⟨50JA358⟩ and (**4**) ⟨91TL5147, 92T8295⟩. Oxidation of perhydro derivatives of (**4**) ⟨60JA5148, 63AP(296)38⟩, and 8,9-benzo derivatives of (**4**) ⟨67AP(300)308⟩ with $Hg(OAc)_2$ or

$Hg(OAc)_2$-EDTA afforded ring-opened products. Treatment of trequinsin (**34**), and other 6,7-dihydro derivatives of the 5,6-benzologue of (**10**) with dimsyl ion gave various ring-opened products ⟨90JOC5117, 91CB111⟩.



(**34**)

8.23.3.2 Reduction, Hydrogenation

Reduction to a methylene group of an oxo group on partly or wholly saturated skeletons of (**3**) ⟨60AP(293)74, 63AP(296)38, 72JCS(P2)1374, 72OMR(4)283⟩, its 6,7-⟨721JC1134⟩, and 1,9*a*,9-benzologues ⟨69CR(C)564⟩, (**8**) ⟨94H(37)441⟩, (**9**) ⟨66KGS91⟩, (**10**) ⟨59CB637, 67YZ663⟩ and its 5,6-benzologue ⟨59YZ1008, 60YZ1414, 77JCS(P2)370⟩, (**11**) ⟨57N62, 59CB240, 60JOC2108, 66JMC311, 67JCS(C)2391, 67YZ668, 68JOC2379, 69JCS(C)1987, 69JHC181, 72JCS(P2)1374, 73CPB1248, 76KFZ88, 91JOC5192, 91T1065, 93JOC690, 95JCS(P1)369⟩, its 6,7- ⟨63YZ679, 64JOC326, 691JC833, 85JMC945⟩, 7,8- ⟨64JOC326, 73CPB2039, 75IJC230, 77IJC(B)70⟩, and 8,9-benzologues ⟨85CB4620, 86M1 823-07, 89H(29)359⟩, and (**12**) ⟨68YZ212, 69JHC181, 69JOC165, 69KGS547⟩, its 6,7- ⟨63YZ682⟩, 7,8- ⟨68CC1423⟩, and 8,9-benzologues ⟨69YZ649, 71MI 823-02⟩ was achieved on treatment with LAH or $LiAlD_4$ ⟨72JCS(P2)1374, 72OMR(4)283⟩, with diborane or diborane-Me_2S complex ⟨85JMC945, 89H(29)359⟩. Treatment of 11-oxo-6,7,8,9-tetrahydro-11*H* derivatives of the 2,3-benzologue of (**12**) with LAH gave 5,5*a*,6,7,8,9-hexahydro-11*H* derivatives ⟨73JMC633⟩. When the reduction was carried out with $NaBH_4$, only saturation of the C(5*a*)=N(5) double bond occurred ⟨66USP3271396⟩.

The (thio)carbonyl group of 11-(thi)oxo-6,7,8,9-tetrahydro-11*H* derivatives of the 2,3-benzologue of (**12**) was reduced to a methylene group with zinc powder in acidic medium ⟨73JMC633, 59LA(623)166, 62CB2182, 35CB2221, 88IJC(B)937⟩ and by the action of Raney nickel in the case of the thiocarbonyl derivative ⟨73JMC633⟩.

Reduction of the keto group of 3-phenyl-6-oxoperhydro derivatives of (**2**) with KS-Selectride in THF at −78 °C gave a 9 : 1 mixture of the axial alcohol and the equatorial alcohol, while the ratio of the alcohols was reversed when $NaBH_4$ was used in MeOH at room temperature ⟨85T2891⟩. The 7-oxo group of 3,7-dioxo-1,5,6,7-tetrahydro-3*H* derivative of the 4,4*a*,5-benzologue of (**2**) was selectively reduced to a hydroxy group with $NaBH_4$ ⟨90CPB1575⟩. Reduction of 3,7-dioxo-3,5,6,7-tetrahydro-2*H* derivatives of 1,9*a*,9-benzologues of (**3**) and (**7**) with an alkali metal borohydride ⟨70CR(C)498, 72AJC1283⟩ or over Raney nickel ⟨69CR(C)564, 70CR(C)498⟩ afforded the corresponding 7-hydroxy-3-one derivatives.

Reduction of the 1-oxo-2,3,4,6,7,8-hexahydro-1*H* derivative of (**11**) ⟨73CPB1248⟩ and the aromatic 1-oxo-1,2,3,4-tetrahydro salt of the 7,8-benzologue of (**11**) ⟨73CPB2039⟩ with $NaBH_4$ yielded the 1-oxoperhydro derivative of (**11**) and 1-oxo-1,2,3,4-tetrahydro-6*H* derivative of the 7,8-benzologue of (**11**), respectively. 2,3,4,6,7,11*b*-Hexahydro derivatives of the 8,9-benzologue of (**8**) were obtained from aromatic 2*H* salts of the 7,8-benzologue of (**11**) with $NaBH_4$, KBH_4, $NaBH_3CN$ ⟨74IJC1242, 81IJC(B)372⟩, and 5*a*,6,7,8,9,11-hexahydro derivative of the 7,8-benzologue of (**8**) from (**29**, X = S) by catalytic hydrogenation over Pd/C ⟨70TL2467⟩.

The 4-oxo group of 2-benzyl-1,4-dioxoperhydro derivatives of (**11**) was regioselectively reduced when the 1-oxo group was alkylated with Me_3OBF_4, the 1-methoxy-4-oxo-3,6,7,8,9,9*a*-hexahydro-4*H* derivative was treated with the borane-THF complex, and finally the 1-oxo group was regenerated ⟨88S963⟩.

Depending upon the condition of catalytic hydrogenation over a catalyst (Pd, Pt, Ni) partially saturated or perhydro derivatives could be prepared from derivatives of (**1**) ⟨85JA5534, 89JOC4088, 91CC1237, 91TL4325, 92JOC2876⟩, (**2**) ⟨91TL4371⟩, and its 5,6-benzologue ⟨71JOC2211, 73JHC435⟩, the 1,9*a*,9-benzologue of (**3**) ⟨44HCA1756, 69CR(C)564, 70CR(C)498⟩, (**9**) ⟨68YZ216⟩ and its 7,8-benzologue ⟨66YZ608⟩, the 5,6-benzologue of (**10**) ⟨81CB61, 84JMC1470⟩, (**11**) ⟨64MI 823-01, 66JOC941, 67JCS(C)2391, 67YZ668, 71JCS(C)861, 76JA246, 93JOC690, 94T1811⟩ and its 6,7- ⟨63YZ679⟩ and 7,8-benzologues ⟨73CPB2039⟩, (**12**) ⟨49JA2587, 52JA4906, 52JA5491, 57DOK(113)343, 71IJC201, 75JOC1440, 76JHC797,

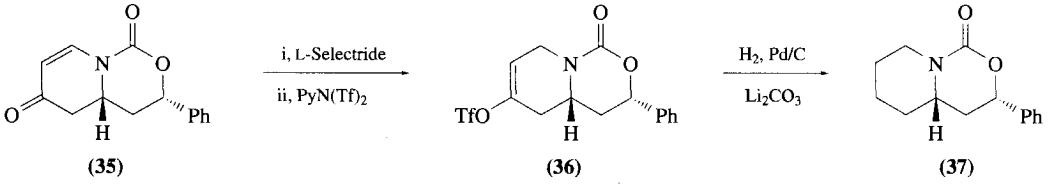
77GEP2705778, 78CB2594, 85JOC2918, 88FES705〉, its 2,3- 〈38CB1657, 62CB2182, 80JCS(P1)633, 87JMC1543, 90PHA109〉, and its 8,9-benzologues 〈69YZ649〉.

Catalytic hydrogenation of 4-oxo-4*H* derivatives of (**12**) usually gave the 6,7,8,9-tetrahydro derivatives 〈69CB455, 71JMC913, 72AF815, 75G1291, 75H(3)927, 77CB2480, 79JHC457, 79M1387, 80ZOR1483, 82JOC4780, 83H(20)1083, 83JMC1126, 86JOC394, 93FES1225, 95H(40)681〉, but the presence of an amino group at position nine prevents the saturation of the pyridine moiety 〈91H(32)1455〉.

In some cases, the C=N double bond of derivatives of (**10**) 〈85JMC1285〉 and its 5,6-benzologue 〈81CB61, 84JHC149〉, (**12**) 〈72AF815, 74JCS(P1)1753, 85JOC2918, 88FES705〉, and its 2,3- 〈82JCS(P1)2801〉, 3,4- 〈76AP(309)503〉, and 8,9-benzologues 〈59YZ1014〉 were saturated on treatment with $NaBH_4$, KBH_4 〈88FES705〉, or LAH 〈85JMC1285〉. When $NaBH_4$ was used C=C double bond(s) were also sometimes saturated, for example (**9**) 〈78JOC2892〉, (**10**) 〈90MI 823-07〉, (**11**) 〈73CPB1248〉, and (**12**) 〈72AF815, 74JPJ44, 82JOC4780〉.

Conjugate reduction of the 1,6-dione (**35**) provided the vinyl triflate (**36**), which was chemoselectively hydrogenated to give (**37**) 〈93JOC5035〉. The 7-amino-3-oxo-3,4,5,6-tetrahydro-2*H* derivative of the 1,9*a*,9-benzologue of (**3**) was obtained from the 7-hydroxyimino derivative, prepared from 3,7-dioxo and $HONH_2$, by catalytic hydrogenation over PtO_2 in AcOH 〈69CR(C)564〉.

The reader is also referred to Section 8.23.3.1.



(**35**) (**36**) (**37**)

Scheme 4

8.23.3.3 Oxidation, Dehydrogenation

Oxidation of perhydro derivatives of (**11**) 〈73CPB1248〉, its 7,8-benzologue 〈73CPB2039, 77IJC(B)70〉 (**12**) 〈76AP(309)471〉, its 2,3-benzologue 〈76AP(309)471〉, and that of the 6-oxo-1,2,3,4,4*a*,5-hexahydro-6*H* derivative of the 3,4-benzologue of (**12**) 〈76AP(309)572〉 was carried out with the $Hg(OAc)_2$-edta and $Hg(OAc)_2$. The 2-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H* derivative of (**12**) was obtained by dehydrogenation of the 2,4-dioxoperhydro derivative 〈66JCS(B)565〉. Oxidation of a 1-oxo-1,3,4,6,11,11*a*-hexahydro derivative of the 7,8-benzologue of (**3**) with SeO_2 afforded a 1-oxo-3,4-dihydro derivative 〈85MI 823-04〉. Dehydrogenation of a 4-oxo-3,4*a*,5,6,7,8-hexahydro-4*H* derivative of (**9**) was carried out with $Hg(OAc)_2$ or over PtO_2 〈71CPB159〉. Dehydrogenation and oxidation of partly saturated derivatives of 2,3- 〈38CB1657, 48LA(559)1, 65CCC2080〉 and 6,7-benzologues 〈73YGK313, 78HCA1146〉 of (**12**) was also carried out. Dehydrogenation of 4-oxo-1,2,3,6,7,11*b*-hexahydro-4*H* derivatives of (**11**) with sulfur 〈75GEP2418111, 89AP(322)795〉 and ddq 〈89AP(322)795〉 gave 2,3,6,7-tetrahydro and 6,7-dihydro derivatives 〈89AP(322)795〉, respectively.

Further examples are to be found in Sections 8.23.3.1 and 8.23.3.4.

8.23.3.4 Reactivity of Ring Heteroatoms

Depending upon the reaction conditions and oxidation agents both sulfoxides and sulfones were obtained from derivatives of the 8,9-benzologue 〈80JHC449, 81CP1101857〉 and 1,9*a*,9-benzologues of (**7**) 〈87JMC465〉, and of (**8**) 〈80CPB1131〉, and its 7,8-benzologue 〈79CPB2372〉. Sulfoxides (sometimes as an epimeric mixture) were prepared from derivatives of (**7**) 〈92BMC1293〉, and the 8,9-benzologue of (**7**) 〈80JHC449〉 with $NaIO_4$, and from derivatives of the 1,9*a*,9-benzologue of (**7**) 〈93JMC3449〉 and (**8**) 〈92JCS(P1)621〉 with 3-chloroperoxybenzoic acid. Sulfoxides could be deoxygenated by treatment with PCl_3 or PBr_3 〈87JMC465, 93JMC3449〉. Sulfones were obtained from perhydro derivatives of (**7**) and (**8**) 〈59AP(292)165〉, the 1,9*a*,9-benzologue of (**7**) 〈81JHC1273, 82JHC237〉, and the 7,8-benzologue of (**8**) 〈81USP4284778〉. From derivatives of the 3,4-benzologue of (**7**) a mixture of epimeric sulfoxides and sulfone was prepared 〈90FES589〉.

Oxidation of perhydro derivatives of (**11**) with 30% H_2O_2 gave a mixture of *cis*- and *trans*- *N*-oxides 〈85BAP39〉, which were converted to 2,3,4,6,7,8-hexahydro derivatives with 25% NaOH

⟨81BAP423⟩. Deoxygenation of *N*-oxides of the 7,8- ⟨67JCS(C)2391, 71JCS(C)861, 72JHC177⟩ and 1,9*a*,9-benzologues ⟨85H(23)1729⟩ of (**11**) could be achieved by treatment with PBr_3 and $NaHSO_3$ or $POCl_3$, respectively. Reduction of an N-oxide of an aromatic salt of (**11**) over PtO_2 gave the perhydro derivative ⟨66JOC941⟩.

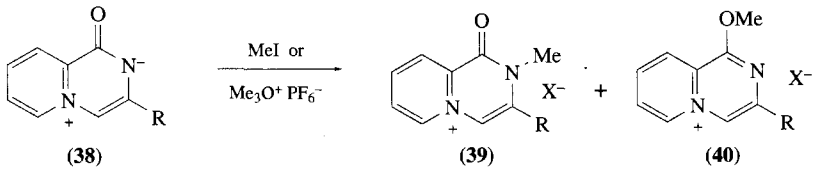
Quaternary salts were prepared from perhydro derivatives of (**2**) ⟨54JA2431, 63AP(296)38, 70T1217⟩, its 3,4- ⟨70T1217⟩, and 4,4*a*,5-cyclohexano derivatives ⟨80JCS(P2)1778⟩, (**4**) ⟨61AP(294)65, 63AP(296)38⟩, (**6**) ⟨59AP(292)165⟩, (**10**) ⟨59CB637⟩; from different derivatives of 8,9-benzologue of (**4**) ⟨66AP(299)817, 85AJC1591⟩, (**11**) ⟨68JOC2379, 73CPB1248⟩ and its 7,8-benzologue ⟨64JOC326, 73CPB2039⟩, (**12**) ⟨65MI 823-01, 71JCS(C)2735, 72AF815, 73JHC821, 74EJM344, 74JCS(P1)1753, 75MI 823-02, 85JOC2918⟩ and its 2,3- ⟨68ZOB2030, 82JCS(P1)2801⟩, 3,4- ⟨88UKZ1079⟩, and 7,8-benzologues ⟨73JOC437, 82JCS(P1)2801⟩ by treatment with alkyl halides, dialkyl sulfates and aralkyl halides.

The reaction of derivatives of perhydro (**4**) ⟨61AP(294)65⟩, and the 1-oxoperhydro derivative of (**11**) ⟨73CPB1248⟩, with MeI afforded a mixture of *cis*- and *trans*-methiodides. The reaction of the linearly fused 11-oxo-11*H* derivative of the 2,3-benzologue of (**12**) with alkylating agents gave exclusively *N*(5)-alkylated quaternary salts. While reaction of the isomeric angularly fused 6-oxo-6*H* derivative of the 3,4-benzologue of (**12**) with the soft electrophile MeI afforded only the *N*(5)-methyl quaternary iodide, the reactions with the hard electrophiles Me_2SO_4 and Et_3OBF_4 yielded mixtures of 5-methyl-6-oxo-6*H*- and 6-alkoxypyrido[1,2-*a*]quinazolinium salts ⟨90JHC2005⟩.

N-Alkyl derivatives have been prepared from fully or partly saturated derivatives of (**9**) ⟨78JA4012⟩ and its 3,4-benzologue ⟨88EUP294599⟩, (**10**) ⟨56CB1642, 57HCA1319, 64JMC146, 69JHC181, 73OMR(5)397, 84JMC1470, 85JMC1285⟩, its 5,6- ⟨69YZ649, 84T4003, 90JOC5117⟩ and 7,8-benzologues ⟨70USP3494922⟩, (**11**) ⟨60JOC2108, 66JMC311, 69JHC181, 69KGS547, 71AF808, 72YZ1339, 73CPB1248, 73YZ854, 76KFZ49, 77JMC821, 78AJC187, 81BAP423, 83IJC(B)664, 91JOC5192, 93JOC690, 95JCS(P1)369, 95JHC857⟩ and its 8,9-benzologue ⟨88MI 823-09⟩, (**12**) ⟨69JHC181, 69KGS547, 72AF815, 74JCS(P1)1753, 75CR(C)953, 85JOC2918, 87JAP(K)87209067⟩ and its 2,3- ⟨66USP3271396, 82JCS(P1)2801⟩, 3,4- ⟨84JHC1609, 84KFZ700⟩, and 8,9-benzologues ⟨69YZ649⟩ under various reaction conditions (e.g. by reductive alkylation ⟨78JA4012, 84JMC995⟩, by reaction with diazomethane ⟨56CB1642⟩, alkyl halides, ethylene oxide, in Eschweiler–Clark ⟨73CPB2039⟩), and Mannich reactions ⟨88MI 823-09⟩. Reaction of 2-(substituted amino)-4-oxo-6,7-dihydro-4*H* derivatives of (**10**) with alkyl iodides gave 3-alkyl-2-(substituted imino)-2,3,6,7-tetrahydro derivatives ⟨86HCA1671⟩.

The 5-methyl derivative was obtained from (**14**, R = H) with Me_2SO_4 ⟨74JHC125⟩. Protonation of (**14**) occurred on the 5-nitrogen and not the oxygen, but its 1,2,3,4,7,8,9-octahydro derivative was protonated on the oxygen to produce the 11-hydroxy salt.

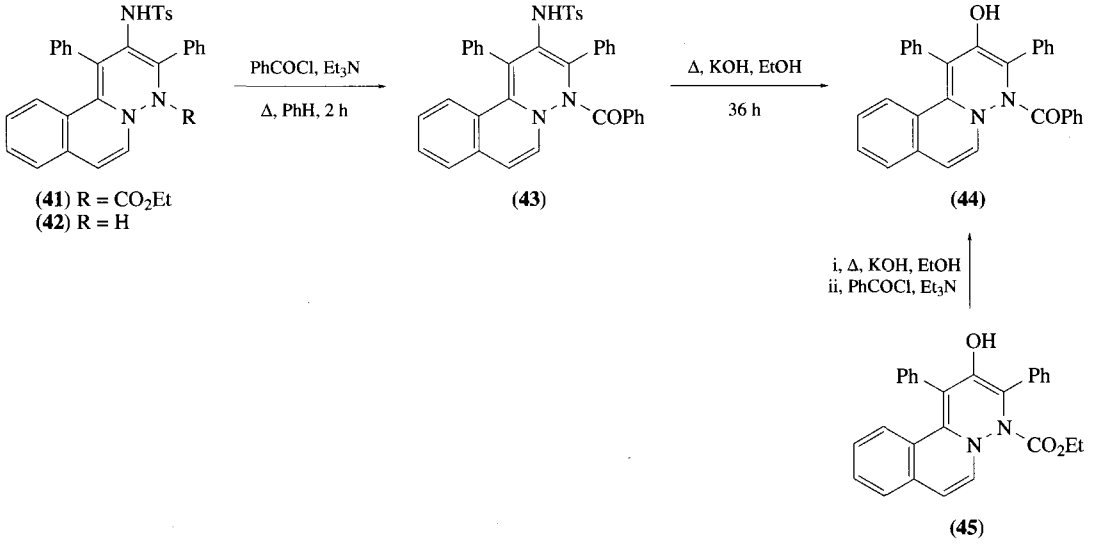
Methylation of (**38**) with the soft electrophile MeI gave either exclusively the *N*-methylated (**39**) or a mixture of the *N*- and *O*-methylated (**39**) and (**40**), usually with an excess of the *N*-methylated derivative. When a hard trimethyloxonium salt was used, the *O*-methylated or a mixture of the *N*- and *O*-methylated (**39**) and (**40**) (with a predominance of the latter) was obtained. The thioxo analogue of (**38**, R = Ph) gave exclusively the 1-methylthiopyrido[1,2-*a*]pyrazinium salt with both methylating agents ⟨90JHC1673⟩. From the isomeric pyrido[1,2-*a*]pyrazinium-3-olate, only the *O*-methylated product could be isolated ⟨90JHC1673⟩. Compound (**13**) and its derivatives exhibit ambivalent reactivity towards alkylating agents to give *N*(1)-substituted and/or *C*(3)-alkylated mesoionic compounds and/or 2-*O*-alkylated products, depending upon the structure of the substrate, the alkylating agent and the reaction conditions ⟨58AP(291)298, 62JCS1544, 67JHC523, 67MI 823-01, 70HCA905, 71MI 823-03, 71M412, 76ZN(B)500⟩. *N*-Hetarylation of derivatives of (**11**) has also been carried out ⟨81AF279, 84PHA812, 91JOC5192, 94T1811, 95TA321⟩.



(38) (39) (40) (1)

N-Acyl derivatives have been prepared from fully or partly saturated derivatives of (**9**) ⟨66KGS91, 68YZ216, 78JA4012⟩ and its 7,8-benzologue ⟨66YZ608⟩; the 5,6-benzologue of (**10**) ⟨84T4003⟩; (**11**) ⟨60JOC2108, 61BSF2135, 66JMC311, 69KGS547, 73CPB1248, 77JMC821, 81KFZ55, 83IJC(B)664, 93JOC690, 94T1811⟩, its 3,4- ⟨75CAR(39)379, 86MI 823-08⟩, 6,7- ⟨47HCA920, 64JOC326, 69IJC833, 70JMC516, 85MI 823-05, 88MI 823-10⟩, 7,8- ⟨64JOC326, 69T725, 77IJC(B)70, 90IJC(B)455⟩, and 8,9-benzologues ⟨83H(20)1731, 85CB4620, 85KGS798, 85MI 823-05, 86MI 823-07, 86MI 823-09, 87MI 823-02, 88MI 823-10, 89AP(322)795, 91AP(324)235, 91MI 823-

05〉; (**12**) 〈69KGS547, 71IJC201, 81GEP2948535〉, with various acylating agents (e.g. acyl chloride, iso-(thio)cyanates, *N*,*N*-diethylcarbamoylchloride, CS_2 + MeI). The acylation of (**13**) and its derivatives has also been studied 〈58AP(291)298, 61M727, 67KGS221, 71MI 823-03, 72M426, 74CPB1542, 78JHC1047〉. Compound (**42**), obtained from (**41**), was *N*-benzoylated 〈83JOC1084〉 to give compound (**43**), which in turn gave (**44**), also prepared from (**45**) by basic hydrolysis and subsequent acylation. *N*-Acyl derivatives of 6,7- 〈75GEP2331713, 76GEP2508947, 85MI 823-05, 87MI 823-02〉 and 8,9-benzologues 〈83H(20)1731〉 of (**11**) were deacylated by acidic hydrolysis.



(**41**) R = CO_2Et
(**42**) R = H

(**43**)

(**44**)

(**45**)

Scheme 5

2-Guanyl derivatives were prepared from perhydro derivatives of (**11**) 〈69JHC181〉. *N*-Nitroso derivatives were prepared from hexahydro derivatives of the 6,7- 〈47HCA920〉 and 8,9-benzologues 〈71JPR825, 87MI 823-02〉 of (**11**) with $NaNO_2$ in an acidic media.

2-Unsubstituted perhydro derivatives of (**11**) were obtained from 2-(*p*-nitrosophenyl) 〈59CB1510〉, 2-ethoxycarbonyl- 〈93JOC690, 95JCS(P1)369〉 (prepared from 2-benzyl derivatives with ClCOOEt), and 2-benzyl derivatives 〈94T1811〉, and a 2-unsubstituted 2,3,4,6,7,11*b*-hexahydro-1*H* derivative of the 8,9-benzologue of (**11**) from the 2-methyl-7-phenyl derivative 〈84JMC995〉.

8.23.3.5 Reactivity of Rings

C(3) in 4-oxo-4*H* derivatives of (**12**) and its 8,9-benzologue 〈80KGS1656〉 react with various electrophiles 〈24CB1168, 39JGU1109, 40JGU1065, 52JA4910, 52JA5491, 52JA5945, 54JA1845, 58JCS209, 67JHC523, 71M412, 71JOC2192, 75JMC726, 76ZN(B)95, 76ZN(B)500, 78JHC801, 84IJC(B)1117, 85JHC481, 86JHC1295, 87JHC329, 89MI 823-05, 91IJC(B)839, 92KGS1660, 92MI 823-09, 93FES1225, 93IJC(B)978, 95H(40)681〉. C(8) of 9-hydroxy-4-oxo-4*H* derivatives of (**12**) could be also substituted in electrophilic reactions 〈84IJC(B)1117, 90JCR(S)308, 92KGS1660〉.

C(8) in (**8**) 〈94H(37)441〉, and C(11) in the 7,8-benzologue of (**8**) 〈76GEP2756067〉, and in that of (**12**) 〈88HCA77〉 were also involved in substitution reactions. C(9) in 4-oxo-2,3,4,6,7,8-hexahydro derivatives of (**8**) was acylated 〈94H(37)441〉. The aromatic *N*-oxide of (**11**) was brominated at position 1 〈67JCS(C)2391〉. Compound (**14**, R = H) gave 2-nitro, while its 2-acetamido derivative afforded 3-nitro derivatives with HNO_3 〈74JHC125〉. 2-Iodo derivatives were obtained with ICl from (**14**, R = H) 〈74JHC125〉.

Various substituents were introduced into the benzo ring of the 1,9*a*,9-benzologue of (**3**) 〈70CR(C)498, 86CC1308, 92MI 823-10〉; the 7,8-benzologue of (**8**) 〈76GEP2756067〉; the 4,4*a*,5-benzologue of (**10**) 〈72MI 823-02〉; the 3,4- 〈88JCS(P1)1997〉, 6,7- 〈72JMC351〉 and 8,9-benzologues 〈84JMC995〉 of (**11**); and the 2,3-benzologue of (**12**) 〈31LA(486)284, 75GEP2436481, 79KGS684, 85IJC(B)336〉.

An oxo group in partly or wholly saturated derivatives of (**10**) 〈57HCA1319〉 and its 5,6-benzologue

⟨82KGS1095, 84JMC1470, 89H(29)1929⟩, and the 8,9-benzologue of (**12**) ⟨90T1323⟩ was converted into the chloride. A Vilsmeier–Haack reaction of the 4-oxo-1,3,4,6,7,11*b*-hexahydro derivative of the 8,9-benzologue of (**7**) gave a 3-formyl-4-chloro-1,6,7,11*b*-tetrahydro derivative ⟨81CP1101857⟩. An oxo group in (**14**, R = H) ⟨74JHC125⟩, in derivatives of the 5,6-benzologue of (**10**) ⟨70USP3494922, 84JMC1470⟩, and in (**12**) ⟨73JHC821, 79JHC457⟩ and its 2,3-benzologue ⟨73JMC633⟩ were transformed into a thioxo group. The thioxo group was converted with $Hg(OAc)_2$ into an oxo group ⟨69YZ649, 74CC487, 75JCS(P1)1969⟩, and with MeI to a methylthio group ⟨73JHC821, 79GEP2848926, 79JHC457⟩. The 8- and 9-oxo groups in derivatives of perhydro (**7**) were converted into amino groups by treatment with $HONH_2$, and subsequent reduction by LAH ⟨92BMC1293⟩. An oxo group in derivatives of (**1**) ⟨85JA5534, 86TL5513, 89JOC4088, 91CC1237, 91TL4325, 92JOC2876⟩, and (**10**) ⟨85JMC1285⟩ was reacted with Grignard reagents, and an oxo group in (**11**) with CH acid compounds ⟨71AP(304)342⟩, $BnPO(OEt)_2$ ⟨95JCS(P1)369⟩, and Grignard reagents ⟨94T1811⟩; an oxo group in (**12**) reacted with Et_3OBF_4 ⟨61LA(640)98⟩. Leuckart–Wallach reaction of the 3,7-dioxo-3,5,6,7-tetrahydro-2*H* derivative of the 1,9*a*,9-benzologue of (**3**) furnished the 7-formylamino derivative ⟨69CR(C)564⟩. A hydrazone was obtained from an 11-oxo-7,8,9,11-tetrahydro derivative of the 2,3-benzologue of (**8**), ⟨91IJC(B)754⟩.

A 4-methyl-2-oxo-2*H* derivative of the 8,9-benzologue of (**12**) ⟨80YZ1261⟩ and a 9,10-dimethoxy-4-oxo-6,7-dihydro-4*H* derivative of the 5,6-benzologue of (**10**) ⟨84JMC1470⟩ were obtained from their 3- and 2-methylthio derivatives, respectively, by reaction with Raney nickel. An alkylthio group in the 2,3-benzologue of (**9**) ⟨74JHC125⟩, and in (**12**) ⟨69JPJ203, 74JPJ44, 91MI 823-06⟩ was substituted by *C*- and *N*-nucleophiles.

The 3-hydroxy group in the 3,4-dihydro-2*H* derivative of (**12**) was converted into a chloride ⟨65MI 823-02⟩. 2-Chloro derivatives were prepared from (**13**) and its derivatives ⟨52JA4910, 52JA5945, 58JCS209, 67JHC523, 70HCA905, 93MIP23398⟩. The 2-chloro atom was exchanged for various *O*-, *N*-, and *S*-nucleophiles ⟨58JCS209, 62JCS1544, 67JHC523, 70CB2828, 70CB3811, 70HCA905, 71JMC913, 71JOC2192, 77AF82, 77JCS(P1)789, 82FES747, 86JHC1295, 87JHC329, 92FES77, 92JHC25, 92JHC559, 92MI 823-09, 93FES1225, 93MIP23398, 95EJM27⟩. The 9-bromo atom(s) in 4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) ⟨83JCS(P2)1413, 83JMC1494, 83OMR(21)687, 85H(23)2289, 85JCS(P1)1015, 85JHC1253, 85TL3621, 87H(26)869⟩ and its 2,3-benzologue ⟨76IJC(B)354, 79KPS180, 81TL4816, 84JHC1301, 87JHC1045⟩ was substituted by *O*-, *S*-, and *N*-nucleophiles. A halogen atom in (**3**) ⟨90SL731, 92T431⟩, its 1,9*a*,9-benzologue ⟨69CR(C)564, 86CC1308⟩; in (**10**) ⟨57HCA1319⟩ and its 5,6-benzologue ⟨82KGS1095⟩; and in the 6,7- ⟨95EJM27⟩ and 8,9-benzologues ⟨67IJC403, 90T1323, 95EJM27⟩ of (**12**) was substituted by *O*-, *S*-, *N*-nucleophiles. The iodo atom of 7-iodo-4-oxo-4*H* derivatives of (**12**) was substituted by ethoxycarbonyl-, vinyl-, (1-ethoxyvinyl) groups ⟨94BMC183⟩, while the bromo atom of 2-bromo-11-oxo derivatives of 2,3-benzologues of (**12**) and the 2-bromo derivative of (**14**, R = H) ⟨74JHC125⟩ was changed to CN and carboxy derivatives ⟨79GEP2812585, 80JMC92⟩.

Usually the 10-F atom in (**46**, $R^1 = R^3 = F$, $R^2 = H$) ⟨90EUP373531⟩; (**47**, $R^1 = F$, Cl, $R^2 = H$, $R^3 = F$) ⟨84CPB4907, 86AAC163, 87CPB1896, 87JMC2283, 88JMC1694, 88JMC2004, 90JHC1509, 90JMC2270, 90MI 823-08, 91CCC1937, 91CCC2406, 91EJM889, 91JHC1061, 91JHC1067, 91JMC1142, 92CCC216, 92MI 823-11, 93JMC801, 93JMC1356⟩, (**48**, $R^1 = R^3 = F$, $R^2 = H$) ⟨91JHC1061, 91JHC1067⟩, (**49**, $R^1 = F$, Cl, $R^2 = H$, $R^3 = F$) ⟨92EUP470578, 92MIP9215584, 93JAP(K)93213951⟩ was regioselectively substituted with *N*-, *O*-, *S*-, and *C*-nucleophiles, but cyclic amines reacted at position nine of 9-F,10-Cl derivatives of (**47**, $R^1 = F$, $R^2 = H$, $R^3 = Cl$) ⟨84CPB4907⟩ and (**48**, $R^1 = F$, $R^2 = H$, $R^3 = Cl$) ⟨87JMC465⟩. When the sulfoxide and sulfone derivatives of (**48**, X = SO, SO_2, $R^1 = F$, $R^2 = H$, $R^3 = Cl$) were used, in the latter case, position 10 was involved in the reaction ⟨87JMC465, 93JMC3449⟩. The regioselectivity of the nucleophilic substitution of the halogen atoms of (**48**, $R^1 = F$, $R^2 = Cl$, $R^3 = H$) with cyclic amines depends on the nature of the solvent ⟨87JMC465⟩. When a boron chelate of (**47**) ⟨87CPB1896⟩ and (**49**) ⟨92EUP470578⟩ was used substitution of the 10-F atom occurred even at room temperature. The 10-Br atom in (**47**, $R^1 = H$, F, $R^2 = H$, $R^3 = Br$) was substituted by *N*- and *C*-nucleophiles ⟨86EUP184384, 89EUP306860⟩.

The active methylene group of 2-oxo-6,7,8,9-tetrahydro-2*H* ⟨82JHC909, 85JCS(P1)1873, 89JHC1061⟩ and 4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) ⟨72AF815, 74EJM344, 79AF1833, 79TL2557, 79TL5039, 80H(14)1953, 82JMC1140, 82OMR(20)229, 82USP4321377, 83JCR(S)161, 83JCS(P1)369, 83JCS(P2)1413, 83JMC1126, 83JMC1494, 83OMR(21)687, 84JMC1253, 84S582, 85ACH305, 85H(23)1093, 85JCS(P2)1873, 85JCS(P2)1881, 85JHC593, 85JHC1253, 87H(26)869, 87JHC393, 89JCS(P2)1613, 91JHC1405⟩ (position 9), and its 2,3-benzo and 2,3-tetramethylene derivatives ⟨72JHC1281, 76IJC(B)354, 78KPS603, 79KGS684, 80MI 823-02, 81TL4816, 82NEP2602, 83OMR(21)687, 84FES968, 84JHC219, 84JHC1301, 85IJC(B)983, 86JHC53, 86MI 823-10, 86ZC251, 87JHC175, 87JHC1045, 89JCS(P2)1613⟩ (position 6), 1-oxo-2,3,4,6-tetrahydro-1*H* derivatives of the 3,4-benzologue of (**12**) (position 4) ⟨86JHC53⟩, 4-oxo-7,8,9,10-tetrahydro-4*H* derivatives of the 7,8-benzologue of (**12**) (position 10) ⟨84KFZ931⟩, and 3,7-dioxo-3,5,6,7-tetrahydro-2*H* derivatives of 1,9*a*,9-benzologues of

(**3**) ⟨70CR(C)498, 72AJC1283⟩ and (**7**) ⟨72AJC1283⟩ (position 6) took part in various electrophilic reactions.

Heating of (**25**, X = O) with Ac_2O gave the 6-acetyl derivative of (**29**, X = O) and (**26**, X = O) ⟨68ZOB2030⟩. From (**25**, X = O) a 5*a*,6,7,8,9,11-hexahydro derivative and quaternary salt (**28**) could be also obtained ⟨65ZOB1389⟩. Compound (**28**, X = S) was obtained from (**25**, X = S), its 5*a*-methoxy derivative, and (**29**, X = S) in a strong acid ⟨70TL2467⟩. The 3,4,6,7,8,9-hexahydro-2*H*-onium salt of (**4**) was converted into 9*a*-alkoxyperhydro, and its quaternary derivatives ⟨70CC900⟩. *N*-Claisen rearrangement of the aromatic salt of the *N*-allyl-9-methoxy-3,5,6,7-tetrahydro-2*H* derivative of the 1,9*a*,9-benzologue of (**3**) gave the 8-allyl derivative ⟨86CC1308⟩. An aromatic salt of 1-oxo-1,2,3,4,6,7,8,9-octahydro derivative of (**11**) was obtained from both 1-oxo-2,3,4,6,7,8-hexahydro-1*H* and 9*a*-cyano-1-oxoperhydro derivatives of (**11**) by the action of $HClO_4$ ⟨73CPB1248⟩.

9-Arylhydrazino groups in 4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) ⟨83JCR(S)161, 83JMC1126, 84JMC1253, 85ACH305, 91MI 823-07, 83OMR(21)687⟩ and its 2,3-benzologue ⟨81TL4816, 84JHC1301, 87JHC1045⟩ were introduced by the reaction of aryldiazonium chloride with 9-dimethylaminomethylene-4-oxo-6,7,8,9-tetrahydro-, and 9-formyl-4-oxo-1,6,7,8-tetrahydro-4*H* derivatives of (**12**) and its 2,3-benzologue.

Alkyl group(s) were introduced into the 2-position of the sulfone of the 2,3,4,6-tetrahydro derivative of the 7,8-benzologue of (**8**) ⟨79YZ993⟩, the 6-position of 6-cyanoperhydro derivatives of (**8**) ⟨88H(27)1575, 91SL44, 91SL878⟩ and (**12**) ⟨87JAP(K)87209067⟩, the 2-position of the sulfone of the perhydro derivative of (**5**) ⟨62AP(295)615⟩, and the 3-position of 1-ethoxy-4-oxo-3,4-dihydro-6*H* derivatives of the 7,8-benzologue of (**11**) ⟨85T2955⟩. 2-Acetoxy and 2-ethoxy derivatives were obtained from the 3,7-dioxo-2,3,6,7-tetrahydro-5*H* derivative of the 1,9*a*,9-benzologue of (**7**) ⟨72AJC1283⟩. A Pummerer reaction of the sulfone of the 6-oxo-2,3,4,6-tetrahydro derivative of the 7,8-benzologue of (**8**) yielded the 2-acetoxy derivative ⟨79YZ993⟩. A diaryl(hydroxy)methyl group was introduced into the position seven of the 2-benzyl-6-oxoperhydro derivative of (**11**) ⟨93JOC690⟩. A Leuckart–Wallach reaction of the 3,7-dioxo-3,5,6,7-tetrahydro-2*H* derivative of the 1,9*a*,9-benzologue of (**3**) furnished a 7-formylamino derivative ⟨69CR(C)564⟩.

The 4-cyano-3-methylthio-1-imino-1*H* derivative of (**10**) was reacted with morpholine and DMAD, and was treated with concentrated H_2SO_4 or AcOH ⟨75YZ13⟩. Hydrolysis of 4-cyano-3-imino-1-(thi)oxo-2,3,5,6,7,8-hexahydro-1*H* derivatives of (**10**) gave 3-oxo derivatives ⟨78MI 823-01⟩.

An elimination reaction occurred from 7-acetoxy- and 6-bromo-3-oxo-3,5,6,7-tetrahydro-2*H* derivatives of the 1,9*a*,9-benzologue of (**3**) ⟨69CR(C)564, 70CR(C)1189⟩, the 6-ethylthioperhydro derivative of (**4**) ⟨71JOC226⟩, the 3,9-dihydroxy-6-methyl-2,3-dihydro-4*H* derivative of (**8**) ⟨70ACS2949⟩, the 2-hydroxy- and 2-acetoxy-2,3,4,6-tetrahydro derivatives of the 7,8-benzologue of (**8**) ⟨79YZ993⟩, 3-hydroxy-6-oxo-2,3,4,6-, and 2-(*tert*-butylthio)-2,6,7,11*b*-tetrahydro derivatives of the 8,9-benzologue of (**8**) ⟨72ACS1620, 86S899⟩, and the 3-acetoxy-3,4,6,7-tetrahydro derivative of the 5,6-benzologue of (**10**) ⟨81CB61⟩. The *cis*-elimination of HCl from the 2-chloro-2,3-dihydro-7*H* derivative of the 1,9*a*,9-benzologue of (**7**) occurred in the presence of LiCl ⟨91JHC1067⟩.

Sulfones of 6-oxo-2,3,4,6-tetrahydro derivatives of 7,8-benzologue of (**8**) gave an 11,11*a*-dichloro adduct with Cl_2, ⟨80CPB1131⟩. 3-Aryl-3-hydroxyperhydro derivatives of (**3**) afforded 3-alkoxy derivatives by treatment with alcohols ⟨89AP(323)53⟩. The 2-methoxy-11*b*-methyl-3,4-diphenyl-2,6,7,11*b*-tetrahydro derivative of the 8,9-benzologue of (**8**) was obtained from the 2-ethoxy derivative in MeOH in the presence of concentrated H_2SO_4 ⟨86S899⟩. The 3-hydroxy group of the 2,4-dioxoperhydro derivative of (**11**) was converted into an ethylthio group ⟨74CB2804⟩.

Representatives of different tricyclic and polycyclic ring junction nitrogen systems were prepared involving the neighboring or peri positions and/or substituent(s) of (**1**) ⟨93JOC6083⟩; of the 8,9-benzologue of (**3**) ⟨92T431⟩, the 7,8-benzologue of (**7**) ⟨81CP1101857⟩, (**8**) ⟨80CL947, 94H(37)441⟩, (**10**) ⟨71JMC878, 74CPB2765, 75IZV2608, 75YZ13, 76IJC(B)391, 78YZ623, 79JCS(P1)2361, 82KGS518, 90MI 823-07, 90TL4543⟩ and its 5,6-benzologue ⟨84T4003, 86CB2553, 89H(29)1929⟩, (**11**) ⟨74HCA750, 78AJC187, 91T1065⟩, and its 7,8- ⟨72JHC177, 87TL4065⟩ and 1,9*a*,9-benzologues ⟨78KFZ89, 80CL951, 80H(14)1107, 87JCS(P1)403, 89JCS(P1)945, 89JCS(P1)965⟩, (**12**) ⟨58AP(291)298, 61M727, 65MI 823-03, 67JHC523, 71JOC2192, 75JPJ13, 78CPB680, 79GEP2757929, 82TL2891, 83EMJ227, 85CB4567, 85H(23)1093, 85H(23)1167, 85H(23)2289, 85JHC593, 87H(26)2615, 87YZ344, 88CP1232904, 90ZC98, 91IJC(B)839, 91JHC1405, 92JHC25, 92KGS1660, 92MI 823-09, 93MI 823-05⟩ and its 2,3- ⟨79NKK398, 81MI 823-04, 81TL4816, 83BCJ1775, 84GEP3300477, 84GEP3315299, 85JHC1373, 87JHC1045⟩, 3,4- ⟨73CB1595, 86CPB3672⟩, 7,8- ⟨84KFZ931, 88HCA77⟩, and 8,9-benzologues ⟨85CPB3034⟩.

9-Nitro-4-oxo-1,6,7,8-tetrahydro- and 9,9-dinitro-4-oxo-6,7,8,9-tetrahydro-4*H*- derivatives of (**12**) and its 2,3-benzologue could be prepared from 9-hydroxyimino-4-oxo-6,7,8,9-tetrahydro- and 9-formyl-4-oxo-1,6,7,8,9-tetrahydro-4*H* derivatives of (**12**) and its 2,3-benzologue using Clayfen ⟨90JOC6198⟩.

8.23.3.6 Reactivity of Substituents Attached to Ring Atoms

An ester group was hydrolyzed to a carboxyl group in 4,4*a*,5-benzologues of (**1**) ⟨92JAP(K)92208288⟩ and (**2**) ⟨90EUP373531⟩, 6,7- ⟨80JHC1729⟩ and 1,9*a*,9-benzologues ⟨70CR(C)498, 84CPB4907, 86AAC163, 86CPB4098, 87ABC1265, 87CPB1896, 88JMC1694, 88JMC2004, 89MI 823-06, 90JHC1509, 90MI 823-08, 91CCC1937, 91JHC1061, 91JHC1067, 92CCC216⟩ of (**3**), 3,4- ⟨86USP4576942⟩ and 1,9*a*,9-benzologues of (**7**) ⟨87JMC465, 91JHC1061, 91JHC1067, 91SC2301, 93JMC3449⟩, (**9**) ⟨71CPB159⟩ and its 2,3- ⟨74JHC125⟩, 3,4- ⟨87EUP226196, 88EUP294599⟩, 7,8- ⟨66YZ613⟩, and 4,4*a*,5-benzologues ⟨92EUP470578⟩ and 3,4-benzologues ⟨66AP(299)139⟩, (**11**) ⟨65ZOR2222, 92JCS(P1)1035⟩, its 2,3- ⟨1895CB119, 77JA2306⟩, and 3,4-benzologues ⟨66AP(299)139⟩ and in (**12**) ⟨95AHC(63)103⟩, and its 8,9-benzologue ⟨89AJC2161, 95AHC(63)103⟩. A carboxyl group was decarboxylated in (**9**) ⟨71CPB159⟩, (**11**) ⟨65ZOR2222, 92JCS(P1)1035⟩ and its 3,4-benzologue ⟨66AP(299)139⟩ and (**12**) ⟨95AHC(63)103⟩. A carboxylic group was converted to the higher homologue in (**2**) ⟨84JA3240⟩, to a chlorocarbonyl group in the 3,4-benzologue of (**9**) ⟨87EUP226196, 88EUP294599⟩ and was esterified in (**9**) ⟨63T1237⟩, (**11**) ⟨66JMC311⟩, and (**12**) ⟨95AHC63)103⟩.

A hydroxyl group was obtained by the hydrolysis of an acyloxy group in (**3**) ⟨85T2007⟩, its 1,9*a*,9-benzologue ⟨86AAC163, 87CPB1896⟩, (**11**) ⟨61BSF2135⟩, (**12**) ⟨84FES837⟩ and its 2,3-benzologue ⟨76IJC(B)354, 79GEP2812586, 79KPS180⟩, or by splitting of an alkoxy group in the 3,4-benzologue of (**3**) ⟨83AJC2307⟩, the 4,4*a*,5- ⟨92EUP470578⟩, 7,8- ⟨66YZ613⟩, and 8,9-benzologues of (**7**) ⟨80JHC449⟩, the 6,7-benzologue of (**9**) ⟨73JHC999⟩, (**12**) ⟨70HCA905, 71M412, 89TL1529, 91JHC1287⟩ and its 2,3-benzologue ⟨76IJC(B)354, 79JMC748, 84GEP3315299⟩, or by conversion of an amino group in the 8,9-benzologue of (**11**) ⟨84JMC995⟩. A hydroxyl group attached to the heterocyclic skeleton or a side chain was alkylated in the 4,4*a*,5-benzologue of (**2**) ⟨90CPB1575⟩, in (**9**) ⟨90JHC1673⟩ and its 4,4*a*,5-benzologue ⟨92EUP470578⟩, the 8,9-benzologue of (**11**) ⟨84JMC995⟩, and (**12**) ⟨73JHC143, 75JHC427, 84FES837, 89MI 823-07, 91IJC(B)839, 92KGS1660, 93MI 823-06, 94BMC183⟩ and its 6,7- ⟨81ZN(B)252⟩ and 8,9-benzologues ⟨89AJC2161⟩. A hydroxyl group attached to the heterocyclic skeleton or a side chain was acylated in (**2**) ⟨94JOC1358⟩, the 5,6-benzologue of (**2**) ⟨90CB803⟩, (**3**) ⟨78JMC460⟩, the 5,6-benzologue of (**6**) ⟨90CB803⟩, (**9**) ⟨71CPB159⟩, the 4,4*a*,5-benzologue of (**9**) ⟨92EUP470578⟩, the 5,6-benzologue of (**10**) ⟨61JMC505, 81CB61⟩, and (**12**) ⟨47JA2902, 52JA4906, 76JHC797, 77MI 823-01, 87EUP218423, 89EUP329126⟩. A hydroxy group was silylated and desilylated in (**3**) ⟨92BMC523, 92T431⟩.

A thiol was obtained from an alkylthio group in the 2,3-benzologue of (**9**) ⟨74JHC125⟩, from an acylthio group in (**12**) ⟨74CPB1542, 87EUP218423⟩, and from a thiourea derivative of (**9**) ⟨71CPB159⟩. A thiol was alkylated in (**9**) ⟨71CPB159⟩ and its 2,3-benzologue ⟨74JHC125⟩, and (**12**) ⟨81CCC2428, 87EUP218423, 91CPB663⟩. A thiol was also acylated in (**12**) ⟨87EUP218423, 89EUP329126⟩, and was treated with $HgCl_2$ in (**9**) ⟨71CPB159⟩, and with nitrile oxides and trichloromethyl chloroformate and then amines in (**12**) ⟨87EUP218423, 89EUP329126⟩.

An amino group was obtained by reduction of a nitro group in the 7,8-benzologue of (**8**) ⟨76GEP2756067⟩, the 2,3-benzologue of (**9**) ⟨74JHC125⟩, (**11**) ⟨81KFZ55⟩ and its 3,4- ⟨83JHC1509⟩ and 8,9-benzologues ⟨84JMC995⟩, (**12**) ⟨90JCR(S)308, 92AJC1825, 92KGS1660⟩ and its 2,3-benzologue ⟨83JHC1339, 91KFZ28⟩. The amino group can be obtained by reduction of an azido group in the 1,9*a*,9-benzologue of (**3**) ⟨89EUP306860⟩, by reduction of a nitroso group in the 8,9-benzologue of (**11**) ⟨87MI 823-02⟩ and (**12**) ⟨91IJC(B)839, 92MI 823-09⟩, by reduction of a benzylamino group in the 4,4*a*,5-benzologue of (**9**) ⟨92EUP470578, 92MIP9215584⟩, by reduction of a phenylazo group ⟨92KGS1660⟩ or by reduction of a hydrazono group in (**12**) ⟨76TL3193⟩, by hydrolysis of an acylamido group in (**7**) ⟨92BMC1293⟩, (**10**) ⟨74JCS(P1)1611⟩ and its 5,6-benzologue ⟨89H(29)1929⟩, and in (**12**) ⟨85JHC481, 95FES69⟩ and its 2,3-benzologue ⟨77GEP2557425⟩, by conversion of a hydroxy group in (**3**) ⟨92BMC523⟩, by conversion of a side chain chloro atom and tosyloxy group in (**12**) ⟨73LA103, 77MI 823-01, 86FES926, 89CCC1376, 95FES69⟩, and by conversion of an oxo group in the 4,4*a*,5-benzologue of (**2**) ⟨90CPB1575⟩ and (**3**) ⟨92BMC523, 92BMC1293⟩. An amino group attached to the heterocyclic skeleton or a side chain was alkylated in the 4,4*a*,5-benzologue of (**2**) ⟨90CPB1575⟩, the 5,6-benzologue of (**10**) ⟨82KGS518⟩, the 7,8-benzologue of (**11**) ⟨87IJC(B)761⟩, and (**12**) ⟨77MI 823-01, 92JMC1920⟩. An amino group attached to the heterocyclic skeleton or a side chain was acylated in (**2**) ⟨70LA(737)24⟩, (**3**) ⟨78JMC460⟩, (**7**) ⟨92BMC1293⟩ and its 1,9*a*,9-benzologue ⟨87JMC465⟩, in the 2,3-benzologue of (**9**) ⟨74JHC125⟩, the 5,6-benzologue of (**10**) ⟨82KGS518⟩, in (**11**) ⟨95TA321⟩ and its 8,9-benzologue ⟨87MI 823-02⟩, and in (**12**) ⟨77MI 823-01, 86FES926, 86JHC1295, 91H(32)1455, 92JHC25, 92MI 823-09⟩ and its 6,7- ⟨79CPB2927⟩ and 8,9-benzologues ⟨67IJC403⟩.

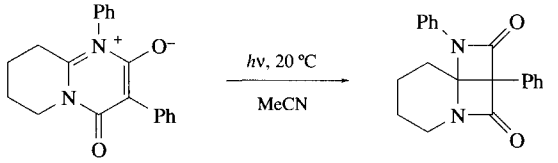
An imino group was hydrolyzed to an oxo group in (**4**) ⟨91SL44⟩, was acylated in (**10**) ⟨75YZ13, 78MI 823-01, 90MI 823-07⟩, and was alkylated in (**10**) ⟨75YZ13⟩ and (**12**) ⟨74JPJ44⟩. A hydroxyimino group in (**12**) was O-alkylated ⟨83JMC1494⟩, and was treated with diphenylboron anhydride ⟨92AP(325)23⟩. A cyano group was reduced to a CH_2NH_2 group with LAH in (**9**) ⟨66KGS91⟩ and

(**10**) ⟨69JHC181⟩. A phenyl group was nitrated in the 8,9-benzologue of (**11**) ⟨84JMC995⟩ and (**12**) ⟨83H(20)1083⟩, was reacted with $NaNO_2$ in acidic media in (**11**) ⟨59CPB1510⟩ and was reacted with $ClSO_3H$ in the 1,9*a*,9-benzologue of (**3**) ⟨86EUP184384⟩.

8.23.3.7 Electrochemical and Photochemical Reactions

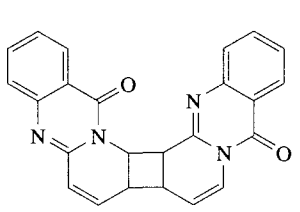
A phenylsulfonyl group was introduced into position eight of the 1-oxoperhydro derivative of (**2**) in an electrochemical reaction which could then be stereoselectively substituted by alkyl groups ⟨90SL48, 90SL749, 91T1311⟩. The electrochemical behavior of derivatives of (**13**) was investigated ⟨91T675⟩. Depending upon the reaction conditions, the 8,9-dihydro derivative or its 8,8′-dimer were obtained from the 2,6-dimethyl-3-ethyl-4-oxo-4*H* derivative of (**12**) by preparative electrolysis ⟨82MI 823-02, 84MI 823-05⟩. The electrochemical reduction of the 5,6-benzologue of (**6**) ⟨87PHA858⟩ and the 5,6-benzologues of (**10**) ⟨87PHA739, 89PHA694⟩ were studied.

Photochemistry of different pyrimidin-4(3*H*)-ones, among them 4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**), was investigated ⟨77H(8)377, 78H(9)505, 79JOC2083, 80TL3067, 81JOC1769, 83JOC2914, 83TL5237, 85JOC166, 85TL3247, 87JOC2455, 88JCS(P1)2653, 89JCS(P1)1231⟩. In the first step a Dewar pyrimidinone (e.g. **51**) was formed, which could be isolated in the case of the 2-*tert*-butyl-4-oxo-6,7,8,9-tetrahydro-4*H* derivative of (**12**) ⟨85JOC166, 89JCS(P1)1231⟩ and of (**50**) ⟨86CC687⟩. Photolysis of the 1,2,3,4-tetraethoxycarbonyl-6-ethoxy-4*aH* derivative of the 3,4-benzologue of (**12**) in MeOH resulted in a more extensively conjugated isomeric 1*H*- derivative ⟨75JCS(P1)2322⟩. Irradiation of the 11-oxo-11*H* derivative of the 2,3-benzologue of (**12**) generated a compound $[C_{12}H_8N_2O]_n$, which, on being heated or by the action of acid, yielded (**52**) ⟨78ZOR2407⟩. The four-membered ring of (**52**) is thermally labile and undergoes [2 + 2] cyclofragmentation to give quantitative regeneration of the starting compound. The photostability of (**20**) was investigated ⟨92AAC1715⟩.

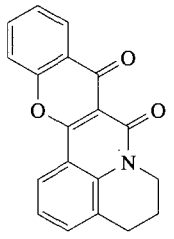


(2)

(**50**) (**51**)



(**52**)



(**53**)

8.23.3.8 Ring Transformations

The following compounds were formed by ring transformations or rearrangements. Quinolizines from (**2**) ⟨88CPB1597, 90H(30)885⟩; benzo[*c*]quinolizines ⟨71JOC2211⟩ and the 5,6-benzologue of (**10**) ⟨73JHC435⟩ from the 7,8-benzologue of (**2**); from the 4,4*a*,5-benzologue of (**2**) 4,4*a*,5-benzologues of (**6**) ⟨78JHC645⟩ and (**10**) ⟨78JHC645⟩, imidazo[2,1-*b*]pyrido[3,2,1-*ij*]quinazoline ⟨78JHC645⟩, pyrido[3,2,1-*ij*]pyrimido[2,1-*b*]quinazoline ⟨78JHC645⟩, benzo[*ij*]quinazoline ⟨78JHC645⟩, benzo-[*ij*]oxazolo[5,4-*b*]quinolizine ⟨78JHC645⟩, (**53**) ⟨79JHC829⟩, and benzo[*ij*]indolo[3,2-*b*]quinolizine ⟨80JHC1785⟩. From (**3**) (**11**) ⟨64CB3566⟩; from the 3,4-benzologue of (**3**) 1,2-dihydropyridines ⟨85H(23)2401, 89JHC847⟩; and from the 8,9-benzologue of (**3**) 3,6-benzoxazecine ⟨79CI(L)319, 80CI(L)421, 85AJC1591, 86AJC893⟩, from (**4**), (**12**) ⟨75H(3)927, 78LA1655, 79CB1585, 82ZN(B)222⟩, quinolizine ⟨79CB1585, 88CB951⟩, 4*a*,10-epoxy-1*H*-pyrido[2,1-*b*][1,3]benzazepine and dibenzo[*b*,*e*][1,4]dioxine ⟨82ZN(B)222⟩, 10-oxo-6-azatricyclo-[6.2.2.$0^{1,6}$]dodecane ⟨88CB951⟩; from the 3,4-benzologue of (**4**) pyrrolo-

[3′,4′ : 5,6]pyrido[1,2-*a*]quinazoline and pyrazino[4′,5′ : 5,6]pyrido[1,2-*a*]quinazoline ⟨89IJC(B)126, 90MI 823-09⟩, from the 6,7-benzologue of (**4**) pyrano[2,3-*b*]quinolines and pyrano[3,2-*c*]quinolines ⟨76M859⟩; and from its 8,9-benzologue 2,6-benzoxazecines ⟨85AJC1591, 86AJC893⟩; from the 4,4*a*,5-benzologue of (**6**) pyrido[3,2,1-*ij*]pyrimido-[2,1-*c*]quinazoline ⟨78JHC645⟩; from (**7**) indolizines ⟨85H(23)33, 87BCJ1867⟩, from (**8**), (**12**) ⟨76CB3668, 89JCS(P1)1231⟩, benzo[*ij*]quinolizines ⟨93JOC5040⟩, cyclopentano[*b*]quinolizinone ⟨93JOC5040⟩, quinolizine ⟨76CB3668⟩, thiazetidino[3,2-*a*]pyridine ⟨82CC1418, 83CC199⟩, [1,2,4]oxathiazolo[4,3-*a*]pyridine ⟨83CC199, 92JCS(P1)621⟩; from the 7,8-benzologue of (**8**) 1,6-methano-1*H*,3*H*-benzo[*g*]-1,5-thiazonine ⟨80CPB1131⟩; from (**9**), (**12**) ⟨77H(8)377⟩ and from its 2,3-benzologue the 2,3-benzologue of (**12**) ⟨77H(8)377⟩ and 3-(2-pyridyl)quinolin-4-one ⟨75JOC2201⟩; from the 5,6-benzologue of (**9**) the 8,9-benzologue of (**12**) ⟨77H(8)377⟩; from the 3,4-benzologue of (**9**) pyrido[1,2-*a*]indoles and 2-arylpyridines ⟨92EUP472166⟩; from (**10**) 1,6-naphthyridines ⟨80KGS1120, 82KGS518⟩; and from its 4,4*a*,5-benzologue pyrimido[5,6,1-*jk*][1,4]-benzodiazepines ⟨72MI 823-02⟩; from (**11**), other (**11**) ⟨62JCS1510⟩; from the 7,8-benzologue of (**11**) 1′-methylindene-2-spiro-2′-piperazines ⟨73CPB2661⟩; from (**12**), other (**12**) ⟨79TL1337, 85JOC2918, 86CB1445, 91H(32)1455, 95MI 823-01⟩, 1-(2-pyridyl)-2(1*H*)-pyridones ⟨72JOC600⟩, imidazo[1,2-*a*]pyrimidines ⟨54JA1845, 80KGS1656, 83H(20)1083⟩, 1,8-naphthyridines ⟨75TL1019, 77JCS(P1)789, 79H(12)1407, 79JHC457, 82JHC1017, 83H(20)1083, 83JHC1053, 87SC319, 88JCS(P2)1287, 88JHC1231, 92JHC559⟩ anthyridines ⟨92JHC559⟩, pyrano[2,3-*b*][1,8]-naphthyridines ⟨92JHC559⟩, pyrano[3,2-*c*][1,8]naphthyridines ⟨92JHC559⟩, quinolizines ⟨71JOC8⟩, quinolines ⟨77M367, 79CB3424, 83M227⟩, pyrido[1,2-*a*]-*s*-triazines ⟨77M367⟩, 2-(1-tetrazolyl)pyridines ⟨75JHC949, 76JOC3152⟩, 2-(1,2,4-triazol-4-yl)pyridines ⟨75JHC949⟩, pyridazino[3,4-*b*]quinoxalines ⟨80CPB3537, 80H(14)611⟩, 1,6-diazaspiro-[4,5]dec-2-ene ⟨77H(8)377⟩; from the 2,3-benzologue of (**12**), 1,7-benzodiazecines ⟨85AJC1007⟩, benzo[*b*][1,8]naphthyridines ⟨67TL2701, 68ZOB2051, 79JHC137⟩, pyrano[2,3-*b*]pyridine ⟨67TL2701, 68ZOB2051⟩; from its 6,7-benzologues, 7,8-benzologues of (**10**) ⟨83M227⟩, and from its 8,9-benzologue, imidazo[2,1-*a*]isoquinolines ⟨80KGS1656⟩.

8.23.3.8.1 Miscellaneous

The enantiomers of partly or wholly saturated derivatives of (**2**) ⟨85T2891, 91ACS716⟩, the 1,9*a*,9-benzologue of (**3**) ⟨86AAC163, 87CPB1896⟩, (**11**) ⟨95TA321⟩ and its 8,9-benzologue ⟨75GEP2331713, 84JMC995⟩, and (**12**) ⟨76MI 823-02, 77MI 823-02, 81T3093, 85T2465⟩ were prepared. Enantiomers of 3-carboxy-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H* derivatives of (**12**) were used as resolution agents ⟨78BRP1494725⟩. Crystalline complexes were formed from derivatives of (**12**) with $ZnCl_2$ and potassium mercury(II) iodide ⟨72AF815, 74MI 823-01, 77MI 823-03, 79MI 823-02⟩. Base catalyzed isomerization of *cis* and *trans* epimers of the 2-(3-benzisoxazolyl)-7-formylperhydro derivative of (**11**) ⟨95TA321⟩ and the 7-(*p*-chlorophenyl)-1-oxo-2,3,4,6,7,11*b*-hexahydro-1*H* derivative of the 8,9-benzologue of (**11**) ⟨89H(29)359⟩ was investigated. The base catalyzed racemization of (**18**, R = Me), derived from optically active pipecolic acid, was studied ⟨81TL3101⟩.

8.23.4 SYNTHESIS

8.23.4.1 By Formation of One Bond α to the Ring Junction Nitrogen Atom

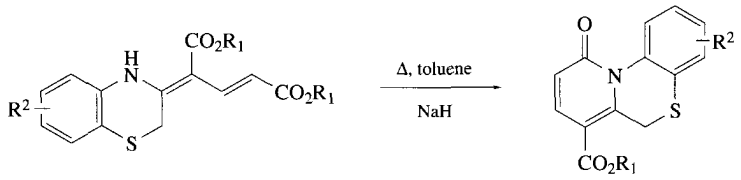
Cyclization of 6,7-difluoro-4-hydroxy-8-(2-hydroxyethyl)quinoline-3-carboxylate ⟨92JAP(K)92208287⟩, 2-(3-chlorosulfonylpropyl)piperidine ⟨62AP(295)615⟩, 1-amino-2-(2-substituted ethyl)piperidines ⟨66KGS91, 68YZ216, 78JA4012⟩ and -pyridinium salts ⟨90JHC1673⟩, 1-amino-2-(*o*-substituted phenyl)-pyridinium salt ⟨92CB929, 92JHC1049⟩, 1-amino-2-(3,3-diethoxypropyl)-1,2,3,4-tetrahydroquinoline ⟨66YZ608⟩, and 1-amino-8-(2-hydroxyethyl)-1,4-dihydroquinoline ⟨92EUP470578⟩ afforded derivatives of the 4,4*a*,5-benzologue of (**1**), (**5**), (**9**), and its 3,4-, 7,8-, and 4,4*a*,5-benzologues, respectively.

Derivatives of (**2**) ⟨86KGS1396⟩, and (**10**) ⟨67YZ663⟩ and its 5,6- ⟨63YZ1043⟩, and 7,8-benzologues ⟨60YZ1414⟩ were obtained from 2-(2-allyloxyethyl)pyridine, and from 2-[2-(acylamino)ethyl]-pyridines and their benzologues. 1-[(*N*-Acylamidino)methylene]-1,2,3,4-tetrahydroisoquinoline afforded derivatives of the 5,6-benzologue of (**10**) ⟨90CB493⟩.

2-(2-Pyridylmethoxy) ⟨60AP(293)74, 91JMC19⟩, 2-(2-piperidylmethoxy) ⟨57N584⟩, 2-(8-quinolinyloxy)- ⟨70CR(C)1189⟩, 2-(2-quinolylmethylthio)- ⟨73IJC1051⟩, 2-(1-isoquinolylmethylthio)-⟨81GEP3023717⟩-acetic acids and esters afforded derivatives of (**3**), and its 1,9*a*,9-benzologue, and the 6,7- and 8,9-benzologues of (**7**). 2-Piperidylmethyl (2-substituted ethyl) ethers ⟨58N516, 60AP(293)74, 63AP(296)38⟩ and thioethers ⟨59AP(292)165⟩ afforded perhydro derivatives of (**3**) and (**7**). Similarly

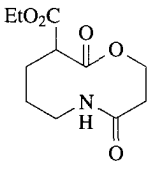
derivatives of (**11**) ⟨57N62, 59CB240, 65LA(685)181, 67YZ668, 69JCS(C)2270, 91JOC5192, 91TA231⟩, its 6,7- ⟨47HCA920, 63YZ679, 69IJC833, 72JMC351⟩, and 1,9*a*,9-benzologues ⟨59JA3984, 68JHC371, 76AP(309)966, 81IJC(B)331, 89JCS(P1)965, 92JMC1076⟩ could be prepared from the appropriately 2-substituted pyridines and their benzologues and 8-substituted quinolines. Cyclization of *N*-substituted 2-pyridinecarboxamides and their perhydro derivatives gave 1-oxo ⟨67NAT919, 76JA246⟩ and 1,4-dioxo derivatives ⟨85BCJ497, 88S963⟩ of (**11**). Cyclization of 2-piperidylmethyl allyl ether ⟨72TL4013⟩, 8-allyloxyquinolines ⟨93MI 823-07⟩ and 8-quinolylbromoacetates ⟨65UKZ1182⟩ furnished derivatives of (**3**) and its 1,9*a*,9-benzologue.

Cyclizations of 3-substituted morpholines and their benzologues and also of 2-substituted pyrazines and their benzologues afforded derivatives of (**3**) ⟨83CL21, 84H(22)1729, 89JHC847⟩ and its 3,4-benzologues ⟨85H(23)2401, 87CPB457, 89JHC847⟩, and of (**11**) ⟨61BSF2135, 83H(20)1721, 87CPB457, 89JHC847, 93JOC690⟩ and its 3,4-benzologue respectively ⟨35CB1716, 65JA1990, 83H(20)1721, 87CPB457, 89JHC847⟩. Heating of (**54**) afforded (**55**) ⟨90FES589⟩.

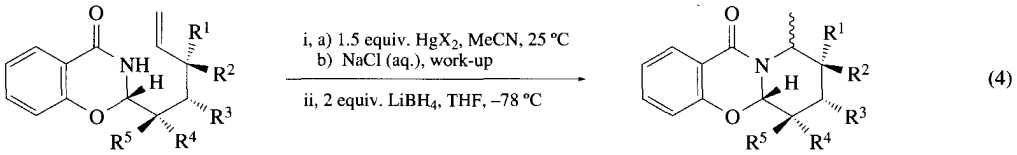


(54) (55) (3)

Cyclization of a 4-(perhydrooxazinyl)butyrate ⟨91JCS(P2)735⟩ or of (**56**) ⟨67ZOB1703⟩ furnished derivatives of (**4**). The electrophilic heterocyclizations of (**57**) and their C(2) epimers afforded diastereomeric mixtures of (**58**) and their C(5*a*) epimers, respectively ⟨89TL7321, 90TL6765⟩. Cyclization of 2-(3-substituted propylthio)pyridines and their benzologues or 2-(3-substituted propylamino)pyridines and their benzologues yielded derivatives of (**8**) ⟨73ACS1059, 80CL947, 92JOC6335⟩ and its 6,7- ⟨84KGS635, 85KFZ804⟩ and 8,9-benzologues ⟨74IJC1242, 81IJC(B)372⟩, and derivatives of (**12**) ⟨68YZ212, 81CB937⟩ and its 6,7- ⟨63YZ682, 64JMC471, 69YZ759, 73YGK313, 89MI 823-08⟩, 7,8- ⟨68CC1423, 88MI 823-11⟩, and 8,9-benzologues ⟨67IJC403⟩ respectively.



(56)



(57) (58) (4)

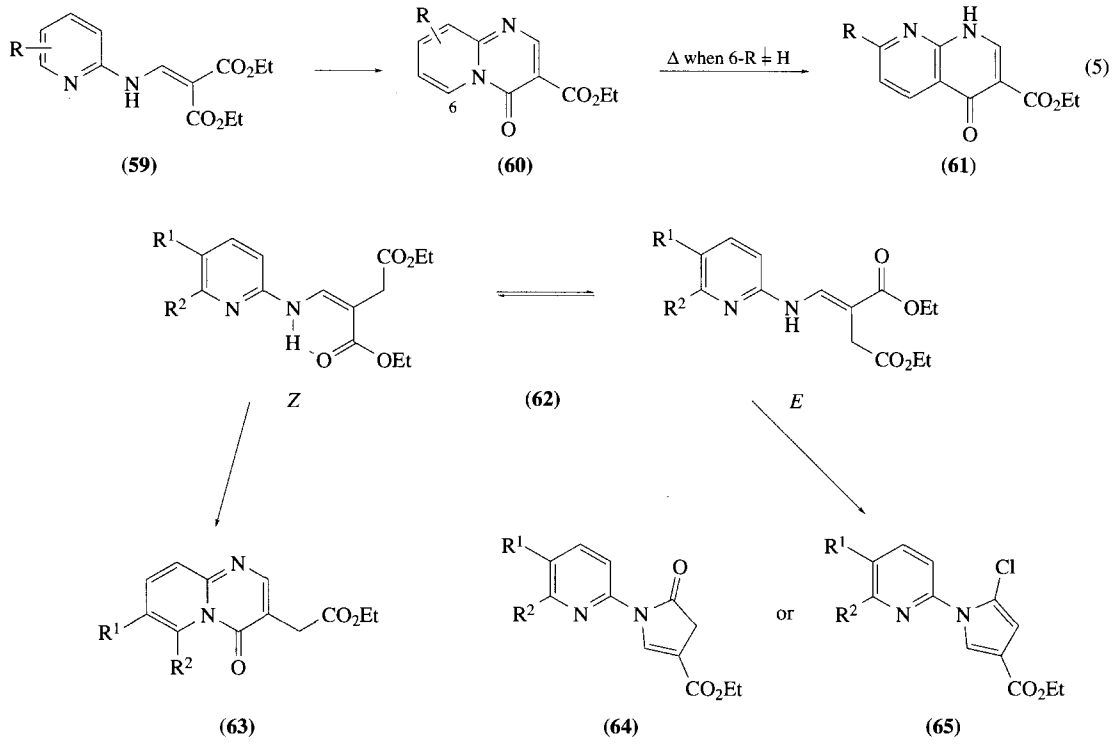
R^1 and R^2 = H, Me, Bn, OBn
R^3 = H, *c*-C_6H_{11}; R^4 and R^5 = H, Me

One of the processes most frequently used for the preparation of (**12**) and its benzologues involves the reaction of 2-aminopyridines and their benzologues with 1,3-bifunctional reagents, the resulting condensation products being cyclized in the next step. In this way pyrido[1,2-*a*]pyrimidinium salts ⟨57DOK(113)343, 73JCS(P1)1138, 78CPB3167, 90T595⟩, 2-oxo-2*H* derivatives of (**12**) ⟨72JOC600, 78KGS90, 88JCS(D)433, 88ZOR1082, 89IZV211, 90IZV2107⟩, and its 8,9-benzologues ⟨80YZ1261⟩ were prepared. 2-(Acylacetamido)pyridines gave 4-oxo-4*H* derivatives of (**12**) as a consequence of rearrangement during cyclizations ⟨25CB352, 39JGU1109, 50JGU1890, 51JCS551, 51JGU1145, 51JGU1249, 62MI 823-01, 68JOC2116, 68JOC3015, 74JHC739, 77JHC637⟩.

Ring closure of *N*-(2-pyridyl)- and *N*-(2-quinolyl)malonamates gave 2-chloro or 2-hydroxy-4-oxo-4*H*-derivatives of (**12**) and its 6,7-benzologues ⟨70HCA905, 81CCC2428, 84S152, 95EJM27⟩.

Cyclization of (**59**) and their benzologues was reviewed in 1992 ⟨92AHC(54)215⟩. The thermal cyclization of 6-substituted (**59**, 6-R ≠ H) usually yielded (**61**) ⟨48JA3348⟩ via (**60**, 6-R ≠ H)

〈77JCS(P1)789, 85JHC481〉, except for the 6,7-benzologue, which gave 6,7-benzologue of (**60**) 〈72JMC1203, 77JCS(P1)789, 78YZ1279, 84S152〉. Competitive cyclization of (**62**) afforded a mixture of (**63**), (**64**), and (**65**) 〈78JCS(P1)795, 80JCS(P1)227, 84JCS(P1)1799, 88JCS(P1)2019〉. While the thermal cyclization of the cyclic isopropylidene esters of (**59**) gave 3-decarboxylated (**60**) 〈69BRP1147760, 77JCS(P1)789, 84S152, 85JHC481, 85SC125, 89TL1529, 91JHC1287〉, cyclization in acidic media afforded (**60**) or their 3-carboxylic acids 〈80MIP17346, 84S152〉.



Scheme 6

By substitution of one of the ethoxycarbonyl groups of (**59**), different 3-substituted 4-oxo-4*H* derivatives of (**12**) 〈58JA3066, 62JOC1371, 67JHC360, 71JHC759, 72AF815, 77CB2480, 78JCS(P1)795, 79M1387, 79USP4122274, 80ZOR1483, 84S152, 84USP4457932, 85JHC481, 86T3537, 90JCR(S)308〉 and its benzologues 〈58JA3066, 77CB2480〉 can be obtained. 3-Cyano and 3-aminocarbonyl-4-oxo-4*H* derivatives of (**12**) and their benzologues could be prepared from 2-pyridylaminomethylenemalononitriles 〈74CPB243, 77ACS(B)235, 77M517, 86JOC2988〉 and their benzologues 〈82S791, 94JHC793〉.

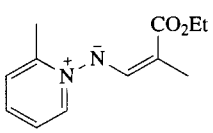
6-Oxo-6*H* derivatives of (**12**) were obtained from 3-[(4-amino-3-ethoxycarbonyl-6-oxo-1,2-dihydro-2-pyridyl)imino]-3-ethoxypropionate 〈83LA753〉 and 2-[2-(2-pyrimidyl)-2-aryl-1-ethoxyethyl]malonates 〈91MIP9116894, 93MI 823-08〉. 6-Methylene-2-methyl-6,7,8,9-tetrahydro-4-oxo-4*H* derivatives of (**12**) were prepared from 2-(1-pentyn-5-yl)-6-methylpyrimidin-4(3*H*)-ones 〈83JHC1407〉.

2,3-Benzologues of (**12**) were prepared from 2-(*o*-carboxyphenylamino)pyridines 〈55G1210, 84MI 823-06, 92MI 823-12〉, their 3,4,5,6-tetrahydro derivatives 〈59LA(623)166〉, 2-[*N*-(*o*-methylphenyl)-acetamido]pyridine 〈77GEP2557425〉, and *N*-[2-(diphenylhydroxymethyl)-2-amino]pyridine 〈65JOC1539〉. While the cyclization of 2-(4-bromobutyl)quinazolin-4(3*H*)-ones led to mixtures of derivatives of 2,3- and 3,4-benzologues of (**12**) 〈93JOC741〉, their 3,4-dihydro- and 1,2,3,4-tetrahydro derivatives gave only a derivative of the 2,3-benzologue of (**12**) 〈61AP(294)556〉. 3,4-Benzologues of (**12**) were obtained from 4-(4-oxo-1,2,3,4-tetrahydro-2-quinazolin)butyric acid 〈75USP3883524〉 and 2-(*o*-chlorobenzoylamido)pyridine 〈90JHC2005〉.

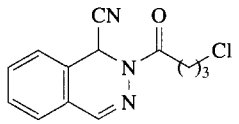
8.23.4.2 By Formation of One Bond β to the Ring Junction Nitrogen Atom

Cyclization of 2-(3-hydroxypropyl)pyridine *N*-oxide gave a derivative of (**1**) 〈58JA2217〉. Derivatives of (**9**) 〈76JOC1570〉, its 3,4- 〈80JHC433〉, and 5,6-benzologues 〈75CPB3056〉 were obtained from

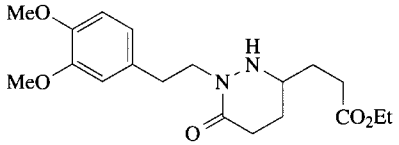
(**66**), (**67**), and (**68**), respectively. A derivative of the 4,4*a*,5-benzologue of (**9**) was obtained from 1-amino-8-(2-hydroxyethyl)-1,4-dihydroquinolin-4-one ⟨92EUP470578⟩.



(**66**)



(**67**)

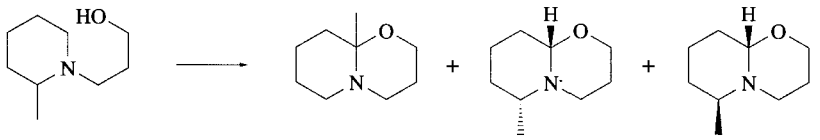


(**68**)

1-Oxo derivatives of (**2**) ⟨83H(20)1325, 86CJC2205, 90CB803, 90T4039, 92T4937⟩ and its 7,8-benzologue ⟨80JA1454, 86CPB2380⟩ were prepared from 1-(alkoxycarbonyl)piperidines and their benzologues. Cyclization of 3-(3-alkenyl)-4-ethoxy-3,4,5,6-tetrahydro-2*H*-1,3-thiazin-2-ones gave 7-formyloxy-1-oxo perhydro derivatives of (**6**) ⟨85T2007⟩, and 3,4- and 5,6-benzologues of (**10**) were obtained from a 4-cyano-3-(4-chlorobutyryl)-1,2,3,4-tetrahydroquinazoline ⟨89JHC1357⟩ and a 1-(2-phenylethyl)-2,4,6-trioxopiperidine ⟨86HCA1671, 89H(29)1929⟩.

Nucleophile-mediated cyclizations of 3-hydroxy- and 3-phenylthio-4-(3-alkenyl)-morpholines gave 8-substituted perhydro derivatives of (**3**) and its 8,9-benzologue ⟨83TL91, 85T2007, 90SL731, 92T431⟩; perhydro (**7**) were similarly prepared ⟨83TL91, 85T2007⟩. 6,7-Benzologues of (**3**) were obtained from 4-(*o*-(2,2-dicyanoethenyl)phenyl)morpholine ⟨84JOC269, 89JOC209⟩, or 1-[2-(trimethylsilyloxy)ethyl]quinolinium salt ⟨84JA6855⟩. 8,9-Benzologues of (**3**) were prepared from 4-[2-(3,4-dimethoxyphenyl)ethyl]-5-oxoperhydro-1,4-oxazine-2-carboxamide ⟨78JMC785, 85AJC1591⟩ and a 4-substituted morpholine ⟨79T2501⟩. Unstable 1,9-*a*-dihydro derivatives of (**7**) were prepared from 1-[2-(substituted methylthio)ethen-1-yl)pyridinium bromides ⟨87BCJ1867⟩. Derivatives of the 8,9-benzologue of (**7**) were obtained from 4-(2-phenylethyl)-2,3-dihydro-1,4-thiazin-3-ones ⟨80JHC449, 81CP1101857, 92KGS994⟩. Dieckman cyclization of 2-[2-(2-methoxycarbonylethyl)piperazin-1-yl)acetates gave 7-oxoperhydro derivatives of (**11**) ⟨92JCS(P1)1035⟩. [*o*-(1-Piperazinyl)phenyl)methylene)propanedinitriles ⟨87S641⟩, or 4-ethoxymethyl-3-(phenylmethyl)-1-methylpiperazin-2-one ⟨89CPB1493⟩ gave derivatives of the 6,7-benzologue of (**11**). Cyclization of 1-(3,4-dimethoxyphenethyl)-4-methylpiperazin-2-one ⟨59YZ1003⟩, 4-substituted 1-phenethyl-6-hydroxy-2-piperazinones ⟨83H(20)1731, 86JHC189⟩ or 4-acyl-1-phenethyl-1,2,3,4-tetrahydro-2-piperazinones ⟨93KGS197⟩ furnished derivatives of the 8,9-benzologue of (**11**).

Oxidation of 1-(3-hydroxypropyl)piperidines (e.g. (**69**)) and 1-(3-aminopropyl)piperidines afforded perhydro derivatives of (**4**) ⟨60JA5148, 63AP(296)38, 71JCS(B)1745, 79TL809, 80H(14)1089, 88JA4829, 88TL4153, 92T8295, 94TL1715⟩, and (**12**) ⟨71JCS(B)1745, 73AP(306)209⟩, 3,4,6,7,8,9-hexahydro derivatives of (**12**) ⟨67TL5173, 73AP(306)209⟩, and other derivatives of (**12**) ⟨77AP(310)200, 82AP(315)1032, 92AP(325)23, 92AP(325)177⟩ sometimes with ring-opened products ⟨60JA5148, 67AP(300)308⟩. Derivatives of the 3,4-benzologue of (**4**) ⟨68JCS(C)1722, 81AP(314)524, 82AP(315)119, 83TL2213⟩, and 2,3- ⟨68JCS(C)1722, 80M627, 80PHA389⟩, 3,4- ⟨70TL997, 73AP(306)541, 78AP(311)586, 79AP(312)838, 90AP(323)405, 90AP(323)889, 90AP(323)915, 91AP(324)313, 92CB1843, 92PHA243⟩, and 8,9-benzologues ⟨73JOC437⟩ of (**12**) were prepared similarly from appropriate starting materials. As oxidation agents MnO_2 ⟨68JCS(C)1722⟩, $Hg(OAc)_2$ ⟨60JA5148⟩, $Hg(OAc)_2$-edta ⟨63AP(296)38⟩, $K_3Fe(CN)_6$ ⟨71JCS(B)1745⟩, and ClO_2 ⟨88JA4829⟩ were applied. Alternatively, anodic oxidation ⟨80H(14)1089⟩ or photolysis ⟨88TL4153⟩ were used. From (**69**) the ratio of diastereomers (**70**), (**71**), and (**72**) varies with reaction conditions.



(6)

(**69**) (**70**) (**71**) (**72**)

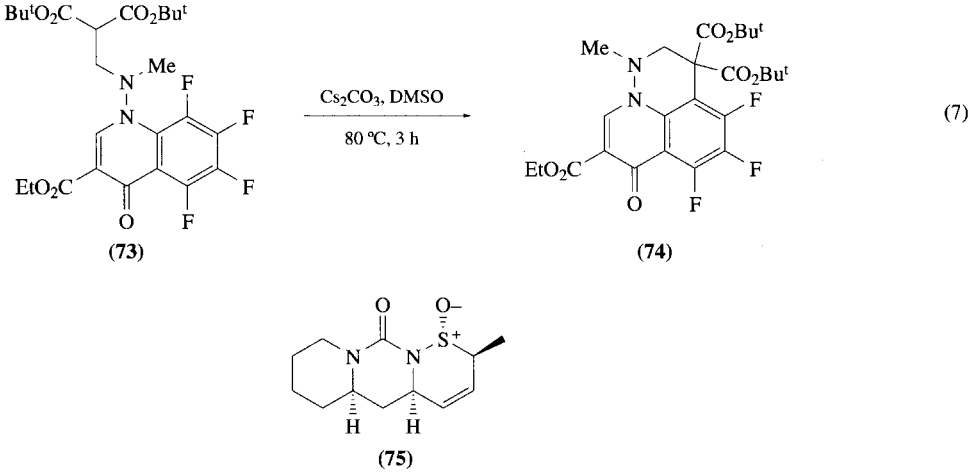
1-(3-Hydroxy or 3-aminopropyl)pyridinium salts or their benzologues gave derivatives of (**4**) ⟨77JCS(P2)759⟩ its 8,9-benzologue ⟨66AP(299)817, 85AJC1591⟩ and (**12**) ⟨78CB2594⟩ and its 3,4- ⟨73JOC437⟩ and 8,9-benzologues ⟨62CB2122, 73JOC437⟩. Cyclization of 1-(3-hydroxypropyl)-2-pyridone ⟨87CPB507⟩, 1-(3-hydroxy or 3-chloropropyl)-2-piperidones ⟨70CC900, 75CJC2791, 79TL809, 92TL507⟩ gave derivatives of (**4**). Similarly derivatives of the 7,8-benzologue of (**4**) ⟨75CJC2791⟩, the 7,8-benzologue of (**8**) ⟨79CPB2372⟩, (**12**) ⟨72AP(306)325, 85JOC166, 85TL3247⟩ and its 3,4-⟨78JAP(K)7877076⟩ and 6,7-benzologues ⟨90JOC4246⟩ were prepared from the appropriate starting materials.

Hydrogenolysis of 1-(*o*-benzyloxybenzoyl)-2-piperidones gave various derivatives of the 2,3-

benzologue of (**4**) [e.g. (**25**, X = O)] ⟨65ZOB1389, 68ZOB2030⟩. Compound (**25**, X = S) was obtained from *N*-(*o*-acetylthioxybenzoyl)-2-piperidone ⟨68AG909⟩. The 3,4- and 8,9-benzologues of (**4**) were prepared from 1-trifluoroacetyl-2-(1-piperidyl)benzenes ⟨83TL3923, 89RTC147⟩ and 2-acyl-1-methylene-1,2,3,4-tetrahydroisoquinoline ⟨92H(34)943⟩. Derivatives of (**12**) and its 3,4-benzologue were prepared from 3-piperidinopropionitrile ⟨74AG134⟩ and 1-(4-chlorobutyryl)-1,2-dihydroquinazoline ⟨86JCS(P1)2295⟩ or 1-(*o*-(azidomethyl)phenyl)glutarimide ⟨89CC602⟩.

8.23.4.3 By Formation of One Bond γ to the Ring Junction Nitrogen Atom

In a radical reaction 2-iodomethyl-1-(2-phenylvinylsulfone)piperidine gave epimers at position 3 of the 3-phenylperhydro-1,1-dioxo derivative of (**5**) ⟨77TL635⟩. Dieckmann condensation of 2-ethoxycarbonyl-3-[2-ethoxycarbonyl-1-piperidyl)imino]butyrate and its 5,6-benzologue furnished a derivative of (**9**) ⟨71CPB159⟩ or its 7,8-benzologue ⟨66YZ613⟩. Zwitterionic derivatives of (**9**) were obtained from *N*-(iminomethylene derivatives of 2-ethoxycarbonylpyridinium salts ⟨81JCS(P1)1495⟩. Cyclization of (**73**) gave (**74**) ⟨92EUP470578, 92MIP9215584⟩.



(73) (74) (75) (7)

Cyclization of 3-(3,1-benzoxazin-1-yl)-, 3-(1,2,3,4-tetrahydroquinazolin-1-yl)propionic acids and 1-(3-chloropropyl)-3,1-benzothiazines afforded derivatives of 4,4*a*,5-benzologues of (**2**) ⟨90CPB1575⟩, (**10**) ⟨72MI 823-02⟩ and (**6**) ⟨88JAP(K)88170385⟩, respectively. Cyclization of 1-(2-hydroxyethyl)-2-aminothiocarbonyl- and 2-(2-hydroxyethyl)-3-aminothiocarbonyl-1,2,3,4-tetrahydroisoquinolines afforded 5,6- ⟨83H(20)1325, 90CB803⟩ and 6,7-benzologues ⟨79GEP2848926, 80GEP3017865⟩ of (**6**). Cyclization of 2-[1-(amino(thio)carbonyl-2-piperidyl)acetates and -acetonitrile or its benzologue furnished derivatives of (**10**) ⟨56CB1642, 64JMC146, 69IJC684, 69YZ649, 75MI 823-03, 76IJC(B)784⟩ and its 5,6-benzologue ⟨95S863⟩. Derivatives of (**10**) or its 5,6-benzologues were obtained from 2-(1-acyl-2-piperidyl)acetamides ⟨85JMC1285⟩ or 1-benzylidene-2-(ethoxycarbonylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolines ⟨84T4003⟩.

Asymmetric bromolactonization of 2-(2,3-dimethylacryloyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid gave derivatives of the 6,7-benzologue of (**3**) ⟨77CL1109, 79T2345⟩.

Derivatives of (**3**) and of its 6,7-, 8,9-, and 1,9*a*,9-benzologues were prepared by cyclization of 2-hydroxymethyl-1-(2-hydroxyethyl)piperidines and their 5,6-benzologue ⟨58N516, 60AP(293)74, 61JMC187, 66JMC311, 72IJC1134⟩, from 2-hydroxyethyl-1-ethoxycarbonylmethylpyridinium salts ⟨64CB3566⟩, 2-ethoxycarbonyl-1-acylmethylpyridinium salts and their 3,4-benzologues ⟨64CB3566⟩, 1-(*o*-hydroxyphenyl)-2-ethoxycarbonylpyridines ⟨85IJC(B)182⟩, the 5,6-benzologue of 1-(2-haloacetyl)-2-(*o*-substituted hydroxymethyl)piperidines ⟨72IJC1134⟩, the 3,4-benzologue of 2-hydroxymethyl-1-cyanomethylpiperazines ⟨66AP(299)997⟩, and 1-(2-chloroethyl- or 2-haloacyl)-8-hydroxyquinolines ⟨44HCA1756, 82S692, 92MI 823-10⟩. Similarly derivatives of 6,7- ⟨81USP4273927⟩ and 7,8-benzologues ⟨86JMC784⟩ of (**7**), derivatives of (**11**) ⟨66JMC311, 67YZ668, 72CCC4060, 72JCS(P2)1374, 72TL1437, 73CCC1940, 74CB2804, 74JMC1, 87MI 823-03, 88MI 823-12, 89MI 823-09, 90MI 823-11, 90MI 823-12, 91TL1417, 93MI 823-09, 95JHC857, 95TA321⟩, its 3,4- ⟨75KGS1578, 82JHC1169, 83JHC1509, 88JCS(P1)1997⟩ 6,7- ⟨64JOC326, 69IJC833, 85JMC945⟩, 7,8- ⟨86JMC1953, 87TL4065⟩, 8,9- ⟨77E1036, 86MI 823-09, 91KGS1107, 91MI

823-05〉, and 1,9*a*,9-benzologues 〈93MIP938188〉 were prepared from the appropriate starting materials.

Dieckman cyclization of 4-(3-ethoxycarbonylpropyl)thiomorpholine-3-carboxylates 〈92BMC1293〉, 4-(2-ethoxycarbonylethyl)thiomorpholine-3-acetate 〈92BMC1293〉, and (1,4-diacetyl-2-piperazinyl)-acetonitrile 〈64MI 823-01〉 afforded derivatives of (**3**), (**7**), and (**11**). Derivatives of the 7,8-benzologue of (**11**) were obtained from 3-oximidomethyl-1-acylmethylisoquinolinium salts 〈72JHC177〉. Derivatives of the 1,9*a*,9-benzologues of (**3**), (**7**) 〈89EUP306860, 91JHC1067〉, and (**11**) were prepared by the cyclization of 3-(1,4-benzoxazin-4-yl)- 〈69CR(C)564, 70CR(C)498, 72AJC1283〉, 3-(1,4-benzothiazin-4-yl)propionic acids 〈72AJC1283〉, of (1,4-benzoxazin-4-yl)methylenemalonates 〈84CPB4907, 86EUP184384, 87ABC1265, 87JHC1509, 89MI 823-06〉, 8-fluoro-1-(2-hydroxyethyl, *O*-substituted hydroxyethyl, and 2-oxoethyl)quinolines 〈86CPB4098, 87JMC2283, 88JMC2004, 88TL1931, 90JHC1509, 90MI 823-08, 91JHC1061, 91JHC1067〉 and their 1-(2-thioethyl) derivatives 〈91JHC1067〉, and 1-(3-bromopropyl)-1,2,3,4-tetrahydroquinoxalines 〈83KGS677, 83KGS682〉.

Cyclization of 1-(1-methoxycarbonyl-5-pentanonyl)-6-hydroxy-2-piperidone 〈94JA10819〉, 1-(*o*-carboxyphenyl)-6-hydroxy-2(1*H*)-pyridone 〈81IJC(B)1050〉, or 1-(2-carboxyethyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolone 〈69MI 823-01〉 gave rise to derivatives of (**4**) and of its 6,7-benzologue. Derivatives of (**12**) and its 6,7-benzologue were prepared from 1-(3-oxo-1-propen-1-yl)-2-aminopyridinium salts 〈74JPR474, 76EGP113542〉, 1-(2,3-dichloropropyl)-2-aminopyridinium chloride 〈65MI 823-02〉, 3-(2-imino-1-pyridyl)propionic acid derivatives 〈46JGU1933, 52JA4906, 52JA5491, 55JA117, 62MI 823-02, 63ZOB1236〉 and their 5,6-benzologue 〈73JOC437〉, 3-(2-amino-1-pyridyl)acrylate derivative 〈90LA901〉 and 1-(*o*-benzoylphenyl)-2-(aminoethylpyrimidin-4-ones) 〈79CPB2927〉, 1-(3-ethoxycarbonylpropyl)quinazoline-2-carboxylate and 1-(2-chloroethyl)-2-(1-ethoxycarbonylethyl)quinazolines 〈83CPB2234〉.

8.23.4.4 By Formation of Two Bonds from [5 + 1] Atom Fragments

A derivative of the 3,4-benzologue of (**9**) was prepared from 1-amino-4,6-diphenylpyridine-2(1H)-thione 〈81AQ248〉. Reaction of 1-methyl-3-[1-(*m*-methoxyphenyl)ethyl]perhydropyridazine with formaldehyde gave a derivative of the 6,7-benzologue of (**9**) 〈73JHC999〉.

Cyclocondensation of 2-(2-piperidyl)ethanols, their benzologues, 2-(2-piperidyl)ethanethiols, their benzologues and 2-(2-piperidyl)ethylamines, or their benzologues with aldehydes or a form of formaldehyde furnished derivatives of (**2**) 〈17CB1407, 50JA358, 54JA2431, 57CLY927, 58CLY2081, 58N516, 60AP(293)74, 60CCC2179, 60JOC2028, 60M840, 63AP(296)38, 65RTC1367, 66MI 823-01, 67RZC1389, 67TL2471, 68CJC1105, 68T4423, 70LA(737)24, 70T1217, 70T3941, 71T2055, 72CC1152, 76IJC(B)777, 76JCS(P2)418, 76OMR(8)258, 85T2891, 87T935, 88TL1691〉, its 3,4-〈70T1217, 76BCJ837, 79JHC21, 91KGS124〉, 5,6- 〈66AP(299)997, 77JCS(P2)370, 90CB803, 92T4937〉, 6,7- 〈77JCS(P2)370〉, 7,8- 〈77JCS(P2)1592, 93JCR(S)170〉, and 4,4*a*,5-benzologues 〈80JCS(P2)1778, 84OMR(22)424〉; of (**6**) 〈70T3941, 82OMR(20)239〉 and its 5,6-benzologue 〈76OMR(8)258, 77JCS(P2)370〉; and (**10**) 〈59CB637, 62JOC1970, 67YZ663, 70T701, 73OMR(5)397, 90TL4543〉 and its 5,6-〈59YZ1008, 78FES237, 90KGS1665〉 and 7,8-benzologues 〈79JCS(P2)581〉. Instead of aldehydes as the C(1) unit dibromomethane 〈76IJC(B)975〉, *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine 〈80HCA1158〉, ethyl chloroformate 〈63AP(296)38〉, Me_2CO_3 〈91T1311〉, Et_2CO_3 〈62JOC1970〉, *N*,*N*-dimethylacetamide dimethyl acetal 〈80HCA1158〉, imino ester hydrochlorides 〈67YZ663〉, triethyl orthoacetates 〈90KGS1665〉, CS_2 〈62JOC1970, 71JMC878〉, 1,1′-carbonyldiimidazole 〈92JMC1076, 93JOC5035〉, BrCN 〈73AP(306)284〉, and $COCl_2$ 〈92JOC5764, 92T4937〉 were also used. 1,2,3,4-Tetrahydroquinoline-8-carboxylic acid with $COCl_2$ gave the 1,5,6,7-tetrahydro-1,3-dioxo-3*H* derivative of the 4,4*a*,5-benzologue of (**2**) 〈78JHC645〉.

Derivatives of (**10**) and its 5,6-benzologue were prepared from various 2-(2-pyridyl)- and 2-piperidineacetamides 〈57HCA1319, 72JCS(P2)1920, 80KGS1120, 82KGS518, 85JMC1285〉 and their 3,4-benzologue 〈61JMC505, 77JCS(P2)370, 81KFZ44, 82KGS1095, 84JMC1470, 90JHC957〉. Derivatives of (**10**) 〈92SL563, 92T4601〉 and its 3,4-benzologue 〈92T4601〉 were also prepared from 2-(2-imino-1-ethylidene)piperidines 〈92SL563〉 and 2-(2-aminovinyl)pyridines 〈92T4601〉. Derivatives of the 4,4*a*,5-benzologue of (**10**) were prepared from 1-aminocarbonyl-1,2,3,4-tetrahydroquinoline and aromatic aldehydes 〈73USP3709887〉. 2-(2-Pyridyl)benzodiazonium tetrafluoroborate and a nitrile afforded derivatives of the 3,4-benzologue of (**10**) 〈72GEP2043665〉.

Perhydro derivatives of (**7**) 〈59CB1510〉, (**11**) 〈59CB1510, 66JMC311, 73CPB1248〉, and its 7,8-benzologue 〈77IJC(B)70〉 were obtained from 1-(2-chloroethyl)-2-chloromethylpiperidines and their 4,5-benzologue with sodium sulfide and primary amines. Primary amines were also reacted with 1-ethoxycarbonylmethylpiperidine-2-carboxylate 〈91T1065〉 and 1-(chloroacetyl)piperidine-2-car-

boxylate ⟨72JCS(P1)2146⟩. Derivatives of (**11**) and its 7,8-benzologue were prepared from 1-(2-aminoethyl)-1,4-dihydro-4-pyridones ⟨78AJC187⟩ and 1-acetyl-3-(2,5-dimethoxyphenylmethyl)-2,5-dioxopiperazine ⟨90AJC773⟩ with aldehydes.

Derivatives of (**12**) were prepared from 2-acetoacetamidopyridines with $COCl_2$ ⟨77JHC241⟩, or PhNCO ⟨95MI 823-01⟩, from a boron complex of 2-acylamidopyridines with $HC(OEt)_3$ ⟨90IZV229⟩, and from 2-benzalamino-1-benzoyl-2(1*H*)-pyridinethione with malononitrile ⟨93JCR(S)8⟩. Derivatives of the 2,3-benzologue of (**12**) were obtained from 2-(*o*-bromoanilino)pyridines by palladium-catalyzed CO insertion ⟨87JOC2469⟩, and 2-[(3-diethylaminophenyl)amino]pyridine with 4,4′-bis(dimethylamino)benzophenone ⟨88HCA33⟩. The 7,8-benzologue of (**12**) was obtained from 2-(3-bromopropyl)-1,2-dihydroisoquinoline with $MeNH_2$ ⟨73JOC437⟩, and the 8,9-benzologue of (**12**) from 2-(*o*-methylphenyl)-1,4,5,6-tetrahydropyrimidines with 4-[2-(3,4,5-trimethoxyphenyl)ethyl]-benzoate ⟨93JMC3098⟩.

8.23.4.5 By Formation of Two Bonds from [4 + 2] Atom Fragments

1,4-Dipolar cycloaddition of 2-chloromethylpyridine *N*-oxides with cyclohexene and quinaldine *N*-oxides with DMAD furnished 2,3- ⟨81AG(E)481⟩ and 7,8-benzologues ⟨86H(24)1095⟩ of (**1**). Reaction of 2-phenyl-5(4*H*)-oxazolone with 3-[(*E*)-2-dimethylaminoethyl]pyridazine gave a derivative of (**9**) ⟨91BSB533⟩ and of the dianion of 1,4-diphenylcinnoline with 1,4-dichlorobutane a derivative of the 3,4-benzologue of (**9**) ⟨86JHC13⟩. A derivative of the 4,4*a*,5-benzologue of (**9**) was obtained from the 1-imino-1,2,3,4-tetrahydroquinolinium ion with 1,1-diphenylethene ⟨66TL2583⟩.

Derivatives of (**6**) and its 6,7- and 4,4*a*,5-benzologues were prepared from 2-(2-hydroxyethyl)piperidine with isothiocyanates ⟨76IJC(B)770⟩, from 3-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline with CS_2 ⟨79GEP2848926⟩, and from 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines with CS_2 or COS ⟨87EUP239927⟩. Derivatives of (**6**) were also obtained in the reaction of 2-(2-haloethyl)piperidines with thiourea ⟨70T3941, 82OMR(20)239⟩, and CS_2 ⟨63JOC981⟩.

Reaction of 2-piperidineacetic acid derivatives with ethyl urethane ⟨56CB1642⟩, KOCN ⟨59CB637, 64JMC146⟩, KSCN ⟨59CB637⟩ and PhNCO ⟨75CJC41, 64JMC146, 87CR(305)441⟩ gave derivatives of (**10**). Derivatives of the 5,6-benzologue of (**10**) were obtained from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acids and esters with urea, (ω-chloroalkyl)isocyanates, PhNCS, *S*-methylisothiourea, or imino ethers ⟨59YZ1008, 76IJC(B)784, 79IJC(B)277, 84JHC149, 95S863⟩. Derivatives of (**10**) were also obtained from 2-vinylpyridine and acylisocyanates ⟨75IZV2608⟩, from a 4-[(*E*)-dimethylaminoethyl]-pyrimidine and 2-phenyl-5(4*H*)-oxazolone ⟨91BSB533⟩, and of the 5,6-benzologue of (**10**) from 1-(2-methyl-3-furyl)-6,7-dimethoxy-3,4-dihydroisoquinoline with PhNCO ⟨86CB2553⟩.

By reaction of 2-carboxy and 2-ethoxycarbonylpyridium salts with 2-aminoethanols ⟨82CS147, 84JHC1609⟩, 2-aminoethanethiol ⟨84JHC1609⟩, ethylenediamine ⟨75KGS1578, 84KFZ700, 84JHC1609⟩ and *o*-phenylenediamine ⟨84KFZ700⟩ derivatives of (**3**), (**7**), (**11**), and the 3,4-benzologue of (**11**) were obtained. A derivative of the 7,8-benzologue of (**11**) was prepared in the reaction of a 3-ethoxycarbonylbenzo[*c*]pyrylium salt and ethylenediamine ⟨74KGS342⟩. Reaction of 2-hydroxymethyl-, 2-carboxy, and 2-ethoxycarbonyl-4*H*-pyran-4-ones with ethylenediamine ⟨54JA1189, 65ZOR2222, 66AP(299)139, 74JMC1, 75AP(308)489, 89MI 823-10⟩ and *o*-phenylenediamines ⟨75CAR(39)379, 85IJC(B)182, 86MI 823-08, 90JHC1837⟩ furnished derivatives of (**11**) and its 3,4-benzologue. Reaction of 3-methoxy-5,6-dihydro-2*H*-1,4-oxazine with *o*-fluorobenzoylacetate and homophthalic anhydride afforded derivatives of the 6,7- ⟨80JHC1729⟩ and 7,8-benzologue ⟨81JHC767⟩ of (**11**).

Derivatives of (**3**) were prepared from 2-hydroxymethylpyridine with bromoacetate ⟨64CB3566⟩, and from 2-hydroxymethylpiperidine with α-bromoacetophenones ⟨76JMC334, 78JMC460, 89AP(323)53⟩. Reaction of 2-chloroacetates with 2-hydroxymethylpiperidines and their 3,4- and 4,5-benzologues, or 8-hydroxyquinolines gave rise 3-oxoperhydro derivatives of (**3**) ⟨58N516, 61AP(294)468, 63AP(296)38, 72OMR(4)509⟩, its 7,8- ⟨72OMR(4)509⟩, 8,9- ⟨72OMR(4)509⟩ and 1,9*a*,9-benzologues ⟨72OMR(4)509, 92JMC1076⟩, but when the reactions were carried out in the presence of sodium in EtOH or benzene, isomeric 4-oxoperhydro derivatives of (**3**) ⟨60AP(293)74, 63AP(296)38, 72OMR(4)283⟩ and its 7,8-benzologue ⟨72OMR(4)283⟩ could be isolated. Reaction of 8-hydroxyquinolines with 1-hydroxy-, 1-bromo-, or 1-alkoxycarbonylalkynes and oxalyl chloride gave derivatives of the 1,9*a*,9-benzologue of (**3**) ⟨79PIA(A)1, 91CCC1937, 92CCC216, 92MI 823-10⟩. Derivatives of (**7**) were obtained from 2-piperidylmethanethiol and 2-chloroacetate ⟨72OMR(4)283⟩, and from 3-ethoxy-5,6-dihydro-2*H*-[1,4]thiazine with dimethyl acetonedicarboxylate ⟨72IJC323⟩. A derivative of the 7,8-benzologue of (**7**) was prepared from 3-[thio(methylthio)methylene]-1,2,3,4-tetrahydroisoquinoline-1,4-dione and

DMAD ⟨74YZ607⟩, and of the 1,9*a*,9-benzologue of (**7**) from 8-quinolinethiol with 1,2-dibromoethane ⟨93MI 823-10⟩.

Reaction of 2-aminomethylpyridines and piperidines and their benzologues with DMAD, ethylene bromide 2-chloroacetate, 2-chloropropionate, lactic acid ethyl ester methanesulfonate, chloroacetyl chloride, dialkyl oxalate, or dimethyl fumarate afforded derivatives of (**11**) ⟨65LA(685)181, 68AF1431, 72JCS(P2)1374, 91TA231, 93JHC1253⟩, and its 6,7- ⟨47HCA920, 69IJC833, 70JMC516⟩, and 8,9-benzologues ⟨59YZ1003, 84JMC995, 85KGS798, 88KGS1115, 91KGS1107⟩. Derivatives of the 1,9*a*,9-benzologue of (**11**) were prepared in the reaction of 8-aminoquinolines and their 1,2,3,4-tetrahydro derivatives with oxalyl chloride ⟨60JOC1138, 65JOC2589⟩, ethyl oxalyl chloride ⟨92JMC1076⟩, benzoin and its derivatives ⟨60JOC1138, 65JOC2589⟩, pyruvic acid ⟨68JHC371⟩, 4-phenyl-2,4-dioxobutyric acid ⟨78KFZ89⟩, diketene ⟨85H(23)1729⟩, α-bromoketones and 2-bromoacetaldehyde ⟨68JHC371, 80CL951, 80H(14)1107, 89JCS(P1)945⟩, and α-halocarboxylic acid halides ⟨89JCS(P1)965⟩. Other derivatives of (**11**) and its 8,9-benzologue were prepared from 2-pyridine- and 2-piperidinecarboxamides with 1-bromoacetate ⟨90JHC1673⟩ and hydroxymaleic anhydride ⟨74CB2804⟩, respectively, and from phenyl 2-pyridyl ketimine and chloroacetyl chloride ⟨90JHC1673⟩, 1-[bis(alkoxycarbonyl)methyl]pyridinium enol betaines, and their 3,4-benzologues with iso(thio)cyanates ⟨71M1120, 93T3185⟩. Derivatives of (**11**) ⟨87AG(E)143, 88LA1025, 91BSB533⟩ and its 3,4- ⟨80JCS(P1)1384⟩, and 7,8-benzologues ⟨78JOC3536⟩ were also prepared from pyrazine and quinoxaline derivatives.

Derivatives of (**4**) were obtained from 1-chloromethyl-2(1*H*)-piperidone with 1-ethoxy-2-methylpropene ⟨91ZOB2743⟩, from valerolactim ethers with diketene ⟨75H(3)927⟩ and 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione ⟨86MI 823-11⟩. Derivatives of the 2,3-benzologue of (**4**) were prepared from 2-styryl-4*H*-1,3-benzoxazin-4-ones with maleic anhydride ⟨91IJC(B)754⟩, the 3,4-benzologue of (**4**) from 2-styryl-4*H*-3,1-benzoxazin-4-ones with diethyl maleate ⟨89IJC(B)126, 90MI 823-09⟩, the 6,7-benzologue of (**4**) from di(trichloroacetyl)carbodiimide with quinoline ⟨73IZV456⟩, and the 8,9-benzologue of (**4**) from 3,4-dihydroisoquinolines with acylthioketenes ⟨88CB1165⟩. Cycloaddition of butadienes with 2-ethoxy-1,3-benzoxazin-4-one or 1,3-benzothiazin-4-one furnished derivatives of the 2,3-benzologue of (**4**) ⟨71JHC865⟩ and (**8**) ⟨73JHC149⟩. Derivatives of (**8**) and its 2,3- and 8,9-benzologues were prepared from 4-phenyl-6-chloro-2(1*H*)-pyridone and 3-aminopropanethiol ⟨79CPB1207⟩, from 2-cyanomethyl-4*H*-benzo[*c*]-1,3-thiazin-4-one with benzoylacetonitrile ⟨86MI 823-12⟩, and from 3,4-dihydroisoquinolines with 3-thiopropionic acids ⟨69FRP1552211, 87MI 823-04⟩.

Reaction of 2-halopyridines, their 3,4,5,6-tetrahydro derivatives, or their 5,6-benzologue with 3-aminoacrylates, anthranilic acids and their esters afforded derivatives of (**12**) ⟨51JCS551, 72CPB142⟩, its 2,3- ⟨38CB1657, 55G1210, 56JCS4694, 78HCA1146, 79CB3424, 79GEP2812586, 79JMC114, 79JMC748, 80JCS(P1)633, 80JMC92, 82JMC742, 83JMC1638, 83ZN(B)248, 84AP(317)824, 87JMC1543, 87JOC2469, 88JMC466, 88JMC707, 92MI 823-12, 92MI 823-13⟩, and its 6,7-benzologues ⟨51JCS551⟩. Reaction of δ-valerolactam and 3-aminocrotonate also give a derivative of (**12**) ⟨91KPS394⟩. Derivatives of the 2,3-benzologue of (**12**) were also prepared by cyclocondensation of anthranilic acids with valerolactim ethers ⟨59LA(623)166, 61ZOB189, 65CC267, 66AJC151, 68ZOB2030, 76IJC(B)354, 83JHC93, 83JHC393, 86JHC53, 87JMC1543⟩ δ-valerolactams ⟨62CB2182, 76H(4)1487, 77JA2306, 77KPS544, 84FES968, 85IJC(B)983, 86JHC53, 87JMC1543, 88IJC(B)937, 91KFZ28⟩, and from isatoic anhydride with valerolactim ethers, or δ-valerolactams ⟨35CB2221, 38CB1657, 59LA(623)166, 67TL2701, 68JCS(C)1722, 68ZOB2030, 68ZOB2051⟩. Anthranilonitrile ⟨75JCS(P1)2182⟩, perhydroanthranilic acids ⟨79JCS(P1)1765, 84H(21)678, 90PHA109⟩, and 3,4-tetramethyleneazetidinone ⟨70CB1797, 79JCS(P1)1765⟩ were also used.

Derivatives of (**12**) were prepared from valerolactam with 3-aminopropionic acids ⟨65JPR18⟩ and aminomethylenemalononitrile ⟨75AJC119⟩, from ethyl *N*-(2-pyridyl)formimidate ⟨75CPB2251, 83CPB2899, 83H(20)597, 84MI 823-07, 85CPB2671⟩, 2-pyridyl iso(thio)cyanates ⟨74CPB1542⟩, *N*-(2-pyridyl)-N′,N′-dimethylformamidine ⟨77CPB3360⟩, and Schiff bases, derived from 2-aminopyridines and aldehydes, ⟨75CPB2251, 76CPB2532, 78T101, 84JHC407, 84MI 823-07, 85CPB2671⟩ with ketene, chloroketene, dichloroketene, diketene, diphenylketene, or from 1-phenyl-2-oxo-1,2-dihydropyridin-5-carboxylate and 1,3-diaminopropane ⟨94JHC393⟩. The Schiff bases, prepared from 2-aminopyridine or its 3,4- and 5,6-benzologues with aromatic aldehydes, reacted with $(Cl_3CCO)_2O$ to give 2-aryl-3-chloro-4-oxo-4*H*-derivatives of (**12**) and of its 8,9- and 6,7-benzologues ⟨77CPB1607⟩.

6-(Thi)oxo-6*H* derivatives of (**12**) were prepared from a 2-(2-pyrimidinyl)acetaldehyde with malonates ⟨91MIP9116894⟩, and from a 2-amino-1-benzoyl-2(1*H*)-pyridinethione with benzylidenemalononitrile ⟨93JCR(S)8⟩.

Derivatives of the 2,3-benzologue of (**12**) were also obtained from 5-nitroanthranilic acid with 4-$MePhSO_2Cl$ in pyridine ⟨72KGS1003, 72KGS1341⟩, from 2,1-benzoisothiazolin-3-one in pyridine ⟨84JHC369⟩, from 2-(1-cyano-2-arylvinyl)quinazolin-4(3*H*)-ones with CH-acid compounds ⟨90JPR610⟩, from *o*-chloromethylaniline with 2-chloropyridine and its tetrahydro derivative ⟨62CB2182⟩, from *o*-aminoacetophenone with 2-bromopyridines ⟨65JOC1539⟩, and from 3,4,5,6-

tetrahydropyridines with 2-aminobenzaldehydes ⟨48LA(559)1, 51CB690, 52CB937, 53CB918, 56CB335, 66LA(692)200, 68CB1, 83T3549⟩. Reaction of 2-aminobenzamide and δ-valerolactone in a sealed tube at 270 °C furnished a mixture of the isomeric 2,3-benzologue of 6,7,8,9-tetrahydro-4-oxo-4*H* and 3,4-benzologue of 6,7,8,9-tetrahydro-2-oxo-2*H* derivatives of (**12**) ⟨73CB1595⟩. The cyclocondensation of 2-pyridylisothiocyanate with 1-morpholinecyclohexene ⟨81CCC2428⟩, and that of 2-(2-arylvinyl)-4(3*H*)-quinazolinones with maleic acid or its diethyl ester ⟨73MI 823-03, 81IJC(B)290⟩ yielded derivatives of the 3,4-benzologue of (**12**). Derivatives of the 8,9-benzologue of (**12**) were obtained from isoquinoline *N*-oxide with dimethylsulfonium acetylcarbamoylmethylide ⟨80YZ1261⟩, from 3,4-dihydroisoquinoline with 3,3-di-*tert*-butyl-1-phenylsulfonyl-4-thioxo-2-azetidinone ⟨88CB689⟩, and from 6,7-dimethoxy-1-methylthio-3,4-dihydroisoquinoline with 3-imino-3-morpholinopropionate ⟨90T1323⟩.

8.23.4.6 By Formation of Two Bonds from [3 + 3] Atom Fragments

Reaction of *N*-aminopyridinium salts with cyclopropenones (but not diphenylcyclopropenone) ⟨75JOC2985⟩, or *N*-(*p*-toluenesulfonyl)diphenylcyclopropenimine, afforded 3-oxo- and 3-(*N*-*p*-toluenesulfonylimino)-4*H* derivatives of (**9**) ⟨78JOC2892, 84H(22)1709⟩. Similar reaction from isoquinolinium *N*-amides gave derivatives of the 5,6-benzologue of (**9**) ⟨83JOC1084⟩.

Reaction of 1-methoxycarbonyl-1,4,5,6-tetrahydropyridine and 2-iodophenol furnished the 6-oxo-6,10,11,11,*a*-tetrahydro derivative of the 3,4-benzologue of (**2**) ⟨90JOC2464⟩. Derivatives of (**10**) were prepared from 2-pyridineacetonitriles and acetates with *N*-cyanodithioiminocarbonate and *O*-ethyl-S-methyl-*N*-cyanothioiminocarbonate ⟨74CPB2765, 75YZ13⟩, and from 4-formylpyridine ⟨80LA542⟩ and 2-(dicyanomethylene)pyridine ⟨78MI 823-01⟩. Derivatives of the 5,6-benzologue of (**10**) were prepared from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate hydrochloride with HOCN ⟨69IJC684⟩ and from 1-methyl-3,4-dihydroisoquinoline with benzoyl isocyanate and ethoxycarbonyl isothiocyanate ⟨75CB1541⟩.

Reaction of ethyl picolinates and their 3,4-benzologue ⟨85MI 823-04⟩ with 2-bromoethanol ⟨64CB3566⟩ and ethylene oxide ⟨66JMC311, 85MI 823-04⟩, of picolinic acid and ethylene carbonate ⟨74BCJ405⟩, and of picolinaldehyde and 2-bromoethanol ⟨78JHC347⟩ gave derivatives of (**3**) and of its 7,8-benzologue. Reaction of 2-hydroxymethyl-4-benzyloxypyran-4-one and glycine afforded a derivative of (**3**) ⟨83AJC2307⟩.

Derivatives of the 3,4-benzologues of (**3**) and (**11**) were prepared from 3-ethoxycarbonylmethyl-2-oxo-2*H*-1,4-benzoxazine, or from 2-methyl-, 2-benzyl-, and 2-ethoxycarbonylmethylquinoxalines with bis(2,4,6-trichlorophenyl) malonates ⟨77M103⟩. Reaction of ethoxymethylenemalonate with 7,8-difluoro-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine and $B(OAc)_3$ ⟨91MI 823-08⟩, with 3,4-dihydro-4*H*-[1,4]benzothiazines then with ppa ⟨87JMC465, 93JMC3449⟩, or with 1,2,3,4-tetrahydroquinoxalines then with ppa ⟨80JAP(K)8049379, 82USP4348521⟩ furnished derivatives of the 1,9*a*,9-benzologue of (**3**), (**7**), and (**11**), respectively. After several unsuccessful experiments ⟨85H(23)1619, 87JCS(P1)1027⟩ 10-oxo derivatives of the 3,4-benzologue of (**7**) were obtained when 3-(alkoxycarbonylmethylene)-3,4-dihydro-2*H*-1,4-benzothiazines were reacted with DMAD ⟨86USP4576942, 90FES577⟩. Other derivatives of the 3,4-benzologue of (**7**) were obtained from 1,4-benzothiazine with methyl propiolate, diethyl ethoxymethylenemalonate, and 1,3-dimethoxycarbonyl-1,2-propanediene ⟨90FES589⟩.

Derivatives of (**11**) ⟨60JOC2108, 69JHC181, 73CPB1248⟩ and its 7,8-benzologue ⟨64JOC326, 73CPB2039, 75IJC230, 77IJC(B)70⟩ were prepared from 2-piperidinecarboxylates or their 4,5-benzologues and ethyleneimine. Derivatives of the 3,4-benzologue of (**11**) were prepared from 2-formylquinoxaline ⟨80LA542⟩, 3-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinolin-2-one ⟨90FES589⟩, and 2-trimethylsilylmethyl-3-methylquinoxaline ⟨92NKK1455⟩. The 1-acetyl-1,2,3,5,6,7-hexahydro derivative of the 1,9*a*,9-benzologue of (**11**) was prepared from 1-acetyl-1,2,3,4-tetrahydroquinoxaline with 1,3-dibromopropane ⟨83KGS677⟩.

Reaction of 2-pyridone with 1,3-diiodopropane ⟨60CB61⟩, or of 2-pyridone, 2-piperidone or their 5,6-benzo derivatives with malonyl dichloride and chlorocarbonyl ketenes afforded derivatives of (**4**) ⟨78LA1655, 79CB1585, 82ZN(B)222, 88CB951⟩ and its 6,7-benzologue ⟨76M859, 79CB1585⟩. Reaction of 3,4,5,6-tetrahydropyridine and its 2,3-benzologue with diphenylcyclopropenone gave a derivative of (**4**) and its 9,9*a*-benzologue ⟨86S899⟩. A derivative of (**4**) was also obtained in the reaction of lithio salt of 2,4,4,6-tetramethyl-5,6-dihydro-4*H*-1,3-oxazine and 1,3-dibromopropane ⟨73JOC36⟩.

Reaction of 2(1*H*)-pyridinethiones and their 3,4-benzologues with 1,3-dihalopropanes afforded derivatives of (**8**) ⟨70ACS2949, 81JCR(S)208⟩ and its 8,9-benzologue ⟨72ACS1620⟩. Derivatives of (**8**)

were prepared from 2(1*H*)-pyridinethiones and their tetrahydro derivatives with malonyl chlorides ⟨72S312, 93JOC5040⟩, C_3O_2 ⟨72S312⟩, (chlorocarbonyl)phenyl ketene ⟨93JOC5040⟩ benzylidenemalononitrile ⟨90MI 823-13, 92MI 823-14⟩ acryloyl chloride ⟨94H(37)441⟩, or diphenylcyclopropenone ⟨71LA(752)136⟩ and from 2-(alkoxycarbonylmethylene)-3,6-dihydro-1,3-thiazine-4-carboxylate with acrylic acids, or propiolic acid ⟨81CC395, 91JCS(P1)3077⟩. Derivatives of the 8,9-benzologue of (**8**) were prepared from 1-substituted 3,4-dihydroisoquinolines with diphenylcyclopropenethione ⟨79TL1213, 86S899⟩, and from 1-thio-4-cyano-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one with 3-bromopropionic acid ⟨89MI 823-11⟩.

The most frequently used synthetic method for the preparation of pyrido[1,2-*a*]pyrimidines and their benzo derivatives is to react a 2-aminopyridine or its benzo derivative with a 1,3-bifunctional compound; 6-substituted 2-aminopyridines (e.g. 2-amino-6-methylpyridine and 2-aminoquinoline) sometimes reacted differently from the 6-unsubstituted 2-aminopyridines.

Aromatic salts of (**12**) were prepared from 2-aminopyridines with 1,3-dioxo compounds ⟨72UKZ262, 73JCS(P1)1138, 73JHC821, 75UKZ186, 90ZAK502, 91KGS1381, 91TL4307⟩ or their acetal and ketal equivalents ⟨57DOK(113)343, 58DOK(118)297, 71JOC2457, 72UKZ262, 73JCS(P1)1138, 78CPB3167, 91KGS1381, 91TL4307⟩ in acidic media ($HClO_4$ or concentrated HBr). 1,2-Diaminopyridinium iodide has also been used instead of 2-aminopyridine ⟨73JHC821⟩, and, instead of 1,3-diketones, triacylmethanes ⟨72UKZ262⟩, β-chlorovinyl aldehydes ⟨73KGS242⟩, β-chlorovinyl ketones ⟨58DOK(118)297, 74JPR474, 75UKZ186⟩, propargylaldehyde ⟨74JPR474, 76EGP113542⟩, ethynyl phenyl ketone ⟨74JPR474, 76EGP113542⟩, 2,6-diphenylpyrylium perchlorate ⟨83KGS893⟩, and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-dichloro-3-iminium-1-propenylamine chloride ⟨79ACH29⟩. The reactions of β-oxo acetals and β-chlorovinyl aldehydes with 6-unsubstituted 2-aminopyridines gave rise to 4-substituted salts of (**12**), and those with 6-substituted 2-aminopyridines to 2-substituted salts of (**12**) ⟨73JCS(P1)1138, 73KGS242⟩. β-Chlorovinyl ketones afforded either 4-substituted or 2-substituted salts of (**12**) ⟨57DOK(113)343, 74JPR474, 76EGP113542, 78ZC121⟩. Similar reactions were carried out with 1-aminoisoquinoline ⟨74KGS1148⟩. Derivatives of the 2,3-benzologue of (**12**) were prepared from 2-aminopyridinium salts with 1-formyl-2-chlorocyclohexene ⟨73KGS242⟩ or with 2-acetylcyclohexanone ⟨73JHC821⟩.

2-Oxo-2*H* derivatives of (**12**) and its 8,9-benzologue were obtained in the reactions of 2-aminopyridines and isoquinoline ⟨72CB108⟩ with 2-bromo-1-alkenecarboxylic acids ⟨52JA5491, 72CPB142⟩, phenylpropiolic acid chloride and 2-bromo-3-phenylacrylic acid chloride ⟨78KGS90⟩, alkyl propiolates ⟨61JOC2350, 61MI 823-01, 67JHC360, 72CB108, 78JHC801⟩, ethyl tetrolate ⟨73JHC821⟩, or 3-dimethylaminocarbonylfuro[2,3-*b*]quinoxaline ⟨80CPB3537, 80H(14)611⟩. 2-Aminopyridines gave 4-amino-2-oxo-2*H* derivatives of (**12**) in reversible reactions with ethyl cyanoacetate in benzene at 14 kbar and 80 °C ⟨89IZV211, 90IZV2107⟩. The reactions of 6-unsubstituted 2-aminopyridines with allenic nitriles and phenylpropynenitrile afforded unstable 2-imino-2*H* derivatives of (**12**), which sometimes underwent ring opening during work-up ⟨88JCS(P1)975⟩. Derivatives of the 6,7-benzologue of (**12**) were prepared from 2-aminoquinoline and *N*,*N*-disubstituted malonamates ⟨95EJM27⟩.

2-Oxo-3,4-dihydro-2*H* derivatives of (**12**) and its 6,7-benzologue ⟨63YZ682, 71KGS482⟩ were prepared in the reactions of 2-aminopyridines or their 5,6-benzologue with alkyl 3-halopropionates ⟨38CB1261, 46JGU1933, 52JA4906, 58JOC1358, 59PIA(A)31, 61MI 823-01, 70CPB1064, 71CPB764, 84MI 823-08⟩, 3-halopropionic acids ⟨52JA4906, 52JA5491, 55PIA(A)289, 64MI 823-02⟩, or alkyl acrylates ⟨52JA5491, 58JOC1358, 59PIA(A)31, 61MI 823-01, 62MI 823-02, 71KGS215, 92KGS80⟩.

In some cases, isomeric 2-oxo-2*H* and 4-oxo-4*H* derivatives of (**12**) and their benzologues are formed simultaneously. The reactions of 2-aminopyridines or 1-aminoisoquinoline with *N*,*N*-disubstituted malonamates containing $POCl_3$ afforded mixtures of 2-oxo-2*H* and 4-oxo-4*H* derivatives of (**12**) ⟨82FES747, 87JHC329, 88FES705⟩ or its 8,9-benzologue ⟨95EJM27⟩. 2-Oxo-2*H* and 4-oxo-4*H* isomers of (**12**) were obtained from reaction of 2-aminopyridine with *N*-phenylmalonamate ⟨87JHC329⟩, or with *N*-cyclohexyl-*N*-(2-pyridyl)carbodiimide and allenic acid ⟨92HCA1262⟩. 2-Oxo-2*H*- and 4-oxo-4*H*-6,7,8,9-tetrahydro derivatives of (**12**) were also formed from 2-amino-3,4,5,6-tetrahydropyridine with β-oxo esters and ethoxymethylenemalonate ⟨82JHC909, 82UP 823-01⟩. From 2-aminopyridines and diethyl 2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxylate, isomeric 11-oxo-11*H* derivatives of the 2,3-benzologue and 6-oxo-6*H* derivatives of the 3,4-benzologue of (**12**) were formed ⟨92PHA336⟩.

The reactions of 2-aminopyridines, 2-amino-3,4,5,6-tetrahydropyridine, 1-aminoisoquinoline ⟨72CB108, 84S152⟩ and β-oxo esters, usually under acidic conditions (most frequently in ppa or in a mixture of $POCl_3$ and ppa) afforded 2-substituted or 2,3-disubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones ⟨25CB352, 39JGU1109, 40JGU1065, 49JOC453, 50JGU1890, 51JCS551, 51JGU1145, 51JGU1249, 68JOC2116, 68JOC3015, 70JCS(C)829, 71JCS(C)2163, 72AF815, 72JHC935, 73JHC123, 73JHC143, 73LA103, 74JHC739, 75BCJ591, 75JHC427, 76AP(309)959, 76CB2908, 76JHC797, 77AP(310)26, 77JCS(P1)789, 77JHC637, 77MI 823-01, 78FES315, 78JHC1047, 79JHC457, 79JMC114, 82JHC1017, 83H(20)1083, 83JHC1053, 83PHA218, 84FES837, 84S152, 87SC319,

90JHC881, 92MI 823-15, 93IJC(B)978, 95FES69〉. When alkyl 2-oxocyclohexanecarboxylates were used, derivatives of the 2,3-benzologue of (**12**) were obtained 〈75BCJ591, 78HCA1146, 79JHC137, 79MI 823-03, 80JCS(P1)633〉. 2-Acetylbutyrolactones 〈72S151, 73LA103, 77MI 823-01〉, 3-methyl-2-thioxene-2-carbonyl chloride 〈73CJC2650〉, 3-aminoacrylates 〈51JCS551, 62JOC1371, 73JHC143, 77JHC637, 77JHC1419〉, or cyclic *β*-oxocarboxamides 〈79JHC137〉 have also been used instead of *β*-oxo ester. Acetoacetate has also been replaced by diketene 〈44JA1805, 64CPB910, 69CB455, 72CPB142, 73JHC123, 73JHC143, 74JHC739, 77JHC241〉. 1-Aminoisoquinoline did not react with ethyl benzoylacetate 〈72CB108〉.

Derivatives of (**13**) and their 8,9-benzo derivatives, which may exist in different tautomeric forms, were prepared from 2-aminopyridines or 1-aminoisoquinoline 〈72CB108, 90T1323〉 with dialkyl malonates on heating (e.g. in Dowtherm A) 〈24CB1168, 50JOC377, 54RTC376, 58AP(291)298, 62JOC1371, 63MI 823-01, 64JPR150, 67JHC523, 67MI 823-01, 72M426, 79JMC114, 84MI 823-09, 89MI 823-07, 90ZC98, 91T675, 93MIP23398, 94BMC183〉. Cyclocondensation could be carried out under both acidic 〈68JOC3015, 72AF815, 74JHC739, 83PJC607〉 and basic conditions 〈70HCA905〉. Compound (**13**) was prepared from 2-aminopyridine and malonic acid in the presence of $PhSO_2Cl$ in boiling pyridine 〈83PJC607〉. The cyclocondensation of 1-amino-6,7-dimethoxy-3,4-dihydroisoquinoline with malonic acid in $POCl_3$ afforded a derivative of the 8,9-benzologue of (**12**) 〈90T1323〉. The reactions of 2-aminopyridines and their 5,6-benzologue with diethyl malonate in a mixture of $POCl_3$ and ppa led to the 2-chloro-4-oxo-4*H* derivative of (**12**) and its 6,7-benzologue 〈72AF815, 84S152〉. The reactions of 2-amino-3,4,5,6-tetrahydropyridines and diethyl malonates furnished 2,4-dioxo-2,3,6,7,8,9-hexahydro-4*H* derivatives of (**12**) 〈73GEP2245386, 75S426〉. The reaction of 2,2-diethylmalonyl chloride or malonate with 2-aminopyridine did not give a derivative of (**12**) 〈24CB1168, 37G327〉, but 1-aminoisoquinoline and its 3,4-dihydro derivative did afford 3,3-diethyl-3,4-dihydro- and -3,4,6,7-tetrahydro-2,4-dioxo derivatives of the 8,9-benzologue of (**12**) 〈69YZ649〉. The thermal reactions between 2-amino-6-substituted pyridines and 2-monosubstituted malonates at around 250 °C gave 1,8-naphthyridines 〈54RTC376, 88JHC1231〉. When an active ester of a malonate [bis(2,4,6-trichlorophenyl) 〈71M412, 71M781, 72M426, 76ZN(B)500, 81JMC1284, 85CB4567, 86CC687, 88JHC1231〉 or bis(pentachlorophenyl) 〈76T2117, 88JHC1231〉] was used, the cyclocondensation proceeded at lower temperature and 2-amino-6-substituted pyridines gave also derivatives of (**12**) 〈88JHC1231〉. Malonyl dichlorides 〈28GEP451733, 61MI 823-02, 61MI 823-03〉 and C_3O_2 〈62M1441, 67KGS221, 71JOC8, 71M781, 72CB108, 74AG529〉 have also been used. 2-(Substituted amino)pyridines, and their 3,4-benzologue gave mesoionic 1-substituted 4-oxo-4*H* derivatives of (**12**) 〈71M412, 71M781, 76ZN(B)500, 81JMC1284, 85CB4567, 86CC687, 91AP(324)863〉 or its 8,9-benzo derivative 〈81JMC1284〉. 2-(Arylamino)quinolines reacted with 1-chloro-formyl-1-benzylketene 〈79CB1585〉, and with bis(2,4,6-trichlorophenyl) 2-substituted malonates 〈83M227, 91AP(324)863〉 to yield derivatives of the 6,7-benzologue of (**12**).

11*H*-Pyrido[2,1-*b*]quinazolin-11-ones were prepared from 2-aminopyridines and 2-chlorobenzoic acids or esters, or from 2-halopyridines and anthranilic acids 〈24LA(440)311, 68IJC758, 78ZOR2407, 83ZN(B)248〉. The cyclocondensation of 2-aminopyridine and ethyl 2,5-dihydro-5-oxo-2-aryl-isoxazole-4-carboxylates at 200 °C gave the 3-aminocarbonyl-2-hydroxy-4-oxo-4*H* derivative of (**12**) 〈93JHC33〉.

While the reactions of perfluoro-2-methyl-2-pentene with 2-aminopyridine or its 4-methyl derivative furnished 2-pentafluoroethyl-3-trifluoromethyl-4-(2-pyridyl)imino-derivatives of (**12**) that with 2-amino-6-methylpyridine gave an 1,8-naphthyridine derivative 〈74CC134〉.

6-Oxo-6*H* derivatives of (**12**) were prepared from various 2-methyleneperhydropyrimidines with methyl propiolate, DMAD, methyl acrylate and ethyl 3-bromopropionate 〈84CB1856, 84CB1926, 86H(24)2247, 87CB1803, 87TL1527, 89SC1801, 93BCJ2118, 93JCS(P1)1085, 93SC1039, 94H(37)1233〉. The reaction of 2-[(*E*)-2-(*N*,*N*-dimethylamino)ethyl]pyrimidine with 2-phenyl-5(4*H*)-oxazolone gave 6-benzoylamido-6*H*-pyrido[1,2-*a*]pyrimidin-6-one 〈91BSB533〉.

The reactions of 2-aminopyridines and 2-(substituted amino)pyridine with epichlorohydrin gave rise to hydrochlorides of 3-hydroxy-3,4-dihydro-2*H* derivatives of (**12**) 〈35CB397, 65MI 823-01, 75MI 823-02〉 and their 1-substituted derivatives 〈65MI 832-02〉, respectively. In place of epichlorohydrin, 1-bromo-3-chloro-2-propanol has been used 〈84MI 823-08〉. A 3,4-dihydro-2*H* derivative of (**12**) was prepared in the reaction of 2-aminopyridine and 1-bromo-3-chloropropane 〈35JGU1586〉. Derivatives of the 8,9-benzologue of (**8**) were prepared from 1-substituted 3,4-dihydroisoquinolines with diphenylcyclopropenethione 〈79TL1213, 86S899〉, and from 1-thio-4-cyano-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one with 3-bromopropionic acid 〈89MI 823-11〉. Cyclocondensation of ethyl (4-oxo-1,4-dihydroquinazol-2-yl)acetate with ethoxymethylenemalonate yielded a derivative of the 3,4-benzologue of (**12**) 〈89JHC161〉.

The reactions of 2-aminopyridinium hydrochloride 〈74CPB243〉 and its 3,4-benzologue 〈85CPB3034, 86JOC2988〉 with ethoxymethylenemalononitrile yielded 3-cyano-4-oxo-4*H* derivatives of (**12**) and its 8,9-benzo derivative, respectively. The reaction of 1-aminoisoquinoline and methyl 3-pyrrolidino-

2-phenylacrylate gave the 3-phenyl-4-oxo-4*H* derivative of the 8,9-benzologue of (**12**) ⟨70JCS(C)881⟩. A 1,2,3,4-tetrahydro-11-oxo-11*H* derivative of the 2,3-benzologue of (**12**) was obtained in the reaction of 2-aminopyridine and methyl 2-pyrrolidinocyclohexenecarboxylate ⟨70JCS(C)881⟩.

The reactions of bis(2,4,6-trichlorophenyl) malonates with 2-methyl-3-arylquinazolin-4(3*H*)-ones gave rise to derivatives of the 3,4-benzologue of (**12**) ⟨81ZN(B)252⟩. (4-Oxo-3,4-dihydroquinazolin-2-yl)acetonitriles reacted with arylidenemalononitriles to furnish 1-amino-2,4-dicyano-3 derivatives of the 2,3-benzologue of (**12**) ⟨90JPR610⟩.

Further derivatives of (**12**) were prepared from 2-aminopyridines with different reagents ⟨62CB2871, 69TL2589, 70JCS(C)881, 74CC487, 75JCS(P1)1969, 75JOC1440, 76JOC3546, 84CPB2602, 89S317, 90DOK(312)619, 90OPP532, 91IZV473, 91MI 823-06, 93AP(326)335, 93JHC1253, 93MI 823-11, 95JHC921⟩.

8.23.4.7 By Formation of Three Bonds from [4 + 1 + 1] Atom Fragments

The 3,4-dioxoperhydro derivative of (**3**) was obtained by cross carbonylation of 2-hydroxymethylpyridine ⟨87CC125⟩. Reaction of Schiff bases, prepared from 2-aminopyridine and its 5,6-benzologue with aldehydes and dichlorocarbene, afforded 2-aryl-3-chloro-4-oxo-4*H* derivatives of (**12**) and its 6,7-benzologue ⟨91KGS810⟩.

8.23.4.8 By Formation of Three Bonds from [3 + 2 + 1] Atom Fragments

A derivative of the 5,6-benzologue of (**2**) was obtained from 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with 35% aqueous formaldehyde ⟨73JHC435⟩. A 3-ethoxycarbonyl-4-oxo-6,7,8,9-tetrahydro-4*H* derivative of (**12**) was obtained from valerolactim ethers, ethoxymethylenemalonate, and NH_4OAc ⟨73JAP(K)7334897⟩. Reaction of 2-(substituted amino)-pyridines and chloroacetyl chloride yielded a 1-substituted 4-chloromethyl-2-oxo-2*H*-1-inium-3-olate derivative of (**12**) ⟨89CCC1376⟩. Some 11-oxo-6,7,8,9-tetrahydro-11*H* derivatives of the 2,3-benzologue of (**12**) were prepared from *o*-iodoaniline, 2-piperidone under 5 atm of CO in the presence of a catalyst ⟨85H(23)2803⟩, and from 2-piperideneacetate and aromatic aldehydes ⟨78LA1476⟩.

8.23.4.9 By Formation of Three Bonds from [2 + 2 + 2] Atom Fragments

Reaction of quinolines, isoquinolines, or 3,4-dihydroisoquinoline with dimethyl and diphenyl ketene afforded derivatives of the 5,6- ⟨67JCS(C)1569, 68AG(E)826, 75JCS(P1)1001, 87JCS(P1)1635⟩ or 7,8-benzologues ⟨67JCS(C)1569, 71JOC2211, 75JCS(P1)1001⟩ of (**2**). Reaction of DMAD with 6,7-dimethoxy-2*H*-1,3-benzothiazine, pyridazines or their 4,5-benzologues, 2,4-dimethylquinazoline, quinoxaline, and quinazolines furnished derivatives of the 3,4-benzologue of (**6**) ⟨82H(19)489⟩, (**9**) ⟨66JCS(C)2218⟩ and its 3,4-benzologue ⟨68RRC513, 79JCR(S)394⟩, the 7,8-benzologue of (**10**) ⟨68JCS(C)926⟩, the 3,4-benzologue of (**11**) ⟨72MI 823-03⟩, and the 3,4-benzologue of (**12**) ⟨75JCS(P1)2322, 75KGS1701, 80H(14)1959⟩. Derivatives of the 8,9-benzologue of (**4**) were obtained from isoquinoline and 3,4-dihydroisoquinoline with acetylacetylene, diethyl ketomalonate, and DMAD ⟨75JCS(P1)446⟩. Reaction of isoquinoline with phenyl isocyanate and DMAD gave a derivative of the 8,9-benzologue of (**12**) ⟨67CB1094⟩.

8.23.4.10 By Formation of Four Bonds from [3 + 1 + 1 + 1] Atom Fragments

Derivatives of the 5,6-benzologue of (**10**) were prepared in the reaction of 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with two moles of formaldehyde and one mole of primary amines, hydroxylamine or acylhydrazide ⟨73JHC435, 81CB61⟩.

8.23.4.11 By Formation of Four Bonds from [2 + 2 + 1 + 1] Atom Fragments

From the reaction of pyridines, Cl(MeS)C = NR and large excess of isonitriles 2-substituted 1-methylthio-3-(substituted imino)-4-(substituted amino) derivatives of (**10**) could be prepared ⟨93TL2319⟩.

8.23.4.12 Ring Transformations

Derivatives of the 2,3- and 3,4-benzologues of (**9**) were prepared from 3-(2-pyridyl)-2,1-benzisoxazoles, and from a thiazolo[2,3-*a*]phthalazine with methyl propiolate ⟨87EUP226196, 88EUP294599⟩, DMAD, fumaronitrile and methyl vinyl ketone ⟨85JOC1677⟩, respectively.

Derivatives of (**2**) and its 4,4*a*,5-benzologue were obtained from perhydroisoxazolopyridinium salt ⟨91G393⟩ and from benzo[*ij*]quinazoline ⟨64M59⟩. Derivatives of the 5,6- and 4,4*a*,5-benzologues of (**6**) were synthesized from the 5,6- ⟨83H(20)1325⟩ and 4,4*a*,5-benzologues ⟨78JHC645⟩ of (**2**) with P_4S_{10}. Ring transformation of 6-chloro-2-methyl-4-[2-(2-hydroxyethyl)-1-piperidyl]-5-nitropyrimidine ⟨74JCS(P1)1611⟩, 2,4-diphenyl-6-methyl-1,3-oxazinium salts ⟨91KGS1556⟩ or (**75**) ⟨93SL551⟩ gave derivatives of (**10**). Derivatives of the 3,4-benzologue of (**10**) were obtained from cycloadducts of thiazolo[3,2-*c*]quinazolines and alkynic and alkenic dipolarophiles by extrusion of S or H_2S ⟨85JOC1666⟩, and derivatives of the 5,6-benzologue of (**10**) were prepared from benzo[*h*]quinolizines ⟨82TL2829, 83JOC5074⟩, and 1-[(6-methyl-5-methylthio-4-oxo-1,3-oxazin-2-yl)methylene]-1,2-dihydroisoquinoline ⟨80YZ1261⟩. Compounds (**24**) were obtained from 1-[(1,2,4-oxadiazol-3-yl)methyl]-3,4-dihydroisoquinolines ⟨87CB1039⟩.

Derivatives of (**3**) and its 7,8-benzologue were synthesized from perhydrooxazolo[2,1-*a*]pyridine ⟨88SC823⟩, and a derivative of isoindoline ⟨95SL237⟩. Derivatives of (**11**) were synthesized from pyrrolo[1,2-*a*]pyridine-2-one ⟨68JOC2379⟩ imidazo[1,2-*a*]pyridines ⟨62JCS1510, 74HCA750⟩, and pyrido[1,2-*a*]pyrido[1′,2′ : 3,4]imidazo[2,1-*c*]pyrazi-5,8-diinium salt ⟨69JCS(C)1987⟩. Ring transformation of spiro[2-oxo-1,2,3,4-tetrahydroquinoxaline-3,4′-1′-cyano-3′-ethoxycarbonyl-2′-hydroxy-2′-cyclobutene] gave a derivative of the 3,4-benzologue of (**11**) ⟨83S1029, 84CPB3366⟩, while that of a cyclobutanobenzene ⟨84JOC5269⟩ led to a derivative of the 8,9-benzologue of (**11**). Derivatives of the 1,9*a*,9-benzologue of (**11**) were obtained from benzo[*f*]-1,5-diazabicyclo[3,2,2]nonene ⟨83KGS677⟩ and 1-(quinolin-8-yl)-1,2,3-triazole-4,5-dicarboxylate ⟨87JCS(P1)403⟩.

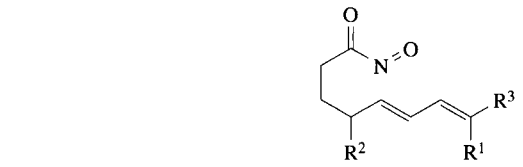
Derivatives of (**8**) were prepared from an imidazo[2,1-*b*]thiazine ⟨88H(27)227⟩, and thiazetidino[3,2-*a*]pyridines ⟨84TL4157, 92T10149⟩. The reaction of a tetramethylene derivative of Dewar pyrimidinone with H_2S gave a mixture of derivatives of (**8**) and (**12**) ⟨89JCS(P1)1231⟩. Derivatives of (**12**) were synthesized from derivatives of 2-(1-tetrazolyl)pyridine ⟨75JHC949⟩, 2-{[(5-oxo-2-phenyl-4-oxazolinylidene)methyl]amino}pyridines ⟨B-49MI 823-01, 81H(16)2149, 84S152, 93H(35)955⟩, 2-{[(5-oxo-2-methoxy-4-thiazolinylidene)methyl]amino}pyridines ⟨94JHC125⟩, 2-{[(2-oxotetrahydrofuranylidene)methyl]amino}pyridine ⟨91EUP453042⟩, pyrimido[1,2-*a*]pyrimidine ⟨73JOC3485⟩, 1,2,4-triazolo[4,3-*a*]pyrimidine ⟨82CC1280⟩, 1-(2-pyridyl)-3-chloropyrrolidinone ⟨74EJM344⟩, indolizine ⟨63HCA1190⟩ cyclodipeptide ⟨65ZOB2231, 65T3537⟩, and thieno[2,3-*d*]pyrido[1,2-*a*]pyrimidine ⟨75KGS765⟩. Rearrangement of 2-(5-oxo-4-ethoxycarbonyl-2-isoxazolyl)pyridines and their 3,4- and 5,6-benzologues led to derivatives of (**12**) and its 8,9- and 6,7-benzologues ⟨89AJC2161, 92AJC1811, 92AJC1825, 92AJC2037, 93T8147⟩. Derivatives of the 2,3-benzologue of (**12**) were prepared from 3-(2-pyridyl)-4*H*-1,2,3-benzothiazin-4-one ⟨80JCS(P1)633⟩, 3,3-dichloro-2-(2-pyridyl)-1,2,3,4-tetrahydroquinoline-2,4-dione ⟨79CB3424⟩, and pirenzepine ⟨84MI 823-04, 84MI 823-06⟩. Derivatives of the 3,4-benzologue of (**12**) were obtained from thiazolo[3,2-*a*]quinazolinones and thiazino[3,2-*a*]quinazolinones ⟨85JOC1666⟩, pyrido[1,2-*a*][1,4]benzodiazepin-1-one ⟨87JHC683⟩ and 2,3-dihydro-3-oxo-spiro[1*H*-indazole-1,1′-piperidinium] inner salt ⟨93JCS(P1)1119⟩. Derivatives of the 8,9-benzologue of (**12**) were synthesized from 2*H*-*s*-triazino[2,1-*a*]isoquinoline-2,4-dione ⟨67CB1107⟩.

8.23.4.13 Miscellaneous

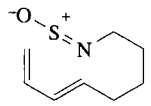
Intramolecular hetero Diels–Alder cycloaddition of compounds (**76**)–(**81**), which all are usually prepared *in situ* from their precursor, gave derivatives of (**1**) ⟨85JA5534, 89JOC4088, 91CC1237, 91TL4325, 92JOC2876, 93JOC6083, 94JOC1358, 94TL595⟩, (**5**) ⟨88TL4233⟩, (**9**) ⟨87JCS(P1)2511, 91T10053, 91TL125⟩, and (**2**) ⟨81JA7573, 84JA3240, 91TL4371⟩.

Derivatives of (**9**) and its 3,4-benzologue were obtained by the solvolysis of the reaction products of pyridazine and phthalazine with maleic anhydride ⟨63T1237, 67RRC109⟩. Derivatives of the 5,6- and 4,4*a*,5-benzologues of (**2**) were prepared from a phenethylamine derivative ⟨85SC883⟩, and piperidines ⟨90JOC1447⟩. 1,4-Dioxo derivatives of (**3**) and (**11**) formed in a base catalysed degradation of rapamycin and FD-506 ⟨89TL671, 93TL3699⟩ and antinomycin D ⟨71CC39⟩. Derivatives of 7,8- and 1,9*a*,9-benzologues of (**3**) and (**7**) were prepared from 3-(2-phenyl-1-cyanoethyl)oxazolidines ⟨87JHC1235⟩ and *o*-fluoro-2-[(2-hydroxy- and 2-thioethylamino)methylene]benzoylacetates ⟨86CPB4098, 88JMC1694, 89EUP306860, 91CCC1937, 91SC2301⟩.

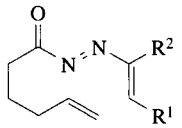
Derivatives of (**10**) were prepared from *N*-(5-hexenyl)-*N*-methylcarbamides ⟨88JA3994, 88JOC5731⟩,



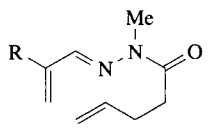
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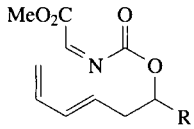
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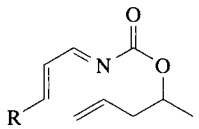
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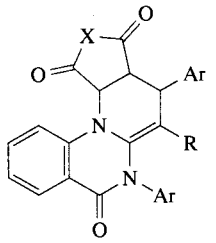
from a mixture of benzylamine, butyraldehyde or 2-ethyl-2-hexenal ⟨89MI 823-12⟩, and the 5,6-benzologue of (**10**) was prepared from a *N*-acylphenethylamine derivative ⟨63YZ1043⟩ and N-phenethylureas ⟨84S1071, 85H(23)2907⟩.

Derivatives of (**11**) were obtained from ethylenediamine with 2,6-dibromocaproate ⟨70ZOR1729⟩, sucrose ⟨64MI 823-01⟩, and glutaraldehyde in the presence of KCN ⟨86H(24)2835⟩. The 3,4-benzologue of (**11**) was obtained from *o*-phenylenediamine with D-*threo*-2,5-hexodiulose ⟨75CAR(39)379⟩, and of the 8,9-benzologue of (**11**) from *N*-acyl phenethylamines ⟨68CC1450, 85SC883⟩.

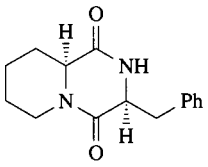
Derivatives of (**4**) were prepared from 2-benzylideneacetoacetates and 3-[(3-hydroxypropyl)amino]acrylates ⟨92EJM527⟩, from [2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]amine ⟨92T6325⟩, from 5-halopentanal ⟨90TL4281, 94JA2617, 94JOC6904⟩, 4-benzoylbutyric acid ⟨69JOC165, 76JMC436⟩, with 1,3-amino alcohols, from glutaraldehyde with KCN ⟨71JOC226, 88H(27)1575⟩ and EtSH ⟨71JOC226⟩, and from *N*-(3-hydroxypropyl-5-aminopentanol) ⟨72BSF4736⟩, *N*-(5,5-diethoxypentyl)-3-hydroxypropionamide, and 3-aminopropanol ⟨61AP(294)65⟩. Derivatives of the 3,4-benzologue of (**4**) were obtained from *N*-(3-(2-carboxyvinyl)propionyl) and *N*-(2-carboxyethyl)anthranilic acids ⟨70KGS879, 89SC3103⟩. Reaction of 3-hydroxypropylamine with *o*-carboxyphenylacetic acids gave derivatives of the 7,8-benzologue of (**4**) ⟨78BEP866987, 79CPB2372⟩, and with *o*-benzoylphenylacetic acid ⟨71MI 823-02⟩, and *o*-(2-bromoethyl)benzaldehyde ⟨61AP(294)645⟩ afforded derivatives of the 8,9-benzologue of (**4**). Reaction of 3-aminopropanethiol with 4-benzoylbutyric acid ⟨65BEP659528⟩, *o*-carboxyphenylacetic acids ⟨79CPB2372⟩ and 2-cyanomethylenecyclohexanecarboxylate ⟨81USP4284778⟩ furnished derivatives of (**8**) and its 7,8-benzologue. Derivatives of (**12**) were prepared in the reaction of 1,3-diaminopropanes with glutaraldehyde and KCN ⟨71JOC226, 87JAP(K)87209078⟩, glutaric acid ⟨65JCS3487⟩, 5-chloropentanal ⟨82TL4181, 93JA6580⟩, 6-halopyridin-2(1*H*)-ones and 3-(ethoxycarbonylmethyl)acrylonitriles ⟨79CPB1207, 79JPJ880⟩, 4-acylbutanoic acids ⟨66BEP659530, 69JOC165, 82EUP65724⟩, 4-halovaleronitriles ⟨64GEP1171928⟩, 2-(3-oxopropylmalonate) ⟨71AP(304)774⟩, from 1-[*N*-(5-hydroxypentyl)-3-aminopropyl]aziridine ⟨75CR(C)953, 80RRC541⟩, from *N*,*N*-dimethyl-*N*-(3-dimethylamino-2-(4-pyridyl)prop-2-enylidene]ammonium salt with malononitrile, cyanoacetamide, and from malononitrile with *β*-alanine methyl ester ⟨90EGP279020⟩. Derivatives of the 3,4-benzologue of (**12**) were prepared from anthranilamides with *δ*-oxo carboxylic acids and esters ⟨68JOC2402, 69G715⟩ and with cinnamylidenemalononitrile ⟨87G385⟩ from anthranilates and *ω*-halovaleronitriles ⟨79KGS1427⟩, from *N*-(2-benzamido)-5-chloropentanamide ⟨86JHC53⟩ and by hydrolysis of (**82**) ⟨81IJC(B)290⟩. Derivatives of the 6,7- and 8,9-benzologues of (**12**) were obtained from *N*-(2-arylethyl)ureas and malonic acid ⟨90T1323⟩ and *N*-(3-chloropropyl)isatoic anhydride and the sodium salt of malononitrile ⟨76JOC825⟩. Cyclocondensation of 1,3-diaminopropanes with *o*-cyanomethyl-, *o*-(aminocarbonylmethyl)-, *o*-(carboxymethyl)benzoic acids ⟨69LA(729)83, 79CPB2372, 88HCA77⟩, and 2-cyanomethylenecyclohexanecarboxylate ⟨79YZ880⟩ gave derivatives of the 7,8-benzologue of (**12**). Similar reaction of 1,3-diaminopropane with *o*-acylphenylacetic acids gave derivatives of the 8,9-benzologue of (**12**) ⟨71MI 823-02, 77RZC691⟩.

8.23.5 APPLICATIONS AND IMPORTANT COMPOUNDS

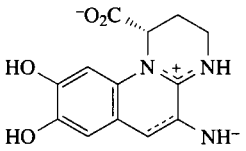
Different perhydro derivatives of (**1**) ⟨85JA5534, 86TL5513, 89JOC4088, 91CC1237, 91TL4325, 92JOC2876, 93JOC6083, 94JOC1358⟩, (**2**) ⟨84JA3240, 85T2891, 90H(30)885, 91TL4371, 93JOC5035⟩, its 6,7-benzologue



(82) X = O, NPh



(83)

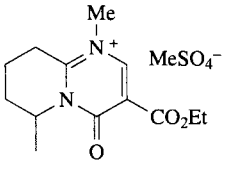


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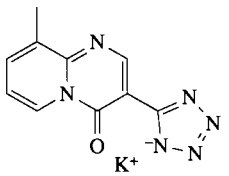
〈80JA1454, 84CC597, 84TL3247, 86CPB2380〉, (**4**) 〈88H(27)1575, 91SL878〉, and (**10**) 〈90TL4543〉 are used as key intermediates in the syntheses of different alkaloids. The perhydropyrido[2,1-*b*][1,3]oxazine moiety occurs as a constituent part of members of Xestospongin/Araguspongine alkaloid family 〈84TL3227, 89CPB1676, 89TL4149, 94JA2617, 94JOC6904〉. Verruculotoxin (**83**) is produced by fungus *Penicillium verruculosum* Peyronel 〈75MI 823-04, 76JA246, 88S963〉. From *Mackinlaya subulata* and *M. macrosciadia* the 6,7,8,9-tetrahydro-11*H* derivative of 2,3-benzologue of (**12**) and its 11-oxo derivative were isolated 〈65CC267, 66AJC151, 85AJC1007〉. 11-Oxo-6,7,8,9-tetrahydro and 1,2,3,4,6,7,8,9-octahydro-11*H* derivative of the 2,3-benzologue of (**12**) and their 6-arylhydrazono derivatives are key intermediates for the synthesis of rutaecarpine alkaloids and their derivatives 〈81MI 823-04, 81TL4816, 85JHC1373, 87JHC1045〉. Siderophores (pseudobactins, pyoverdin, azoverdin), iron chelating peptides of bacteria, contain moiety (**84**) 〈81B6446, 81B6457, 83TL4877, 84B3534, 84BBA(800)11, 85MI 823-06, 86JBC(261)795, 86MI 823-13, 86ZN(C)497, 87MI 823-05, 87T2261, 88B2745, 88MI 823-13, 89LA375, 90B7348, 90B11041, 90TL7611, 90ZN(B)1437, 91MI 823-09, 91ZN(C)522, 91ZN(C)527, 91ZN(C)534, 91ZN(C)993, 92M151, 92MI 823-16, 92TL1737, 92TL1889, 92ZN(C)26, 92ZN(C)487, 93JPR83, 93JPR157, 93ZN(C)425〉.

6-Carboxy-9-fluoro-10-(cyclic amino)-7-oxo-1*H*,3*H*,7*H* derivatives of the 4,4*a*,5-benzologue of (**2**) 〈90EUP373531〉, 9-fluoro-10-(substituted amino)-7-oxo-2,3-dihydro-7*H* derivatives of the 1,9*a*,9-benzologue of (**3**) 〈84CPB4907, 87CPB1896, 88JMC1694, 88JMC2004, 88MI 823-14, 90JHC1509, 90JMC2270, 91CCC1937, 91CCC2406, 91EJM889, 91JHC1061, 91JHC1067, 91JMC1142, 92AF70, 92CCC216, 93JMC801, 93JMC1356〉, and 9-fluoro-10-(cyclic amino)-7-oxo-2,3-dihydro-7*H* derivatives of the 1,9*a*,9-benzologue of (**7**) 〈87JMC465, 91JHC1061, 91JHC1067, 93JMC3449〉 have been intensively investigated as antibacterial agents. Of these derivatives ofloxacin (**15**) 〈86CPB4098, 91MI 823-10〉, its optically active (S)-form, levofloxacin 〈86AAC163, 87JMC2283〉, and rufloxacin (**20**) 〈87JMC465〉 were introduced into human therapy, as highly active antibacterial agents against Gram-positive and Gram-negative pathogens respectively. Actisomide (**19**), an antiarrhythmic agent is in the course of introduction into human therapy 〈85JMC1285, 87MI 823-06, 88MI 823-15〉. Trequinsin (**34**) was under clinical investigations as a very potent antihypertensive peripheral vasodilator having platelet aggregation inhibitory properties 〈82LS2037, 84JMC1470, 87MI 823-07〉. The anthelmintic praziquantel (**17**) exhibits a broad spectrum with excellent activity against schistosomes and cestodes, and it is widely used in human and veterinary therapy 〈77E1036, 78H(11)521, 83MI 823-08, 90KFZ60〉. Biological activities of various derivatives of (**12**) have been reviewed 〈88MI 823-01〉. Their outstanding representatives, rimazolium (**85**), pemirolast (**86**), and risperidone (**87**) were introduced into human therapy, as analgetic, orally active antiallergic—antiasthmatic, and antipsychotic agents, respectively.

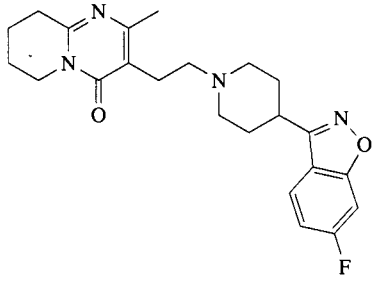
The 2-oxo-3,4-dihydro-2*H* derivative of (**12**) is used as a neutral hydrogen chloride acceptor in organic syntheses 〈76CL13, 76CL57, 76H(4)1707, 79CS108, 80T2409, 86JCS(P1)999〉.



(85)



(86)



(87)

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8.24
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 2 : 0

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8.24.1 INTRODUCTION

This chapter covers those bicyclic ring systems with one bridgehead nitrogen and two extra heteroatoms, and their benzo derivatives.

The total number of the possible bicyclic ring systems containing nitrogen(s), oxygen(s), and sulfur(s) is 54, and, of these, 19 are known. Far fewer bicyclic systems are known with other heteroatoms; only three such systems have been described so far. The number of known tricyclic ring systems falling within the scope of this chapter is 28. Of these broad classes of compounds, pyridotriazines have been the most completely explored, less being known of pyridooxadiazines and pyridothiadiazines, whereas pyridooxathiazines, pyridodioxazines, and pyridodithiazines have been the least extensively investigated.

Three bicyclic ring systems, pyrido[1,2-*c*][1,3,2]oxazaborine, pyrido[1,2-*c*][1,3,2]phosphorine, and pyrido[1,2-*c*]diazaphosphorine, have been described which contain as extra heteroatoms at least one heteroatom other than nitrogen, oxygen, or sulfur. Benzologues of these systems have not been reported.

The only previous review of these classes of compounds appeared in the early 1960s ((**8**) and (**23**) only were discussed ⟨B-61MI 824-01⟩), and none of these ring systems was the primary subject of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). Therefore, for all systems, the full literature is surveyed briefly in this chapter.

The known bicyclic systems and the benzo-fused derivatives are listed in Tables 1–4, where the

name and the ring file number of the system are also included. Within each table, the bicyclic ring systems are generally ordered according to their ring file numbers and are always followed by the structurally related benzologues, in the same order as they are discussed in the text.

For any heterocyclic system only one tautomeric form is shown. Throughout this chapter the *Chemical Abstracts* nomenclature is used.

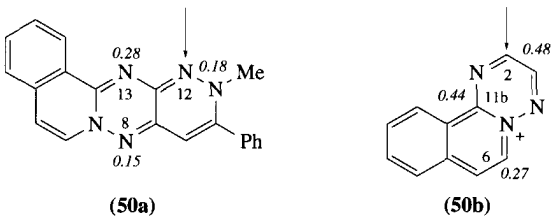
Each of the following sections of this chapter is devoted to a specific system, because of the diversity of the systems. Within each section, discussion is structured according to the standard CHEC format. The systems are: pyridotriazines and their benzo derivatives (Table 1); pyridooxadiazines, pyridothiadiazines, and their benzo derivatives (Table 2); pyridooxathiazines, pyridodioxazines, pyridodithiazines, and their benzo derivatives (Table 3); pyridooxazaborines, pyridooxazaphosphorines, and pyridodiazaphosphorines (Table 4).

8.24.2 PYRIDOTRIAZINES AND THEIR BENZO DERIVATIVES

All six possible pyridotriazines have been reported in the literature.

8.24.2.1 Theoretical and Experimental Structural Methods

Semiempirical AM1 calculations were done for the pyridazino-fused thiazino[3,2-*a*]isoquinoline derivative (**50a**). The preferred site of alkylation was explained on the basis of the highest *n*-HOMO density found by this calculation (Figure 1) ⟨92M1181⟩.

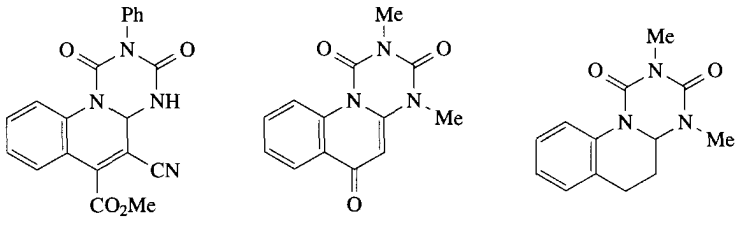


(**50a**) (**50b**)

Figure 1 *n*-HOMO and LUMO densities (numbers in italics) for compounds (**50a**) and (**50b**), respectively. The most reactive positions found by experiments are shown by the arrows. In the case of (**50a**), N-13 is sterically hindered; therefore, N-12 is the most reactive site.

The PM3 method was used for calculating LUMO electron densities of the [1,2,4]triazino[3,2-*a*]isoquinolinium cation (**50b**). The regiospecific attack of hydroxide ion could be rationalized by using these data ⟨92BSB597⟩.

For a number of pyridotriazines, x-ray analyses have been reported. Compounds (**51**)–(**53**), derivatives of the [1,3,5]triazino[1,2-*a*]quinoline ring system, were investigated. The heterocyclic ring was found to be nonplanar in (**51**) ⟨76CSC13⟩. Neither abnormal bond lengths, nor bond angles were found for (**52**) and (**53**) ⟨86BCJ949⟩. Crystal data of 9-amino-3-methyl-4*H*-pyrido[2,1-*c*][1,2,4]triazin-4-one ⟨87CPB80⟩ as well as bond lengths and angles of 8-methyl-4-dimethylamino-2-phenylpyrido[1,2-*a*][1,3,5]triazinium perchlorate ⟨92JHC1551⟩ were reported.



(**51**) (**52**) (**53**)

Table 1 Pyridotriazines and their benzo derivatives.

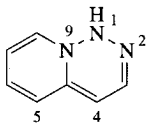
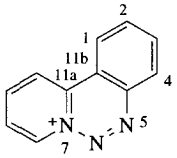
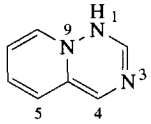
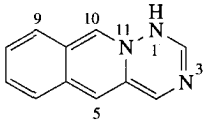
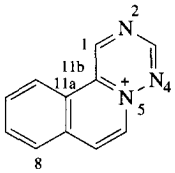
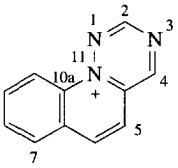
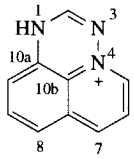
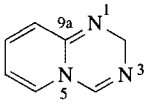
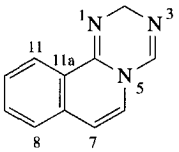
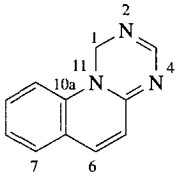
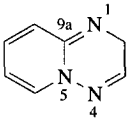
Compound	*Ring system*	*Name and ring file number*
(1)		1*H*-Pyrido[1,2-*c*][1,2,3]triazine RF 13382
(2)		Pyrido[1,2-*c*][1,2,3]benzotriazin-7-ium RF 34698
(3)		1*H*-Pyrido[2,1-*f*][1,2,4]triazine RF 13383, 13391
(4)		1*H*-[1,2,4]Triazino[1,6-*b*]isoquinoline RF 34703, 34710
(5)		[1,2,4]Triazino[6,1-*a*]isoquinolin-5-ium RF 34713
(6)		[1,2,4]Triazino[1,6-*a*]quinolin-11-ium RF 34721
(7)		1*H*-Pyrido[3,2,1-*ij*][1,2,4]benzotriazin-4-ium RF 34699
(8)		2*H*-Pyrido[1,2-*a*][1,3,5]triazine RF 13384, 13388
(9)		2*H*-[1,3,5]Triazino[2,1-*a*]isoquinoline RF 34709
(10)		1*H*-[1,3,5]Triazino[1,2-*a*]quinoline RF 34720
(11)		2*H*-Pyrido[1,2-*b*][1,2,4]triazine RF 13385, 13389

Table 1 (continued).

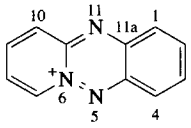
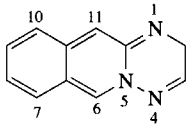
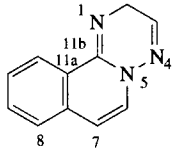
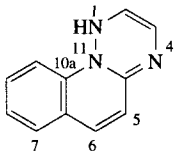
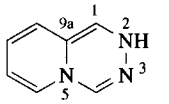
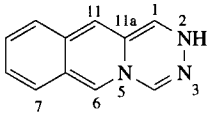
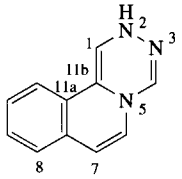
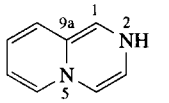
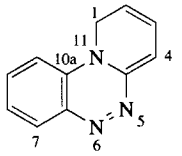
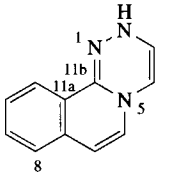
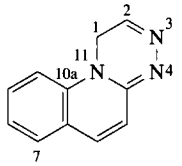
Compound	*Ring system*	*Name and ring file number*
(12)		Pyrido[1,2-*b*][1,2,4]benzotriazin-6-ium RF 34697
(13)		2*H*-[1,2,4]Triazino[2,3-*b*]isoquinoline RF 34704, 34711
(14)		2*H*-[1,2,4]Triazino[3,2-*a*]isoquinoline RF 34705, 34712
(15)		1*H*-[1,2,4]Triazino[2,3-*a*]quinoline RF 34718, 34722
(16)		2*H*-Pyrido[1,2-*d*][1,2,4]triazine RF 13386
(17)		2*H*-[1,2,4]Triazino[4,5-*b*]isoquinoline RF 34707
(18)		2*H*-[1,2,4]Triazino[5,4-*a*]isoquinoline RF 34708
(19)		2*H*-Pyrido[2,1-*c*][1,2,4]triazine RF 13387, 13390
(20)		1*H*-Pyrido[2,1-*c*][1,2,4]benzotriazine RF 34696
(21)		2*H*-[1,2,4]Triazino[3,4-*a*]isoquinoline RF 34706
(22)		1*H*-[1,2,4]Triazino[4,3-*a*]quinoline RF 34719

Table 2 Pyridooxadiazines, pyridothiadiazines, and their benzo derivatives.

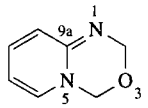
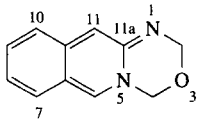
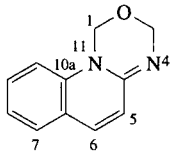
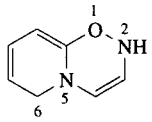
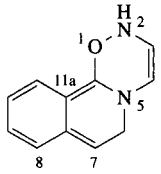
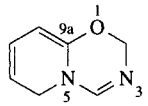
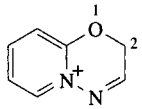
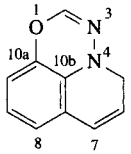
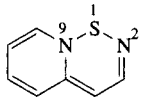
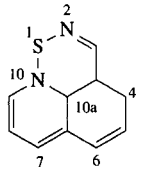
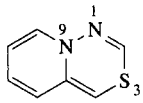
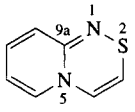
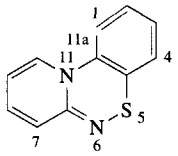
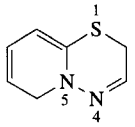
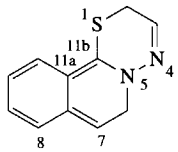
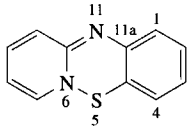
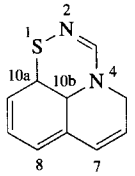
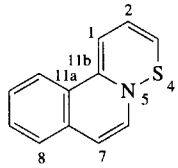
Compound	*Ring system*	*Name and ring file number*
(23)		2*H*,4*H*-Pyrido[1,2-*c*][1,3,5]oxadiazine RF 13215
(24)		2*H*,4*H*[1,3,5]Oxadiazino[3,4-*b*]isoquinoline RF 34516
(25)		1*H*,3*H*-[1,3,5]Oxadiazino[3,4-*a*]quinoline RF 34518
(26)		2*H*,6*H*-Pyrido[1,2-*e*]-1,2,5-oxadiazine RF 13216
(27)		2*H*,6*H*-[1,2,5]Oxadiazino[6,5-*a*]isoquinoline RF 34517
(28)		2*H*,6*H*-Pyrido[2,1-*b*][1,3,5]oxadiazine RF 13217
(29)		2*H*-Pyrido[2,1-*b*][1,3,4]oxadiazin-5-ium RF 13218
(30)		5*H*-Pyrido[3,2,1-*i,j*][4,1,2]benzoxadiazine RF 34522
(31)		Pyrido[1,2-*b*][1,2,6]thiadiazine RF 13280
(32)		4*H*-Pyrido[3,2,1-*i,j*][2,1,3]benzothiadiazine RF 34583
(33)		Pyrido[1,2-*d*][1,3,4]thiadiazine RF 13281
(34)		Pyrido[2,1-*c*][1,2,4]thiadiazine RF 13282

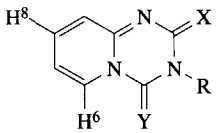
Table 2 Continued.

Compound	*Ring system*	*Name and ring file number*
(35)		Pyrido[2,1-*c*][1,2,4]benzothiadiazine RF 34580
(36)		2*H*,6*H*-Pyrido[2,1-*b*][1,3,4]thiadiazine RF 13292, 13294
(37)		2*H*,6*H*-[1,3,4]Thiadiazino[2,3-*a*]isoquinoline RF 34590
(38)		Pyrido[1,2-*b*][1,2,4]benzothiadiazine RF 34579
(39)		5*H*-Pyrido[1,2,3-*de*][1,2,4]benzothiadiazine RF 34584
(40)		1,2,5-Thiadiazino[3,2-*a*]isoquinoline RF 34589

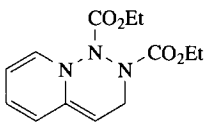
8.24.2.1.1 NMR spectroscopy

In the ^{1}H NMR spectra of pyrido[1,2-*a*][1,3,5]triazine derivatives (**54**), δ H6 and δ H8 were investigated as functions of the C=X group. The deshielding electronic through-bond effect followed the order C=NPh < C=O < C=S, while the through-space effect was in the order C=O < C=NPh < C=S. The latter order was determined by the effect of C=Y on the *peri* proton H6 ⟨87JPR108⟩. Kinetics of the formation of 2-pyridylisothiocyanate from its dimer, the pyrido[1,2-*a*][1,3,5]triazine derivative, were studied by ^{1}H NMR ⟨88JHC1459⟩. Characteristic differences were also found in the ^{13}C NMR data for the dimer and monomer ⟨76JHC873⟩. On the basis of analyses of ^{1}H and ^{13}C NMR spectra of betainic pyrido[3,2,1-*ij*][1,2,4]benzotriazines, the contributions of different resonance forms to the total structure could be suggested ⟨83JCS(P1)349⟩.

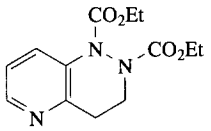
Values of vicinal coupling constants were shown to be of diagnostic use in distinguishing pyrido[1,2-*a*][1,3,5]triazines of type (**54**) from their pyridine monomers ($J_{(H6,\ H7)} \approx 7$ Hz and 5 Hz, respectively) ⟨81CCC2557⟩. Compounds (**55**) and (**56**) could also be easily distinguished by the multiplicity of H4, which is a doublet of doublets in (**55**) ⟨79T2027⟩.



(**54**) X,Y = O, S, NPh



(**55**)



(**56**)

Table 3 Pyridooxathiazines, pyridodioxazines, pyridodithiazines, and their benzo derivatives.

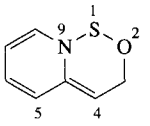
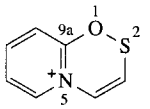
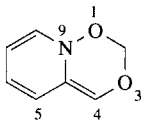
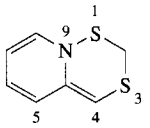
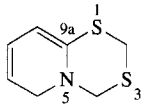
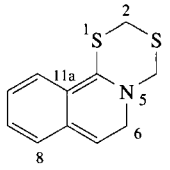
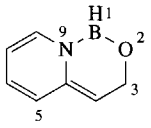
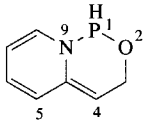
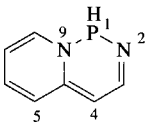
Compound	*Ring system*	*Name and ring file number*
(**41**)		3*H*-Pyrido[1,2-*c*][1,2,3]oxathiazine RF 13133
(**42**)		Pyrido[1,2-*e*][1,2,5]oxathiazinium RF 13134
(**43**)		Pyrido[1,2-*b*][1,5,2]dioxazine RF 13164
(**44**)		Pyrido[1,2-*b*][1,5,2]dithiazine RF 13183
(**45**)		4*H*,6*H*-Pyrido[2,1-*d*][1,3,5]dithiazine RF 13185
(**46**)		4*H*,6*H*[1,3,5]Dithiazino[4,5-*a*]isoquinoline RF 34500

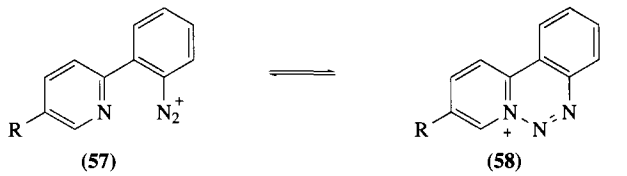
Table 4 Pyridooxazaborines, pyridooxazaphosphorines, and pyridodiazaphosphorines.

Compound	*Ring system*	*Name and ring file number*
(**47**)		1*H*,3*H*-Pyrido[1,2-*c*][1,3,2]oxazaborine RF 13070
(**48**)		1*H*,3*H*-Pyrido[1,2-*c*][1,3,2]oxazaphosphorine RF 13118, 13119
(**49**)		1*H*-Pyrido[1,2-*c*][1,3,2]diazaphosphorine RF 13245

8.24.2.1.2 IR spectroscopy

Investigation of the equilibrium between 2-pyridyl phenyldiazonium fluoroborates (**57**) and pyrido[1,2-*c*][1,2,3]benzotriazinium fluoroborates (**58**) was carried out by IR spectroscopy (Equation (1)) ⟨87JHC1133⟩. The diazonium isomers were detected by the $\nu N{=}N^+$ absorption at 2270 cm^{-1}, whereas (**58**) could be determined by the presence of a C—H stretching band at 3120 cm^{-1}. The

potential tautomeric equilibrium between enamine (**59**) and ketimine (**60**) (Equation (2)) was studied by IR in the solid phase ⟨72LA(757)100⟩.



(57) (58) (1)



(59) (60) (2)

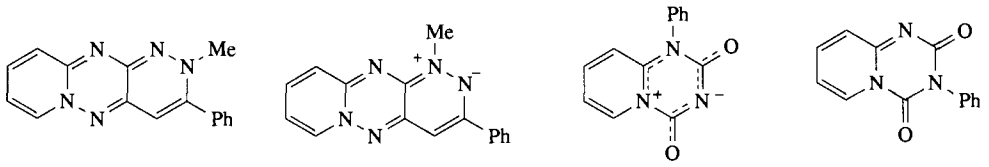
8.24.2.1.3 Mass spectrometry

Electron impact mass spectra of the tricyclic triazine derivatives (**52**) and (**53**) were measured by means of low-resolution, high-resolution, and linked-scan methods ⟨86BCJ949, 86NKK560⟩. The initial fragmentation of (**53**) mainly proceeds by the loss of a neutral MeNCO dimer via N(4)—C(4a) bond cleavage. On the other hand, loss of a MeNCO monomer was found to proceed via C(1)—N(11) bond cleavage in (**52**). FAB mass spectra were also measured for these compounds.

Pyrido[1,2-*a*][1,3,5]triazines (**54**) formed by cyclodimerization of pyridyl heterocumulenes, gave typically retro Diels–Alder fragmentations in their mass spectra ⟨81CCC2557, 82ZC140, 83JPR463⟩. The molecular ions could also be identified in most cases.

8.24.2.1.4 UV and photoelectron spectroscopy

UV spectroscopy could be successfully employed for discrimination between neutral 2-methyl and mesoionic 1-methyl isomers of pyridazino-fused triazines (**61**) and (**62**) ⟨90CB1415⟩. The UV spectrum of (**62**) showed significant negative solvatochromy. Intramolecular ring closure (e.g., by aminolysis) ⟨86JHC375⟩ or cyclodimerization ⟨81CCC2557⟩ resulting in extended conjugation usually caused a bathochromic shift. The tautomeric equilibrium between (**59**) and (**60**) was also studied by UV spectroscopy ⟨72LA(757)100⟩. Because of the participation of the C-3 substituent in the chromophoric system, (**59**) gave three UV maxima, whereas only two maxima could be observed for (**60**). UV and MCD (magnetic circular dichroism) spectra of a [1,2,4]triazino[2,3-*b*]isoquinoline derivative were reported ⟨76JHC1343⟩. Photoelectron spectroscopic studies on a mesoionic pyrido[1,2-*a*][1,3,5]triazine derivative (**63**) and its neutral analogue (**64**) showed that the N-1's binding energies measured could be correlated to the differences in charge distributions ⟨80ZC441⟩.



(61) (62) (63) (64)

8.24.2.2 Thermodynamic Aspects

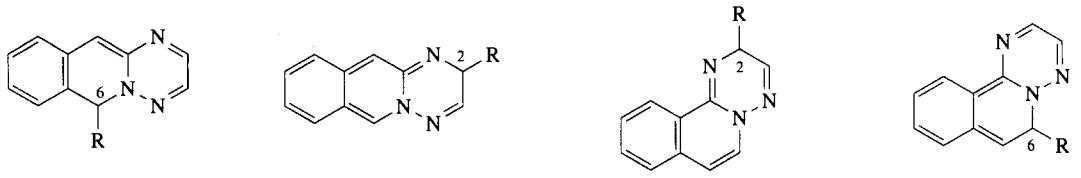
Prototropic tautomerism of pyrido[1,2-*a*][1,3,5]triazin-2,4-dione (**65**) was investigated ⟨77M367⟩. It was found that this compound predominantly exists in the uncharged form (**65a**) (Equation (3)). Prototropic tautomerism involving the side chain substituent was also studied for (**59**) and (**60**) ⟨72LA(757)100⟩. In the solid phase the enamine form (**59**) dominates, whereas in $CDCl_3$ solution

the ketimine form (**60**) predominates (~90%). Valence bond isomerization between 2-pyridyl phenyldiazonium salts (**57**) and pyrido[1,2-*c*]benzotriazinium salts (**58**) has been studied (Equation (1)) ⟨87JHC1133⟩. The equilibrium was found to be dependent on the substituent R, and to a lesser extent, on the solvent. Ring closure is favored by electron-withdrawing substituents. A ring–chain tautomerism was supposed to exist in the case of 3,6-dihydro-4*H*-pyrido[1,2-*d*][1,2,4]triazine thiones ⟨80JOC4372⟩.



(65a) (65b) (3)

The aromatic characters of the linearly and angularly fused tricyclic [1,2,4]triazines were considered ⟨93ACS296⟩. The exclusive formation of the 6-substituted pseudo base (**66a**) and the 2-substituted pseudo base (**67a**) from the linearly and angularly fused derivatives, respectively, could be interpreted by considering the aromatic stabilities of these compounds (Figure 2). Liquid chromatography with electrochemical detection was applied for the detection of the isoquinolino[1,2-*f*][1,2,4]triazinium derivative ⟨87JC25⟩.



(66a) (66b) (67a) (67b)

Figure 2 Comparison of the aromatic stabilities of pseudo bases (**66**) and (**67**).

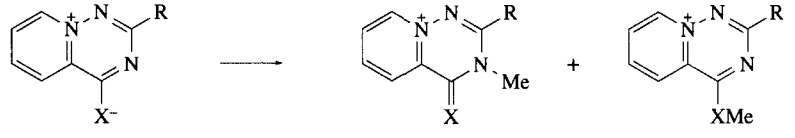
8.24.2.3 Reactivity

8.24.2.3.1 Pyrido[1,2-c][1,2,3]triazines

Reactions of this bicyclic ring system have not been reported. For the benzologue (**2**), a ring-opening reaction has been discussed in Section 8.24.2.1.2.

8.24.2.3.2 Pyrido[2,1-f][1,2,4]triazines

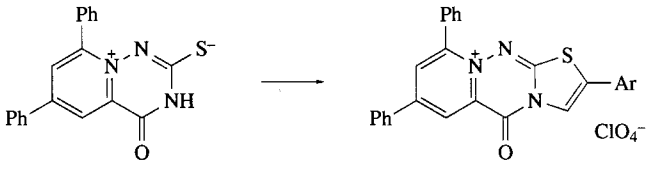
Regioselectivity of methylation reactions of pyrido[2,1-*f*][1,2,4]triazinium-4-olates and 4-thiolates (obtained from the 4-olates with P_2S_5) (**68**; X = O or S) was studied ⟨88JHC437, 90JHC1673⟩. With methyl iodide, 3-NMe and SMe derivatives, respectively, were exclusively formed. Mixtures of (**69**) and (**70**) were obtained with trimethyloxonium fluoroborate (Equation (4)). Phenylation of the 4-olate with diphenyliodonium tetrafluoroborate gave a 3-NPh derivative, whereas phenylation of the 4-thiolate afforded 4-SPh derivatives of type (**70**; X = S)



(68) X = O, S (69) (70) (4)

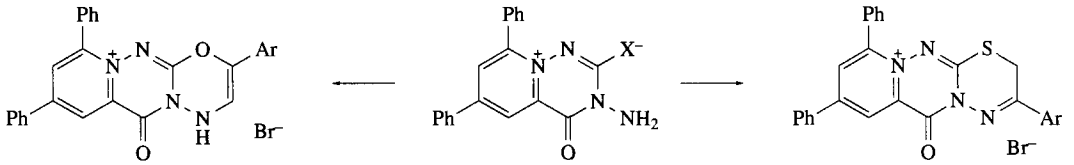
The 2-olate and 2-thiolate analogues gave OMe and SMe derivatives, respectively, upon methylation ⟨84S697, 87H(26)2183, 88JHC437, 93T3185⟩. Compound (**71**) was converted into the thiazolo derivative (**72**) by treatment with phenacyl bromides (Equation (5)) ⟨87H(26)2183⟩. The 3-amino-2-olate

(X = O) and 2-thiolate (X = S) derivatives (**73**) were also reacted with phenacyl bromides to give 2-aryl and 3-aryl derivatives (**74**) and (**75**), respectively (Scheme 1) ⟨84S697, 86JCR(S)460⟩.



(5)

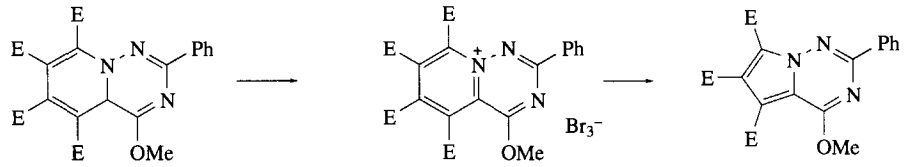
(71) (72)



(74) (73) (75)

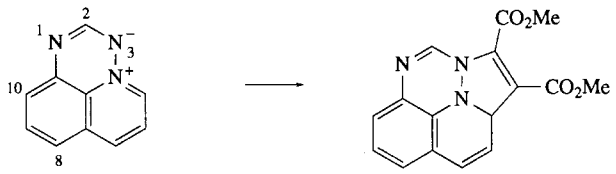
Scheme 1

Oxidation of the 4a*H*-pyrido[2,1-*f*][1,2,4]triazine (**76**) with bromine was reported ⟨77LA1718⟩. The fully conjugated tribromide (**77**) underwent ring contraction with water to give (**78**) (Scheme 2). Bromination of the mesoionic (**79**) with pyridinium hydrobromide perbromide gave 8-mono and 8,10-dibromo derivatives. Compound (**79**) with DMAD afforded the tetracyclic 1 : 1 adduct (**80**) (Equation (6)) ⟨83JCS(P1)349⟩.



(76) (77) (78)

Scheme 2



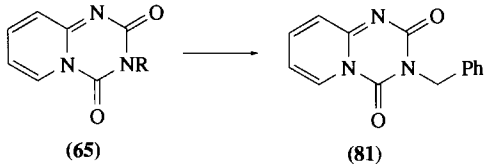
(6)

(79) (80)

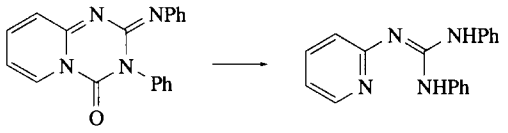
Photolyses of pyrido[2,1-*f*][1,2,4]triazinium-4-olates and a [1,2,4]triazino[6,1-*a*]isoquinolinium-4-olate in methanol gave 2-pyridinecarboxamide and 1-isoquinolinecarboxamide, respectively ⟨91H(32)649⟩.

8.24.2.3.3 Pyrido[1,2-a][1,3,5]triazines

Alkylation of (**65**) with benzyl chloride in DMF/K_2CO_3 or toluene/NaH proceeded smoothly to afford the 3-benzyl derivative (**81**) ⟨77M367⟩. Hydrolytic cleavage of (**81**) gave *N*-2-pyridyl-*N'*-benzyl urea ⟨77M367⟩, whereas a guanidine derivative (**83**) was formed from (**82**) by refluxing in dilute H_2SO_4 (Scheme 3) ⟨83JPR463⟩.



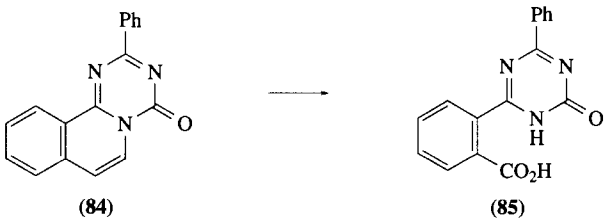
(65) (81)



(82) (83)

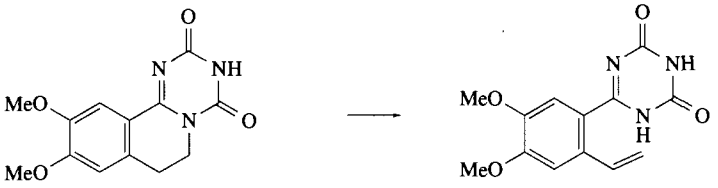
Scheme 3

Oxidation of the benzo-fused derivative (**84**) with $KMnO_4$ gave (**85**) (Equation (7)) ⟨75CB3799⟩. A facile carbon–nitrogen bond cleavage in the tetrahydropyridine ring of (**86**) to give (**87**) could also be induced by treatment with excess of sodium hydride in DMF (Equation (8)) ⟨90JOC5117⟩. Reaction of (**86**) with $POCl_3$ gave a 2-chloro-4-oxo derivative which on treatment with amines afforded 2-amino analogues ⟨84IJC(B)1268⟩. Cycloreversion of pyrido[1,2-*a*][1,3,5]triazines to pyridyl heterocumulenes by retro Diels–Alder reaction has been extensively investigated ⟨81CCC2557, 82ZC140, 83JPR463⟩. The rate of dissociation of (**88**) was also measured ⟨88JHC1459⟩. The dimer decomposes to (**89**) with a half life of 13 minutes at 55 °C (Equation (9)). Activation parameters were calculated, and values of $E_a = 28.1$ kcal mol^{-1} (117.6 kJ mol^{-1}), $\Delta S^* = 11$ eu were obtained.



(84) (85)

(7)



(86) (87)

(8)

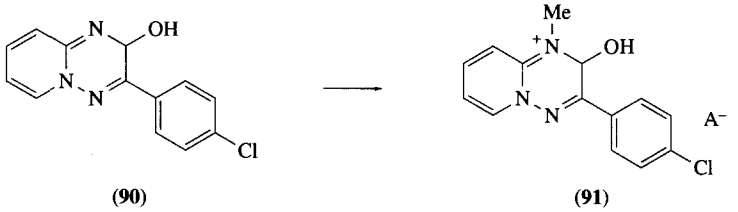


(88) (89)

(9)

8.24.2.3.4 Pyrido[1,2-b][1,2,4]triazines

Methylation of the 1,2-dihydro-2-hydroxy pseudo base (**90**) with trimethyloxonium hexafluorophosphate led to the formation of the 1-methyl derivative (**91**) (Equation (10)) ⟨92T8459⟩. Compound (**92**) was cyclized on treatment with polyphosphoric acid to the furo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium salt (**93**) (Equation (11)) ⟨89CB1935⟩, which proved to be a versatile starting material for 2-methoxy- and 2-pyrrolidinopyrido[1,2-*b*][1,2,4]triazines ⟨89CB1935⟩, and also for pyridazino-fused derivatives ⟨90CB1415⟩.



(90) (91)

(10)

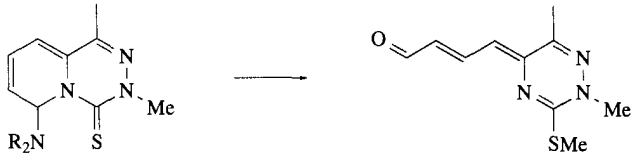


(11)

(92) (93)

8.24.2.3.5 Pyrido[1,2-d][1,2,4]triazines

Treatment of compounds (**94**) with iodomethane in aqueous base afforded the aldehyde (**95**) by ring opening and alkylation (Equation (12)) ⟨80JOC4372⟩.

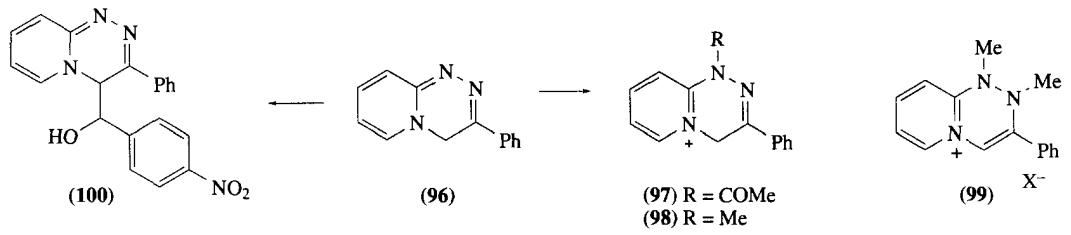


(12)

(94) (95)

8.24.2.3.6 Pyrido[2,1-c][1,2,4]triazines

Acetylation and methylation of the 3-phenyl derivative (**96**) were thought to proceed at the *N*-1 position to give (**97**) and (**98**), respectively. The methylated derivative (**98**) was also synthesized in an independent way ⟨69JOC2129⟩. Compound (**96**) reacted with 4-nitrobenzaldehyde at position 4 to afford the adduct (**100**). Selective demethylation of (**99**) could be achieved on heating with 16% hydrobromic acid.



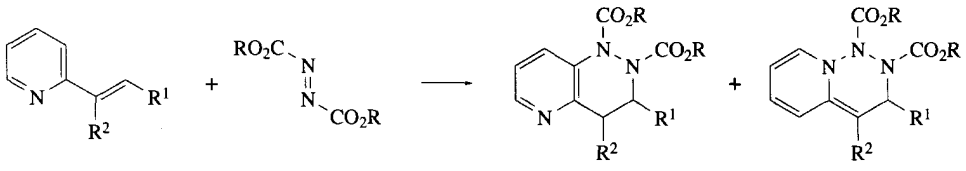
(100) (96) (97) R = COMe (98) R = Me (99)

Scheme 4

8.24.2.4 Synthesis

8.24.2.4.1 Pyrido[1,2-c][1,2,3]triazines

Cycloaddition reaction of 2-vinylpyridines and dialkyl azodicarboxylates in boiling benzene gave two isomeric 1 : 1 adducts. The minor products were identified as pyrido[1,2-*c*][1,2,3]triazine diesters (**101**) (Equation (13)) ⟨78TL2731, 79T2027⟩. When the cycloaddition reaction was performed in the presence of biocatalyst (*Saccharomyces cerevisiae*), no (**101**) was formed ⟨93BCJ2429⟩.



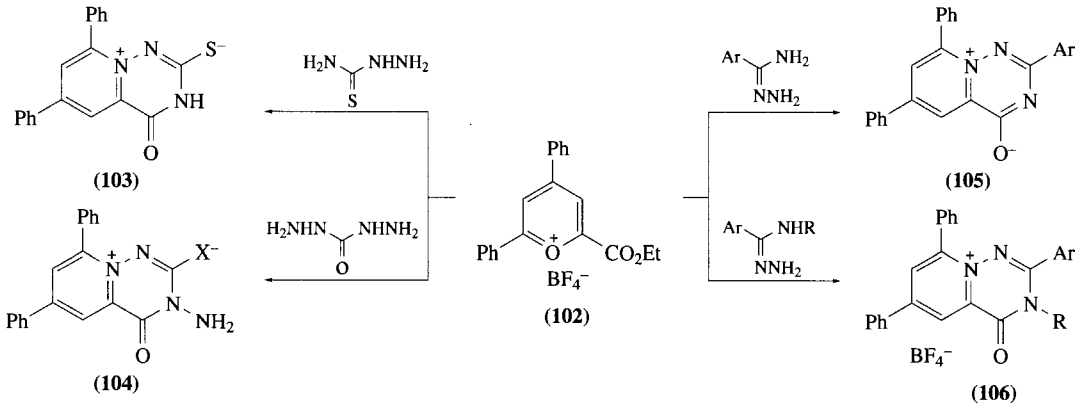
(13)

(101)

Of the benzologues, only pyrido[1,2-*c*][1,2,3]benzotriazinium derivatives have been described. They were formed by valence bond isomerization of α-pyridyl phenyldiazonium salts (see Section 8.24.2.2) ⟨87JHC1133⟩.

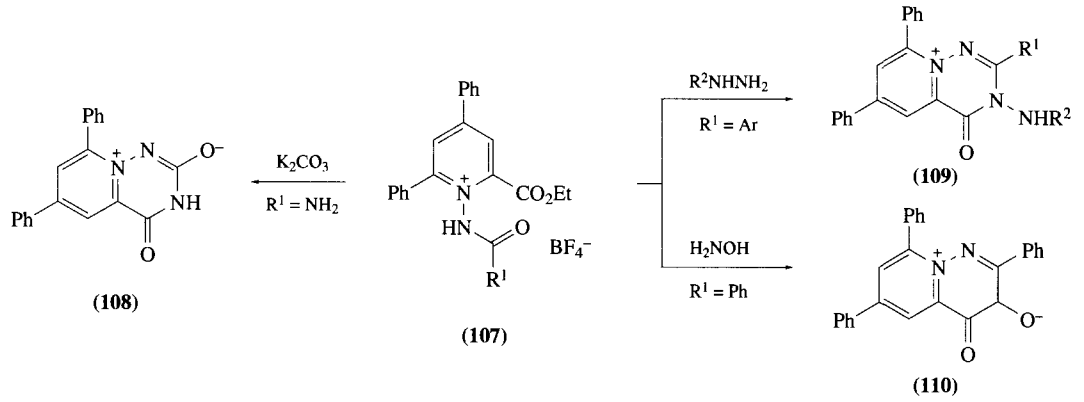
8.24.2.4.2 Pyrido[2,1-f][1,2,4]triazines

Pyrylium salts have been found to be particularly useful starting materials for preparation of pyrido[2,1-*f*][1,2,4]triazines. Reaction of (**102**) with thiosemicarbazide ⟨87H(26)2183⟩, carbonohydrazide ⟨86JCR(S)460⟩, thiocarbonohydrazide ⟨84S697⟩, or amidrazones ⟨91H(32)649⟩ gave the bicyclic compounds (**103**)–(**106**), generally in high yields (Scheme 5).



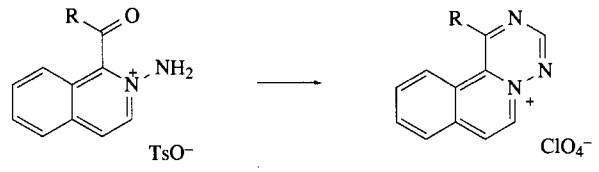
Scheme 5

When (**102**) was allowed to react with semicarbazide ⟨81JCS(P1)1495⟩ or hydrazides ⟨86S234⟩, the corresponding ureido and amidopyridinium salts (**107**) were obtained. These compounds could then be cyclized with K_2CO_3 ⟨81JCS(P1)1495⟩, hydrazines, or hydroxylamine ⟨86S234⟩ to give 2-olate (**108**), 3-amino (**109**), or 3-olate (**110**) derivatives, respectively, of the bicyclic ring system (Scheme 6).



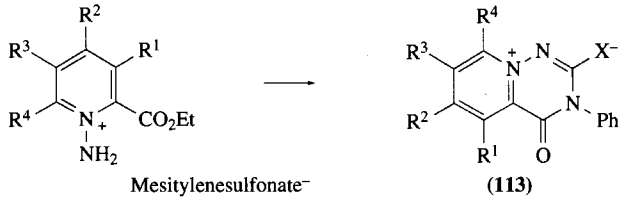
Scheme 6

A similar approach uses as starting materials *N*-aminopyridinium salts having *ortho* amide, ester, or aldehyde function. These compounds were reacted with orthocarboxylic acid esters, formamide, or urea, respectively, to give pyrido[2,1-*f*][1,2,4]triazines in fairly good yields ⟨86JHC375, 88JHC437⟩. By this route, *N*-aminoisoquinolinium derivatives (**111**) could also be cyclized with formamide in the presence of $TiCl_4$ and perchloric acid to give (**112**) (Equation (14)) ⟨92BSB597⟩. The 3-acyl analogues of (**111**) gave linearly fused [1,2,4]triazino[1,6-*b*]isoquinolines.



(14)

(111) (112)

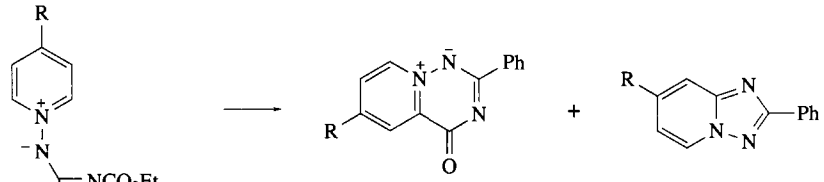


(15)

Mesitylenesulfonate⁻ (113)

Ethoxycarbonyl pyridinium salts were successfully reacted with phenyl isocyanate or thiocyanate to afford (**113**) via *N*-ylides (Equation (15)). This reaction could be extended to the benzologues ⟨93T3185⟩.

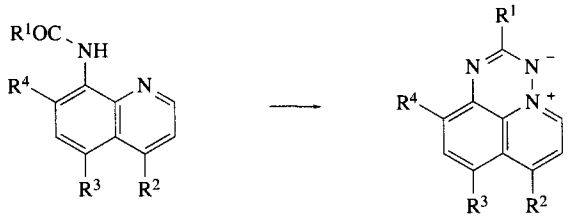
Pyridinium *N*-ylides (**114**) were cyclized to (**115**), but triazolopyridines (**116**) were also formed (Equation (16)). The product ratio was about 1.5 : 1 ⟨76CL413, 77JOC443⟩.



(16)

(114) (115) (116)

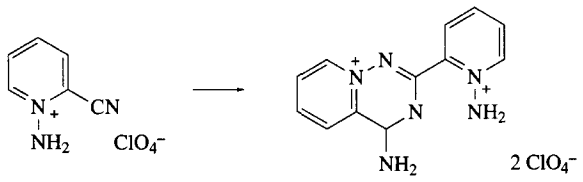
On *N*-amination of 8-acylaminoquinolines (**117**) and subsequent treatment with K_2CO_3, cyclization occurred to give the pyrido[3,2,1-*ij*][1,2,4]benzotriazine derivatives (**118**) (Equation (17)) ⟨77H(6)281, 83JCS(P1)349⟩.



(17)

(117) (118)

The cyano-substituted *N*-aminopyridinium salt (**119**) dimerized to (**120**) with the participation of the cyano group (Equation (18)), but the quinoline and isoquinoline analogues reacted differently ⟨89JOC3062⟩. The dimerization of (**119**) could be suppressed by treatment with triethyl orthoformate. The iminoformate formed could then be cyclized with amines ⟨90H(31)289⟩.

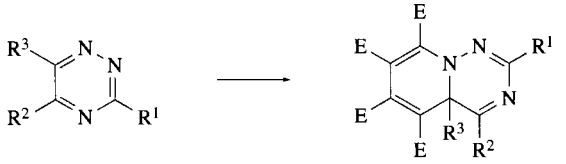


(18)

(119) (120)

Only one synthetic approach has been reported in which a pyridine ring was elaborated onto a triazine. The reaction of (**121**) with dimethyl acetylenedicarboxylate gave several products, and the

yield of the pyrido[2,1-*f*][1,2,4]triazine derivatives (**122**) was moderate (Equation (19)) ⟨77LA1421, 77LA1718⟩.

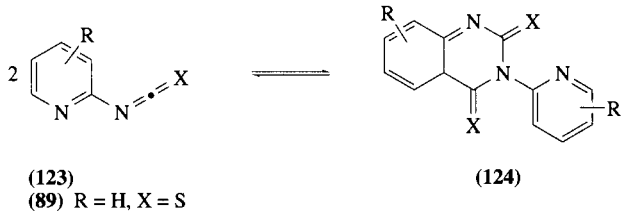


(**121**) (**122**) E = CO_2Me + other product (s) (19)

8.24.2.4.3 Pyrido[1,2-a]-1,3,5-triazines

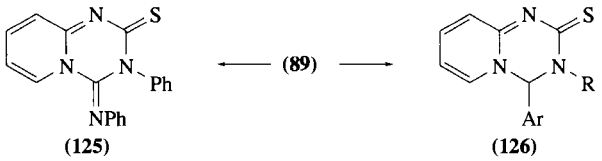
Pyridyl heterocumulenes have most frequently been used as starting materials which could serve as dienes in a Diels–Alder reaction.

Pyridyl isocyanates ⟨68AG362, 71AG406, 75TL2783, 80CPB3570⟩, isothiocyanates ⟨76JHC873, 77S582⟩, and carbodiimides ⟨77ZC371, 83JPR463⟩ (**123**; X = O, S, or NR) dimerized to give (**124**) (Equation (20)). Addition of aryl isocyanates to 2-pyridyl isocyanate ⟨68AG362, 80CC313⟩, 2-pyridyl isothiocyanate ⟨81CCC2557, 82ZC140, 87JPR108⟩, and 2-pyridyl formamidine ⟨70CB3525⟩ also took place smoothly to give 3-aryl derivatives of this ring system. Aldimines ⟨81CCC2557⟩ and diphenyl carbodiimide ⟨82ZC140⟩ could be reacted with pyridyl isothiocyanate (**89**) in [4 + 2] cycloaddition to give (**126**) and (**125**), respectively (Scheme 7).



(**123**) (**124**) (20)

(**89**) R = H, X = S



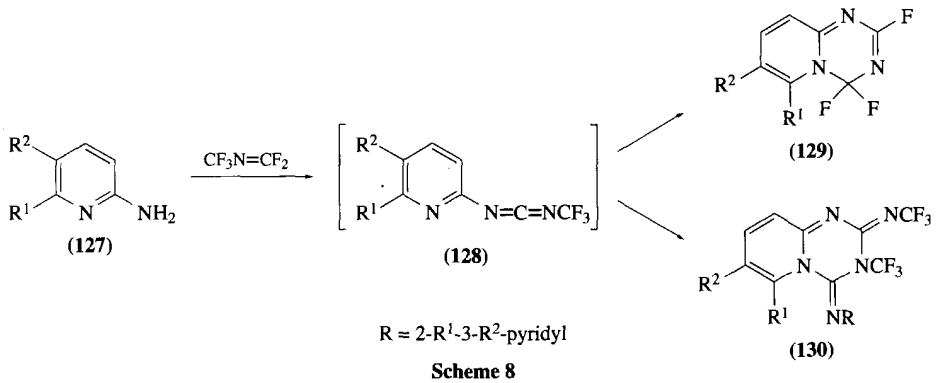
(**125**) (**126**)

Scheme 7

Pyridyl azomethines as dienes were also shown to undergo Diels–Alder reaction with diphenyl carbodiimide, isocyanates, and diphenyl ketene ⟨78T101⟩. Pyridyl carbodiimides prepared *in situ* reacted with dienophiles, such as phenyl isocyanate, to give a 3-phenylpyrido[1,2-*a*][1,3,5]triazine derivative, or underwent cyclodimerization ⟨79ZC59, 83JPR463⟩. *N*-Phenyl-*N'*-quinolinyl carbodiimide reacted analogously with phenyl isocyanate. By varying the substituents of (**127**), different products could be obtained from reaction with the carbodiimide (**128**), formed *in situ* (Scheme 8) ⟨76CC567⟩. Electron-withdrawing substituents facilitate the dimerization to (**130**). The self-addition could be completely suppressed by steric effects. In the cases of 2-amino-6-methylpyridine and 2-aminoquinoline, products of type (**129**) only were formed. Pyrido[1,2-*a*][1,3,5]triazines could also be prepared from 2-aminopyridines. Chlorinated isocyanates ⟨78JPR625⟩, chlorocarbonyl isocyanate ⟨85S892, 92JMC189⟩, phenoxycarbonyl isocyanate ⟨92JMC189⟩, 1,3-bifunctional iminium halides ⟨79ACH29, 92JHC1551⟩, (*N*-chloroalkylidene)carbamic acid chlorides ⟨66AG981⟩, and *N*-cyanoacetimidates ⟨75JHC407⟩ served as appropriate C—N—C fragments.

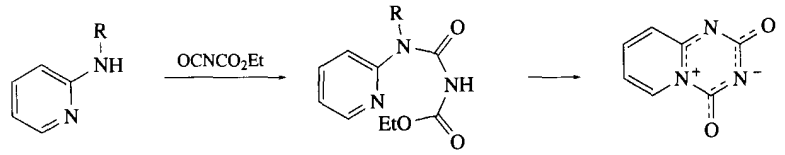
Dichloromethylenebenzamide could also be reacted with 2-aminoisoquinoline to give the angularly fused 2-phenyl-4-oxotriazino[2,1-*a*]isoquinoline derivative in poor yield ⟨76CB118⟩. Ethoxycarbonyl isocyanate with 2-(substituted amino)pyridines (**131**) gave 1-substituted betaines (**133**) via allophanates (**132**) (Scheme 9) ⟨76CB3661⟩.

Using 1-amino-6,7-dimethoxy-3,4-dihydroisoquinoline and ethoxycarbonyl isocyanate, the



(127) (128) (129) (130)

Scheme 8



(131) (132) (133)

Scheme 9

benzo-fused triazino[2,1-*a*]isoquinoline derivative (**86**) was obtained ⟨84IJC(B)1268⟩. Alternatively, 2-(ethoxycarbonylamino)pyridine could be reacted with aryl isocyanates ⟨77M367⟩. Phenoxycarbonyl isocyanate reacted with tetrahydropyridyl aniline in the same way as (**131**) ⟨88CB1579⟩).

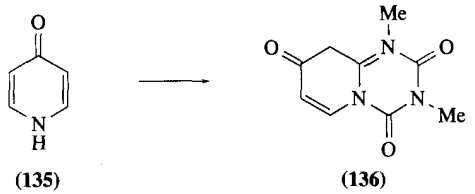
The third main route for the preparation of pyrido[1,2-*a*][1,3,5]triazines involves cyclization of pyridine precursors, such as 2-pyridyl urea ⟨77M367⟩, ethoxycarbonyl thiourea ⟨72S308⟩, cyanoguanidines ⟨78JMC773⟩, biurets ⟨75BSF1419⟩, or their thio analogues ⟨82H(19)531⟩, and thiourethans ⟨91SUL225⟩. Using 2-cyanimino-1-(phenylcarbamoyl)piperidine, tetrahydropyrido[1,2-*a*][1,3,5]-triazine (**134**), could be obtained (Equation (21)) ⟨91LA975⟩.



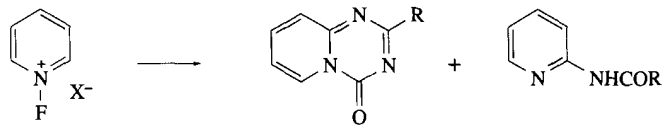
(134) (21)

The cyclization step can also proceed via Michael addition. Thus, reaction of 4-pyridone (**135**) with methyl isocyanate in the presence of base afforded (**136**) in quantitative yield (Equation (22)) ⟨83S593⟩. This reaction could also be carried out with 4-quinolone ⟨83S593, 82TL3181⟩.

An interesting synthetic approach was reported in 1994. In this reaction, *N*-fluoropyridinium salts (**137**) were treated with nitriles in the presence of cyanate ion, affording pyridotriazines (**138**) together with the amides (**139**) (Equation (23)) ⟨94TL207⟩. A carbene, derived from (**137**), was proposed as intermediate.



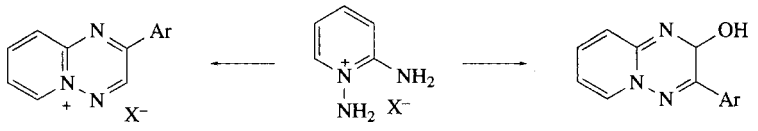
(135) (136) (22)



(137) (138) (139) (23)

8.24.2.4.4 Pyrido[1,2-b][1,2,4]triazines

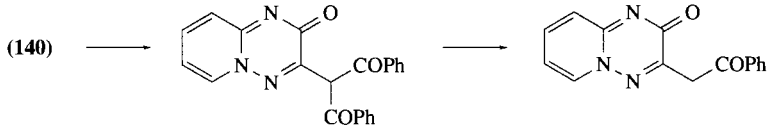
For the synthesis of this ring system, two routes have mainly been employed. Mono- or bicyclic 1,2-diaminopyridinium salts were reacted with 1,2-dicarbonyl compounds or *N*-aminopyridinium salts were treated with various azirines. 1,2-Diaminopyridinium salts (**140**) with arylglyoxals gave 2-arylpyrido[1,2-*b*][1,2,4]triazines (**141**), whereas 3-aryl-2-hydroxy derivatives (**142**) were formed under neutral conditions (Scheme 10). The latter compounds could then be dehydrated ⟨70KGS1148, 73KGS1266, 92T8459⟩.



(**141**) (**140**) (**142**)

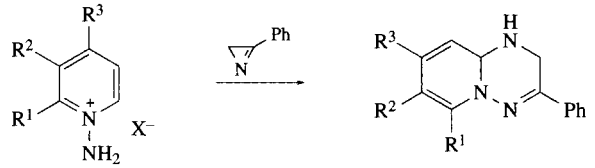
Scheme 10

These reactions were extended to 1,2- and 2,3-diaminoisoquinolinium salts ⟨93ACS296⟩. Diacetyl, however, reacted only with the 2,3-diaminoisoquinolinium salt. In contrast, diacetyl could smoothly undergo cyclocondensation with 6-thioxo ⟨73JPR679⟩ or 6-oxo ⟨90JCR(S)186⟩ analogues of (**140**), affording 2,3-dimethyl-6-thioxo or 2,3-dimethyl-6-oxopyrido[1,2-*b*][1,2,4]triazines, respectively. The linearly fused benzologue was obtained when 2,3-diamino-1-oxoisoquinoline was used ⟨75YZ340⟩. On treatment of (**140**) with 4-benzoyl-5-phenyl-2,3-furanedione, (**143**) was obtained, which could be converted to (**144**) (Scheme 11) ⟨89CB1935⟩. Two benzologues of (**140**), the 1,2-diaminoquinolinium and 1,2-diaminoisoquinolinium salts, reacted with the above furanedione in the same way ⟨92M1181⟩. In the other synthetic pathway, (**145**) were reacted with azirines to afford (**146**) (Equation (24)) ⟨75JOC544, 76JOC2739, 77JOC2514⟩. Isoquinolinium salts, or isoquinolinium and quinolinium imine dimers were shown to undergo the same cyclization reaction ⟨75MI 824-01, 76JOC2739⟩.



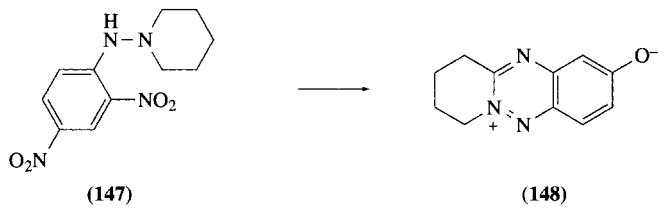
(**140**) (**143**) (**144**)

Scheme 11



(**145**) (**146**) (24)

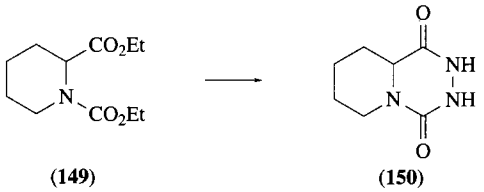
Two more synthetic methods have been described, but are of limited scope. A linearly fused benzologue (**148**) was synthesized from 2,4-dinitro-*N*-piperidinoaniline (**147**) by treatment with acid (Equation (25)). A benzimidazole derivative was also formed in this reaction probably via *tertiary* amino effect, Cope elimination, cyclization, and a hydrolytic step ⟨77JCS(P1)478⟩. Ring transformation of 3,5-dinitro-1-(2-pyridyl)-2-pyridone with sodio acetoacetate lead also to the formation of this ring system, but in poor yield ⟨79TL1393⟩.



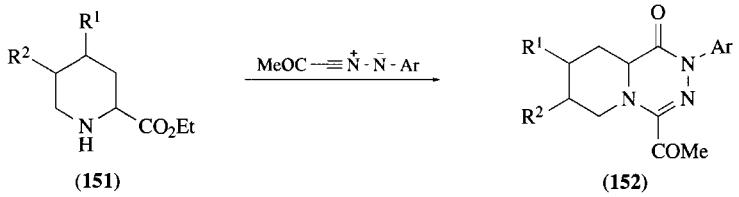
(**147**) (**148**) (25)

8.24.2.4.5 Pyrido[1,2-d][1,2,4]triazines

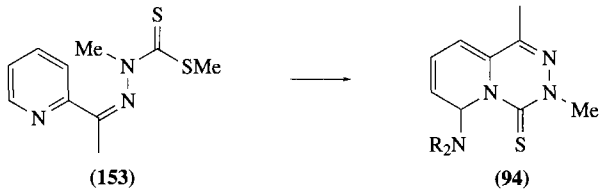
The first synthesis of this ring system was accomplished by treatment of diethyl piperidinedicarboxylate (**149**) with anhydrous hydrazine in the presence of sodium ethoxide, affording (**150**) (Equation (26)). Compound (**150**) could also be obtained in two steps, starting from picolinic acid hydrazide, which was reacted with ethyl chloroformate and the product thus formed was then hydrogenated ⟨71AP(304)216⟩. Piperidine-2-carboxylates (**151**) with nitrile imines gave 1-oxo-2-aryl derivatives (**152**) (Equation (27)) ⟨91H(32)1879⟩. Tetrahydroisoquinoline-3-carboxylate reacted similarly to give the linearly fused benzologue. Reaction of hydrazone (**153**) with dialkylamines provided access to 6-dialkylamino-4-thiones (**94**) (Equation (28)) ⟨80JOC4372⟩.



(149) (150) (26)

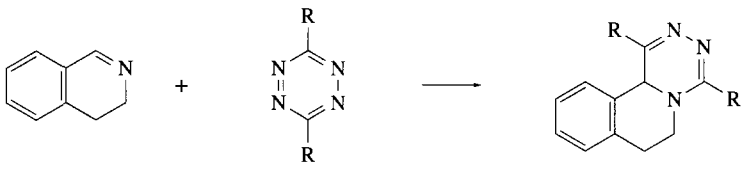


(151) (152) (27)



(153) (94) (28)

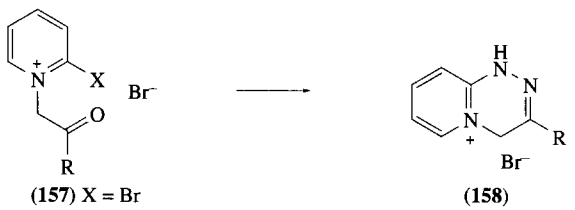
The other known benzologue (**156**) was obtained by Diels–Alder reaction of tetrazines (**155**) with 3,4-dihydroisoquinoline (**154**) followed by elimination of N_2 (Equation (29)) ⟨82AP(315)428⟩.



(154) (155) (156) (29)

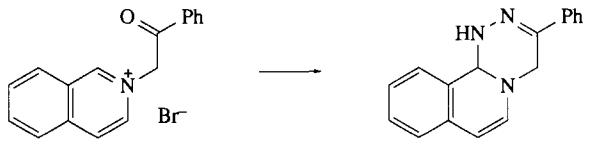
8.24.2.4.6 Pyrido[2,1-c][1,2,4]triazines

Mono- or bicyclic pyridines or their hydrogenated derivatives have been used as starting materials. Acylmethylpyridinium salts (**157**) could be easily reacted with hydrazines to give (**158**) (Equation (30)) ⟨69JOC2129, 86EJM417⟩. Instead of (**157**), 2-chloro-1-propargylpyridinium bromide was also used successfully ⟨84JHC1765⟩.

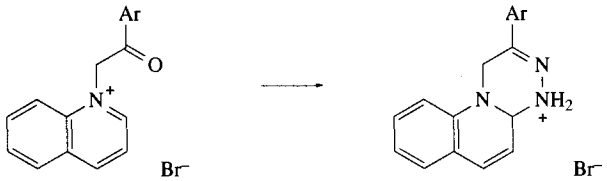


(157) X = Br (158) (30)

Phenacylisoquinolinium bromide (**159**) and the quinolinium analogues (**160**) with hydrazine gave the triazino[3,4-*a*]isoquinoline (**161**) (Equation (31)) ⟨71JOC2767, 73CB1549, 76KGS372⟩ and triazino[4,3-*a*]quinoline derivatives (**162**) (Equation (32)) ⟨80CZ203⟩, respectively. The same reaction also took place with 1-acylmethyl-3-cyanopyridinium bromides, when the 7-cyanopyrido[2,1-*c*]triazines were formed. Apparently the cyano substituent is essential for this cyclization ⟨73CB1549, 76KGS372⟩.

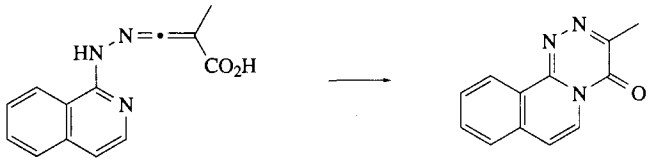


(159) (161) (31)

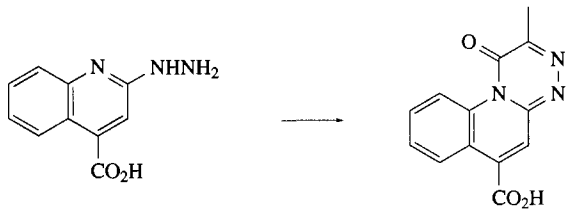


(160) (162) (32)

In the other route, condensation products of hydrazinopyridines with α-ketocarboxylic acids or esters (alternatively, dimethyl acetylenedicarboxylate can be used) were cyclized ⟨71CB2793, 72LA(755)101, 72LA(757)100, 87CPB80⟩. Thus, for example, (**163**) could be converted into the tricyclic (**164**) in boiling xylene (Equation (33)). Cyclization could not be observed in the case of the quinoline analogue ⟨71CB2793⟩, whereas (**166**) could be prepared from (**165**) (Equation (34)) ⟨91KGS1227⟩.



(163) (164) (33)

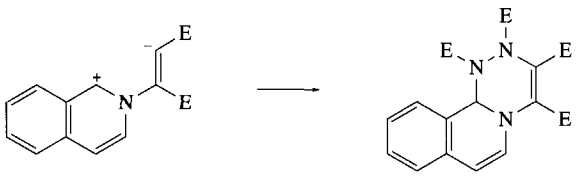


(165) (166) (34)

Oxidative ring closure of 2-piperidinophenylacetic acid hydrazide (**167**) with Hg(II)-EDTA also provided an access to the bicyclic ring system. However, a rearrangement took place affording the 4-oxo-derivative (**168**) rather than the expected 3-oxo-analogue (Equation (35)) ⟨77AP(310)588⟩. Interesting syntheses of triazinoisoquinoline (**170**) and triazinoquinoline (**172**) have been described (Equations (36) and (37)). The three-component reactions of isoquinoline or 2-methylquinoline, respectively, dimethyl acetylenedicarboxylate and dimethyl azodicarboxylate proceeded via 1,4-dipoles (**169**) and (**171**) formed *in situ* ⟨67CB1094⟩.

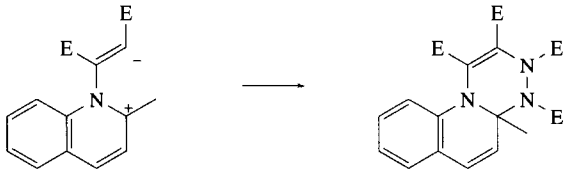


(167) (168) (35)



(169) E = CO_2Me (170)

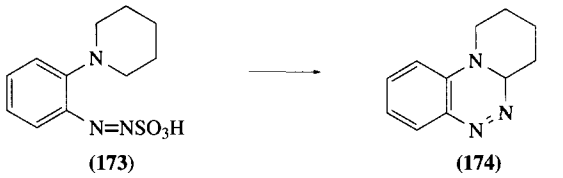
(36)



(171) (172)

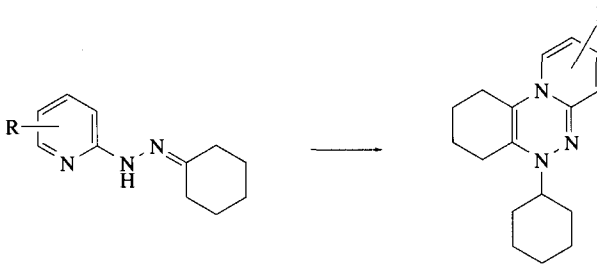
(37)

The third known benzologue, the pyrido[1,2-*c*][1,2,4]benzotriazine ring system, was synthesised by two different methods. In the first synthesis *ortho*-piperidinophenyl diazonium sulfonate (**173**) was cyclized with sulfur dioxide, then treated with warm dilute sodium hydroxide to give (**174**) (Equation (38)) ⟨68CC923⟩. The other synthesis is based on an abnormal reaction of cyclohexanone hydrazones (**175**). Instead of Fischer cyclization to carboline derivatives, another reaction took place in HCl affording 6-cyclohexyl derivatives (**176**) (Equation (39)) ⟨70KGS186⟩.



(173) (174)

(38)



(175) (176)

(39)

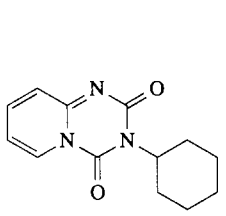
8.24.2.5 Important Compounds and Applications

Relatively few studies have been reported for fused triazines having biological activities or other uses.

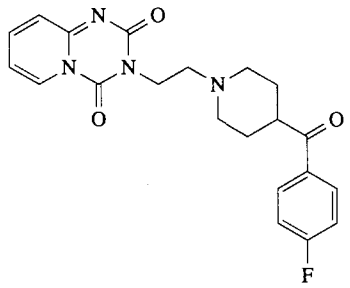
Compound (**177**), *triazindione* (Agripat), is useful as a herbicide, being a potent inhibitor of the photosynthetic electron flow of chloroplasts ⟨74ZN(C)232⟩. The pyrido[1,2-*a*][1,3,5]triazine derivative (**178**) (DV-7028) has been selected for clinical studies as a potent and selective 5-hydroxytryptamine (5-HT_2) receptor antagonist, being potentially effective in several vascular diseases ⟨92MI 824-01⟩. A tricyclic triazine derivative, (**179**) (*trazium esilate*), has been found to possess excellent antidepressant properties without exhibiting serious sedative effects ⟨89AF775⟩.

8.24.3 PYRIDOOXADIAZINES, PYRIDOTHIADIAZINES, AND THEIR BENZO DERIVATIVES

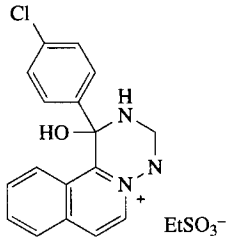
Twelve pyridooxadiazines and 12 pyridothiadiazines with one bridgehead nitrogen are possible. Of these, four bicyclic oxadiazines and four bicyclic thiadiazines have been reported (Table 2). The bicyclic parent systems of the (**30**) and (**38**)–(**40**) benzologues have not yet been described.



(177)



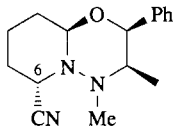
(178)



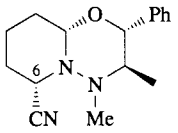
(179)

8.24.3.1 Theoretical and Experimental Structural Methods

Theoretical calculations on these classes of compounds have not yet been recorded. The structures of two hexahydropyrido[2,1-*b*][1,3,4]oxadiazines (**180**) and (**181**) have been determined by x-ray crystallography. The analysis revealed that the six-membered rings are chair shaped and the ring fusion is *cis* ⟨93AX(C)1786⟩.



(**180**)
(2*R*,3*S*,6*R*,9a*S*)



(**181**)
(2*R*,3*S*,6*R*,9a*R*)

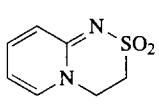
8.24.3.1.1 NMR spectroscopy

In the ^{1}H NMR spectra of those compounds which possess a methylene group in the oxa- or thiadiazine ring, the multiplicity of the methylene signal seems to be dependent on the type and position of the heteroatoms. Thus, the 4-methylene protons of 3-methyl- and 3-phenyl-4*H*-derivatives of (**27**) appear as an *AB* quartet ($J = 18.5$ Hz) ⟨86AP(319)774⟩, whereas no splitting was found for the SCH_2 signals in some derivatives of [1,3,4]-thiadiazines (**36**) ⟨82S645⟩ and (**37**) ⟨88H(27)733⟩. Broadening of these signals was observed for derivatives of (**33**) ⟨73CPB2146⟩. The two stereoisomers of 4,4a-dihydro derivatives of (**33**) gave significantly different ^{1}H NMR spectra ⟨84H(22)2237, 85BCJ1432⟩.

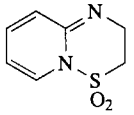
Conformation and ring-chain tautomerism of 3-substituted-1,1-dioxide derivatives of (**39**) were studied by ^{1}H NMR (see Section 8.24.3.2).

8.24.3.1.2 IR spectroscopy

The IR spectrum can be a valuable tool for distinguishing ring isomers. Thus, the structure of the reaction product (**182**) from 2-aminopyridine with 2-chloroethylsulfonyl chloride was easily assigned on the basis of the C=N absorption (1570 cm^{-1}). Compound (**183**) should exhibit a much higher C=N frequency, since there is no conjugation with the SO_2 group ⟨73BSF985⟩.



(**182**)



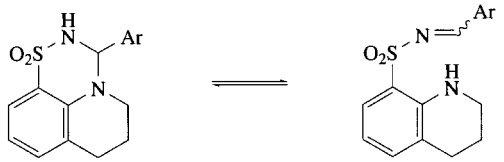
(**183**)

8.24.3.1.3 Mass spectrometry

Most of the pyridooxadiazines and pyridothiadiazines possess readily identifiable molecular ions. Compounds containing a quaternary pyridine nitrogen with a halide as counterion show a characteristic peak at M^+—HX. Fragments most frequently arise from the loss of HCN, CO, HCNO, SO_2H, and from combinations thereof. Retro Diels–Alder cleavage can also be a characteristic process ⟨86ZC100⟩.

8.24.3.2 Thermodynamic Aspects

For a series of 3-arylpyrido[1,2,3-*de*][1,2,4]benzothiadiazine-1,1-dioxides (**184**), it was concluded that the aryl group is in a pseudo equatorial position and twisted out of the plane ⟨92IJC(B)310⟩. In the same work, a ring-chain tautomerism was also described (Equation (40)). The position of the equilibrium was found to depend on the substituent of the aryl ring.



(184) (185) (40)

Differential thermal analysis was conducted for 2-methoxy-7,8,9,10-tetrahydropyrido[2,1-*c*][1,2,4]benzothiadiazine-5,5-dioxide, and it was found that this compound exists in two polymorphic forms, one of them being remarkably unstable. Detailed conformational analyses for hexahydro[2,1-*b*][1,3,4]oxadiazines ⟨93AX(C)1786⟩ and hexahydropyrido[2,1-*e*][1,2,5]oxadiazines ⟨92AP(325)157⟩ were described on the basis of x-ray and NMR studies, respectively.

8.24.3.3 Reactivity

8.24.3.3.1 Pyrido[1,2-c][1,3,5]oxadiazines

No reactions of this ring system have been reported.

8.24.3.3.2 Pyrido[1,2-e]-1,2,5-oxadiazines

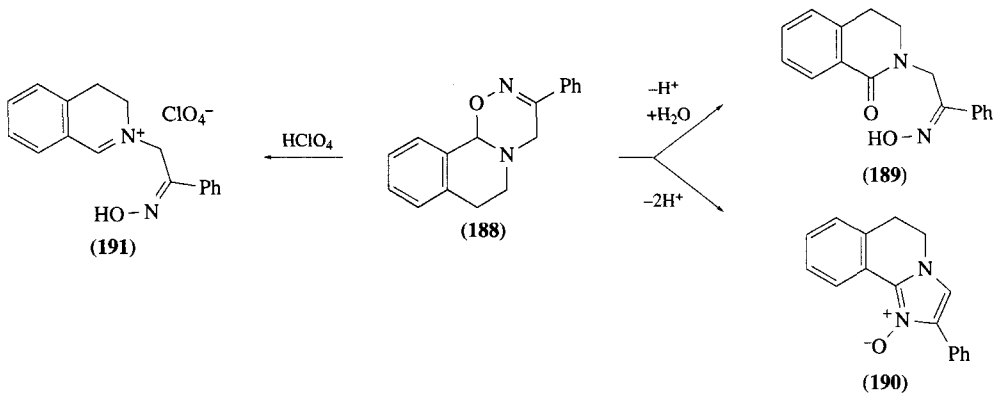
Upon treatment of the hexahydropyrido[1,2-*e*][1,2,5]oxadiazine (**186**) with Grignard reagents, the oximes (**187**) were obtained, in which the piperidine ring was substituted (Equation (41)) ⟨92AP(325)335⟩.



(186) (187) (41)

The benzo-fused derivative (**188**) afforded two isolable products in almost 1 : 1 ratio, on heating in aqueous ethanol. Compound (**189**) was supposed to be formed by hydrolysis, and (**190**) via ring

contraction (Scheme 12) ⟨86AP(319)774⟩. Ring opening of (**188**) also takes place by treatment with perchloric acid at room temperature, yielding the immonium salt (**191**).



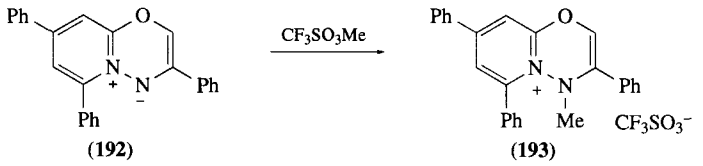
Scheme 12

8.24.3.3.3 Pyrido[2,1-b][1,3,5]oxadiazines

No reactions of this ring system have been described.

8.24.3.3.4 Pyrido[2,1-b][1,3,4]oxadiazinium salts

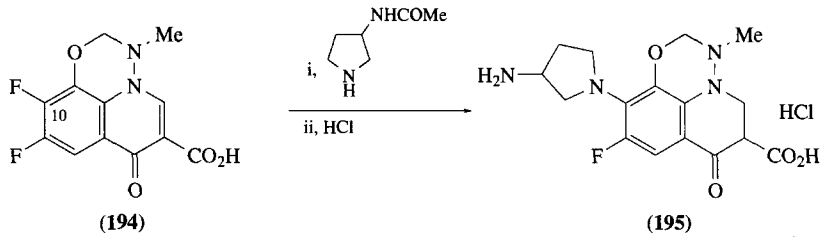
The only reaction reported for this ring system is its methylation with methyl triflate. From the fully unsaturated derivative (**192**), the *N*-methyl compound (**193**) can be obtained in fairly good yield (Equation (42)). Such reactions were also carried out with other 3-aryl derivatives ⟨83JHC381⟩.



(42)

8.24.3.3.5 Pyrido[3,2,1-ij][4,1,2]benzoxadiazines

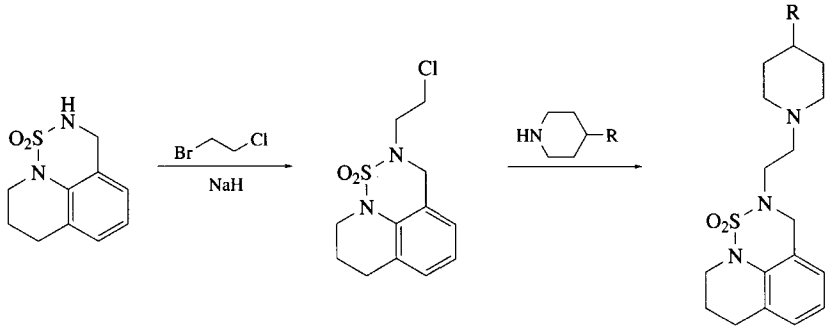
The parent bicyclic ring system has not yet been reported. By selective displacement of the fluoro atom at position-10 of (**194**), an amino substituent can be introduced to give (**195**) (Equation (43)) ⟨92JOC744⟩.



(43)

8.24.3.3.6 Pyrido[1,2-b][1,2,6]thiadiazines

Alkylation of the benzo derivative (**196**) with 1-bromo-2-chloroethane furnished compound (**197**), which upon treatment with a piperidine derivative gave (**198**) (Scheme 13) ⟨93MI 824-01⟩.

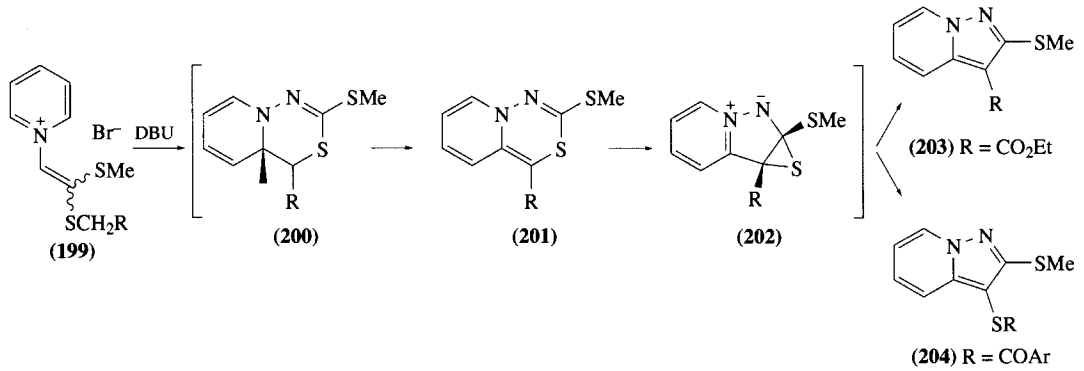


(196) (197) (198)

Scheme 13

8.24.3.3.7 Pyrido[1,2-d][1,3,4]thiadiazines

In the base-induced conversion of pyridinium salts (**199**) to pyrazolo[1,5-*a*]pyridines, 4,4a-dihydropyrido[1,2-*d*][1,3,4]thiadiazine intermediates (**200**) could be identified by ^{1}H NMR, but were not isolable. Their subsequent oxidation may afford 12π antiaromatic systems (**201**) which upon disrotatory cyclization to tricyclic thiiranes (**202**), followed by desulfurization or acyl migration, gave differently substituted pyrazolo[1,5-*a*]pyridines, (**203**) and (**204**), respectively (Scheme 14) ⟨85BCJ1432, 84H(22)2237⟩. A similar desulfurization reaction of this ring system has also been reported ⟨73CPB2146⟩.

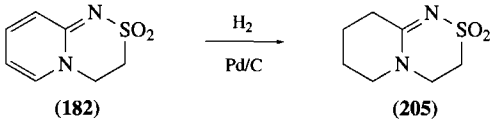


(199) (200) (201) (202) (203) R = CO_2Et (204) R = COAr

Scheme 14

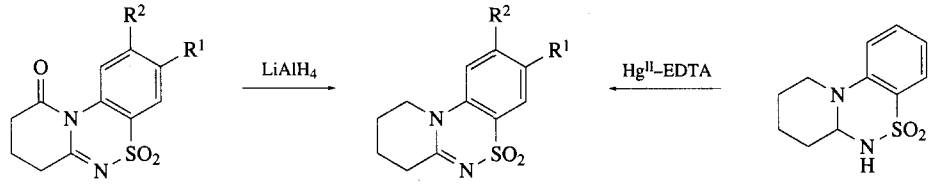
8.24.3.3.8 Pyrido[2,1-c][1,2,4]thiadiazines

The 3,4-dihydro derivative (**182**) was hydrogenated in the pyridine ring to afford the corresponding 3,4,6,7,8,9-hexahydro derivative (**205**) (Equation (44)) ⟨73BSF985⟩. Another synthesis of the latter has also been described ⟨79JOC3847⟩.



(182) (205) (44)

In the case of the benzo-fused pyrido[2,1-*c*][1,2,4]benzothiadiazine ring system, reduction of the carbonyl group of (**206**) with lithium aluminum hydride to (**207**) ⟨91AP(324)317, 72FES670⟩, and oxidation of a 2,2a-dihydro derivative (**208**) with mercury (II)-EDTA to (**209**) have been reported (Scheme 15) ⟨91AP(324)317, 90AP(323)911⟩.

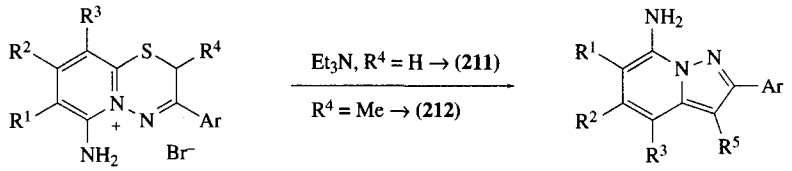


(206) (207) (208)
(209) $R^1 = R^2 = H$

Scheme 15

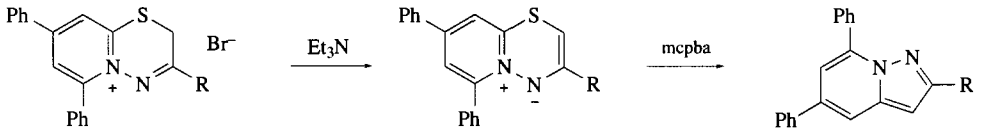
8.24.3.3.9 Pyrido[2,1-b][1,3,4]thiadiazines

Pyrido[2,1-*b*][1,3,4]thiadiazinium derivatives (**210**), including an angularly fused benzologue (R^2, $R^3 = (CH_2)_4$), easily undergo base-catalyzed ring contraction to give pyrazolo[1,5-*a*]pyridines (**211**) and (**212**) (Equation (45)) ⟨88H(27)733⟩. The same type of rearrangement reaction proceeded with the ylides (**214**), obtained from (**213**), which upon treatment with *m*-chloroperbenzoic acid afforded (**215**) (Scheme 16) ⟨82S645⟩.



(210) (211) $R^5 = SH$
(212) $R^5 = Me$

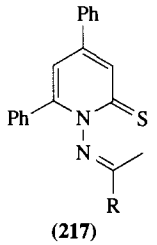
(45)



(213) (214) (215) $R^1 = H$
(216) $R^1 = SH$

Scheme 16

Electroreduction of (**213**) on a mercury pool cathode in aprotic medium has also been studied. Two products could be isolated: the fused pyrazoles (**216**) and the corresponding ketimines (**217**) ⟨90T5797⟩.



(217)

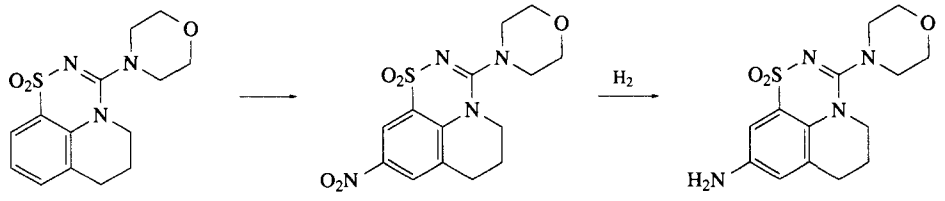
Methylation of the ylides (**214**) with trimethyloxonium tetrafluoroborate in dichloromethane affords 3-methyl derivatives ⟨82S645⟩.

8.24.3.3.10 Pyrido[1,2-b][1,2,4]benzothiadiazines

No reactions of this ring system have been reported.

8.24.3.3.11 Pyrido[1,2,3-de][1,2,4]benzothiadiazines

Nitration of (**218**) leads to the 9-nitro derivative (**219**), and catalytic reduction of (**219**) gave the amino derivative (**220**) (Scheme 17) ⟨92IJC(B)310⟩.



(**218**) (**219**) (**220**)

Scheme 17

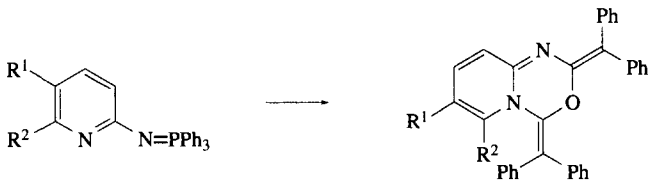
8.24.3.3.12 [1,2,5]Thiadiazino[3,2-a]isoquinolines

No reactions of this ring system have been described.

8.24.3.4 Synthesis

8.24.3.4.1 Pyrido[1,2-c][1,3,5]oxadiazines

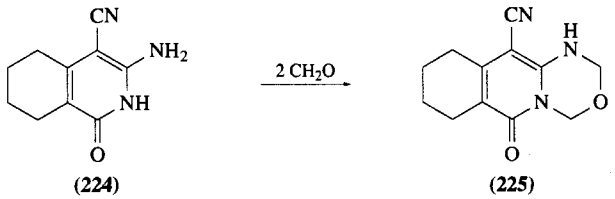
The bicyclic compound (**222**) and its angularly fused benzologue (**223**) can be obtained from phosphoranylidene compounds (**221**), in excellent yields using 2 mol of diphenylketene (Equation (46)). The reactions are thought to proceed via ketenimine intermediates ⟨80ZC211, 86ZC100⟩.



(**221**) (**222**) $R^1 = R^2 = H$
(**223**) $R^1 + R^2 = -CH=CH-CH=CH-$

(46)

The linearly fused benzo derivative (**225**) was easily obtained by cyclocondensation reaction of the aminoisoquinoline (**224**) with 2 mol of formaldehyde in aqueous sodium hydroxide solution (Equation (47)) ⟨82JPR519⟩.

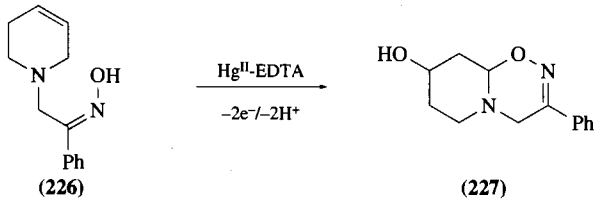


(**224**) (**225**)

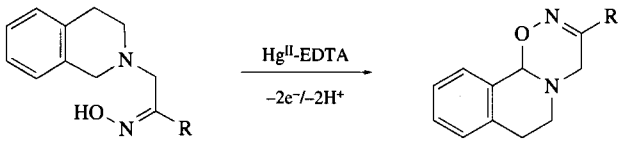
(47)

8.24.3.4.2 Pyrido[1,2-e][1,2,5]oxadiazines

Oxidative ring closure of the *Z*-ketoximes (**226**) and (**228**) with Hg(II)-EDTA gave (**227**) and (**229**) (Equations (48) and (49)). It is noteworthy that the *E*-ketoximes afford the corresponding nitrones instead of the dihydrooxazines, via nucleophilic addition of the oxime nitrogen to the immonium ion ⟨86AP(319)774⟩.



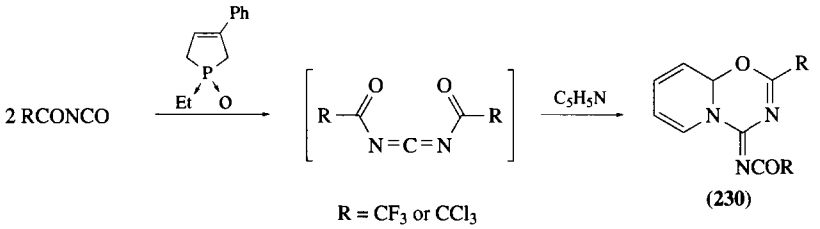
(226) (227) (48)



(228) R = Me, Ph (229) R = Me, Ph (49)

8.24.3.4.3 Pyrido[2,1-b][1,3,5]oxadiazines

The 2-trifluoromethyl and 2-trichloromethyl derivatives (**230**) were obtained in quantitative yields by treatment of a phospholene oxide with trifluoroacetyl or trichloroacetyl isocyanate, respectively, followed by addition of pyridine (Scheme 18) ⟨77IZV927⟩.

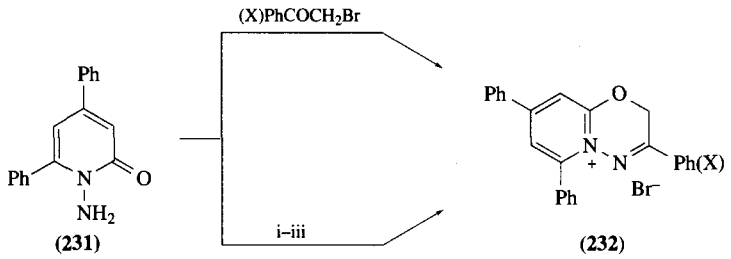


R = CF_3 or CCl_3

Scheme 18

8.24.3.4.4 Pyrido[2,1-b][1,3,4]oxadiazinium salts

The oxadiazine ring has been elaborated onto the pyridine ring in both routes reported so far. Cyclocondensation of (**231**) with phenacyl bromides afforded bicyclic products (**232**) directly (Scheme 19) ⟨78PJS1, 83JHC381⟩. When using phenylmethylketones, the ketimine intermediates formed were metallated and then treated with bromine ⟨83JHC381⟩. In both approaches excellent yields can be achieved.



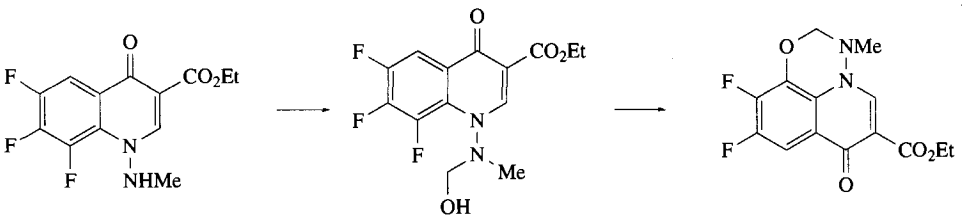
(231) (232)

i, (X)PhCOMe; ii, Bu^{n}Li; ii, Br_2

Scheme 19

8.24.3.4.5 Pyrido[3,2,1-ij][4,1,2]benzoxadiazines

Starting from (**233**), the oxadiazine ring was formed by a novel hydroxymethylation-intramolecular cyclization process. Upon heating (**233**) with an excess of paraformaldehyde in water, (**234**) could be isolated in excellent yield (Scheme 20). Attempted ring closure under a variety of basic conditions (NaH/THF, BuLi/THF, KF/MeCN) failed, however; only deformylation and/or decomposition took place. The desired product (**235**) could be obtained in good yield when the cyclization was carried out with Bu_4NF in THF at reflux under anhydrous conditions. However, no cyclization could be achieved from the 7-(3-acetylaminopyrrolidinyl) analogue of (**234**) ⟨92JOC744⟩.

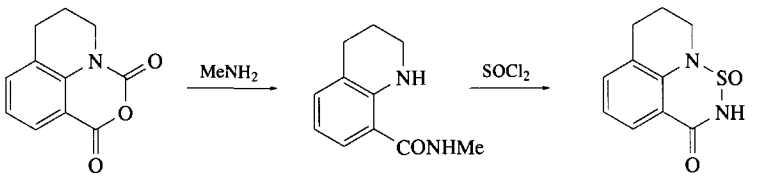


(**233**) (**234**) (**235**)

Scheme 20

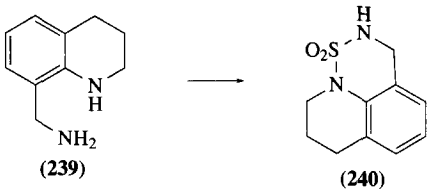
8.24.3.4.6 Pyrido[1,2-b][1,2,6]thiadiazines

Pyrido[3,2,1-*ij*][2,1,3]benzothiadiazines have been prepared from 1,5-diamino precursors. Reaction of (**237**), prepared from (**236**), with thionyl chloride gave (**238**) (Scheme 21) ⟨78JHC645⟩, whereas (**240**) was formed from (**239**) with sulfamide (Equation (50)) ⟨92FRP2675801⟩.



(**236**) (**237**) (**238**)

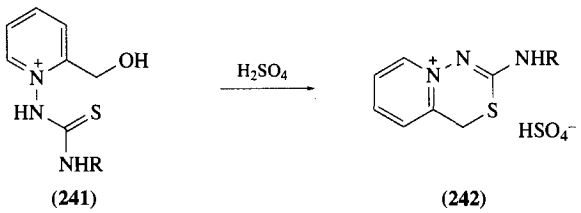
Scheme 21



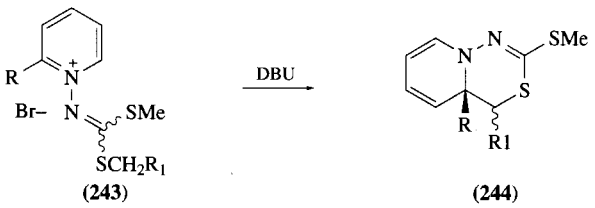
(**239**) (**240**) (50)

8.24.3.4.7 Pyrido[1,2-d][1,3,4]thiadiazines

Pyrido[1,2-*d*][1,3,4]thiadiazines are conveniently prepared from 1-aminopyridinium salts. Specifically (**241**) and (**243**) served as useful intermediates for the synthesis of (**242**) and (**244**), respectively (Equations (51) and (52)) ⟨73CPB2146, 85BCJ1432⟩.



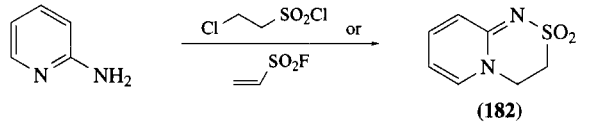
(**241**) (**242**) (51)



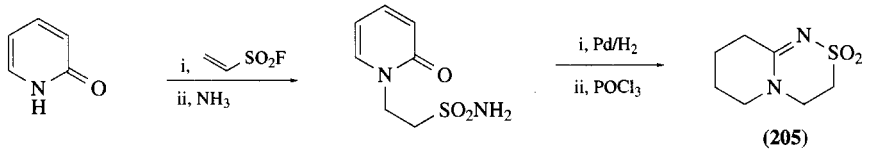
(243) (244) (52)

8.24.3.4.8 Pyrido[2,1-c][1,2,4]thiadiazines

The first reported preparation of this ring system involved the reaction of 2-aminopyridine with chloroethylsulfonyl chloride to give (**182**) (Equation (53)) ⟨73BSF985⟩. Much higher yields could be achieved by using ethenesulfonyl fluoride ⟨79JOC3847⟩. The hexahydro derivative (**205**) can also be obtained in an unambiguous synthesis, starting from 2(1*H*)-pyridone (Scheme 22) ⟨79JOC3847⟩. The direct reduction of (**182**) afforded (**205**) in a better yield.



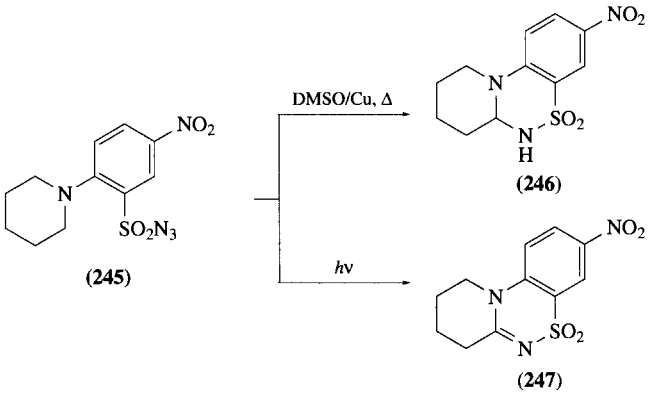
(182) (53)



(205)

Scheme 22

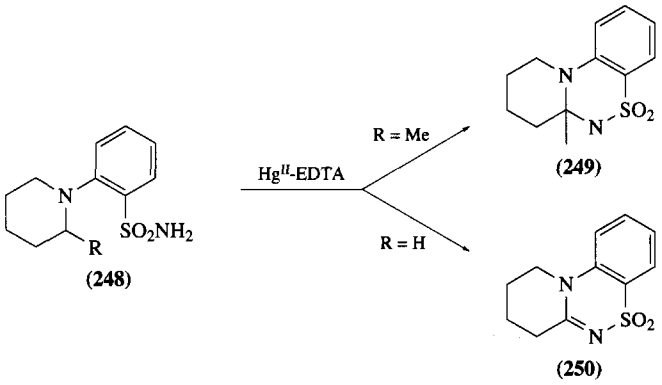
Principally, three different routes have been described for the angularly fused pyrido[2,1-*c*][1,2,4]benzothiadiazines. In the first route, the thiadiazine ring is formed in the final step of the synthesis, as exemplified by ring closure of appropriately *ortho*-functionalized piperidinobenzenes. By thermolysis of the sulfonyl azide (**245**) in DMSO, in the presence of copper, the hexahydro derivative (**246**) was formed as main product, whereas photolytic decomposition afforded the tetrahydro derivative (**247**) (Scheme 23) ⟨71CC1319, 74JCS(P1)2451⟩.



(245) (246) (247)

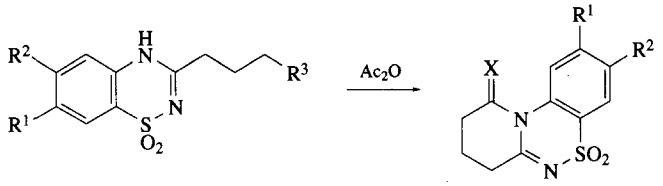
Scheme 23

Benzenesulfonamides (**248**) were cyclized by treatment with Hg(II)-EDTA ⟨90AP(323)911, 91AP(324)317⟩. Compounds (**249**) and (**250**) were prepared in this way (Scheme 24).



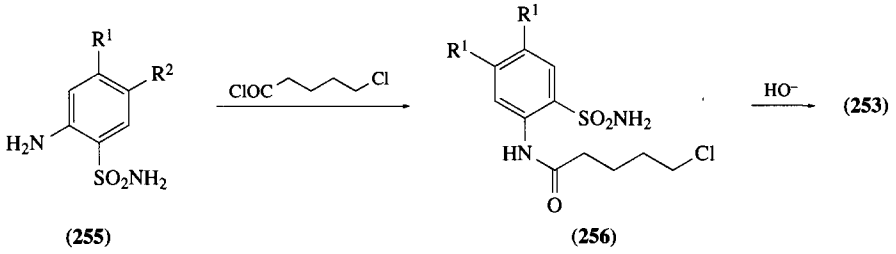
Scheme 24

In the second route, the piperidine ring was formed by intramolecular alkylation from (**251**) or by acylation from (**252**) to afford (**253**) and (**254**), respectively (Equation (54)) ⟨72FES1104, 72FES670⟩.



(54)

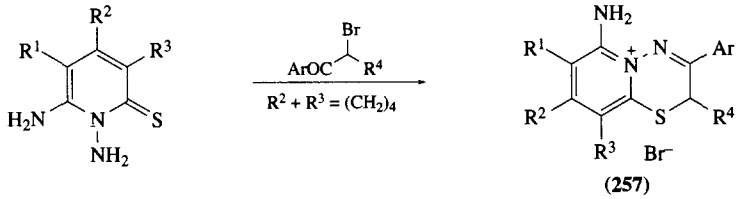
The third approach can be considered as a combination of the above two: the piperidine and the thiadiazine rings are formed from *ortho*-aminobenzenesulfonamides (**255**). Cyclization of (**256**) was carried out in alkaline medium to give (**253**) (Scheme 25) ⟨72FES670⟩.



Scheme 25

8.24.3.4.9 Pyrido[2,1-b][1,3,4]thiadiazines

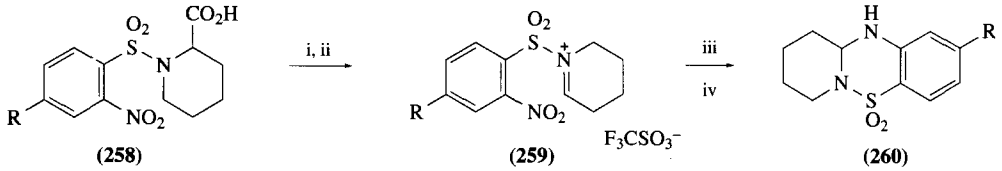
Synthesis of (**257**) including the tricyclic derivatives, involves a cyclocondensation reaction of 1-amino-2-pyridinethiones with α-bromocarbonyl compounds at reflux temperature in benzene or ethanol (Equation (55)) ⟨82S645, 88H(27)733⟩.



(55)

8.24.3.4.10 Pyrido[1,2-b][1,2,4]benzothiadiazines

The key intermediates, *N*-(arylsulfonyl)tetrahydropyridinium salts (**259**), were regiospecifically obtained by triflate-assisted decarbonylation reaction from (**258**). The final step to (**260**) is a nucleophilic–electrophilic *exo–tet* type cyclocondensation process (Scheme 26) ⟨90JCS(P1)1835⟩.



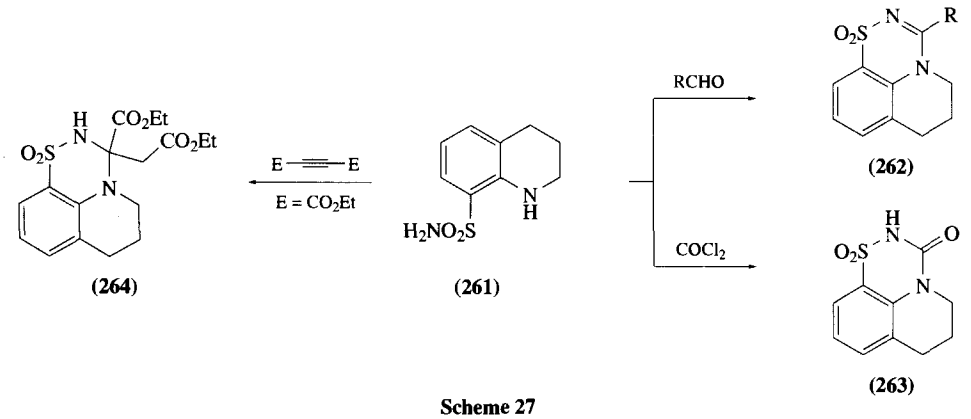
(258) (259) (260)

i, $SOCl_2$; ii, CF_3SO_3Ag; iii, Pd/C; iv, TFA

Scheme 26

8.24.3.4.11 Pyrido[1,2,3-de][1,2,4]benzothiadiazines

Tetrahydroquinoline-8-sulfonamide (**261**) with various aldehydes gave (**262**), whereas the oxo analogue (**263**) could be formed by treatment with phosgene. The ring closure to (**264**) was achieved by using diethyl acetylenedicarboxylate which served as a C-1 fragment (Scheme 27) ⟨92IJC(B)310⟩.



Scheme 27

8.24.3.4.12 [1,2,5]Thiadiazino[3,2-a]isoquinolines

The 2-cyclohexylhexahydro-4,4-dioxide derivative has been described ⟨92MI 824-02⟩.

8.24.3.5 Important Compounds and Applications

A wide antibacterial spectrum has been identified for pyrido[3,2,1-*ij*][1,3,4]benzoxadiazine derivatives ⟨87EUP259804⟩.

8.24.4 PYRIDOOXATHIAZINES, PYRIDODIOXAZINES, PYRIDODITHIAZINES, AND THEIR BENZO DERIVATIVES

Of the possible 24 bicyclic ring systems, only five have been described (Table 3). Among them, pyrido[1,2-*b*][1,5,2]dioxazines were postulated as reactive intermediates in the reaction of 1,2-dihydro-1-hydroxy-2-oxopyridine-6-carboxylic acid with phosgene ⟨88JMC11⟩ but they have never been isolated.

The chemistry of pyrido[1,2-*e*][1,2,5]oxathiaziniums has also been scarcely explored; such com-

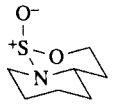
pounds have been described in Japanese patents ⟨81JAP81110762, 89JAP01112236, 91JAP03136034, 92JAP04149430⟩.

The other three bicyclic systems, together with the known benzo-fused system, are discussed.

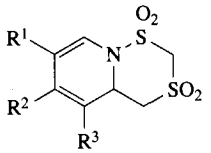
8.24.4.1 Theoretical and Experimental Structural Methods

Theoretical calculations on these classes of compounds have not yet been published. ^{1}H NMR studies on the pyrido[1,2-*c*][1,2,3]oxathiazine (**265**) established that the two rings are *trans* fused. Both rings adopt a chair conformation with axial sulfoxide group ⟨90TA885⟩.

Crystal structure analysis of (**266**) by x-ray indicated that the C(5)—C(6)—C(7)—C(8) moiety is not coplanar, and the two rings are *cis* fused, as is also the case in solution. Compounds without methyl groups are *trans* fused ⟨78CJC1183⟩.



(265)



(266)

8.24.4.2 Synthesis and Reactivity

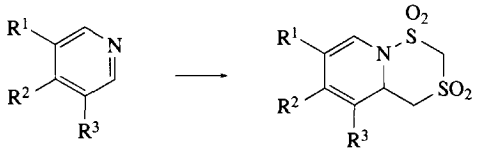
8.24.4.2.1 Pyrido[1,2-c][1,2,3]oxathiazines

Compound (**265**) was synthesized from piperidine ethanol with thionyl chloride in the presence of pyridine. Subsequent oxidation with ruthenium tetroxide gave the *S,S*-dioxide derivative ⟨90TA885⟩.

8.24.4.2.2 Pyrido[1,2-b][1,5,2]dithiazines

Reaction of sulfene generated from methanesulfonyl chloride with triethylamine in the presence of a pyridine derivative resulted in (**266**) (Equation (56)). The methylene protons could be exchanged with deuterium ⟨78CJC1183⟩.

The tetrahydro derivative (**268**) was prepared by reacting the bicyclic sultam (**267**) with lithium diisopropylamide (Equation (57)) ⟨89AP(322)17⟩.



(56)

(266)



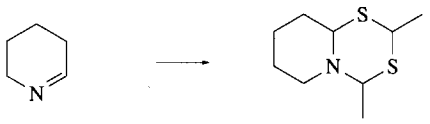
(57)

(267) (268)

8.24.4.2.3 Pyrido[2,1-b][1,3,5]dithiazines

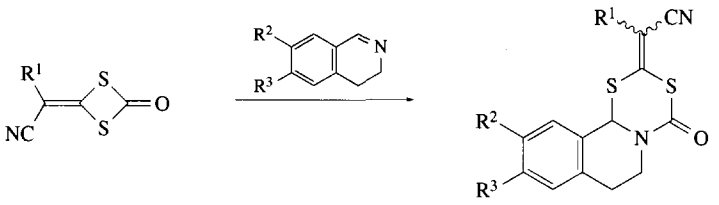
Only one paper reports this bicyclic ring system. The perhydro derivative (**269**) was synthesized from tetrahydropyridine, acetaldehyde, and hydrogen sulfide (Equation (58)) ⟨91MI 824-01⟩.

The benzo-fused [1,3,5]-dithiazino[4,5-*a*]isoquinoline system (**271**) could be obtained from 1,3-dithietanone (**270**) with 3,4-dihydroisoquinoline (Equation (59)) ⟨84CB2205⟩.



(269)

(58)



(270) (271)

(59)

8.24.4.3 Important Compounds and Applications

Pyrido[1,2-*e*][1,2,5]oxathiazinium derivatives are used as photographic gelatin hardening agents ⟨81JAP81110762⟩.

8.24.5 PYRIDOOXAZABORINES, PYRIDOOXAZAPHOSPHORINES, AND PYRIDODIAZAPHOSPHORINES

8.24.5.1 Theoretical Methods

The boric acid complexes of α-pyridoin have recently been investigated using semiempirical calculations. For AM1-optimized structures, spectroscopic parameters were calculated by CNDO/S and INDO/S methods and a good agreement with observed values was found ⟨93JPC8602⟩.

8.24.5.2 Experimental Structural Methods

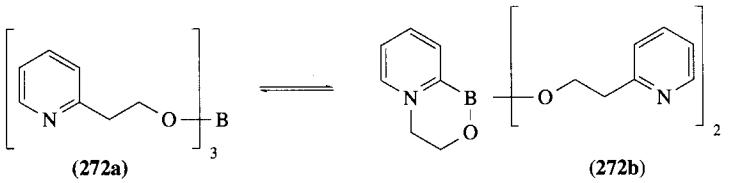
The cyclic structure of the compound obtained from 2-(2-pyridyl)ethanol with diphenylboronic acid was established by x-ray analysis. Bond angles and distances found are normal for unsaturated six-membered rings ⟨92JCS(P2)527⟩. Complete carbon assignment of the same compound was achieved from 2D HETCOR spectra. ^{13}C NMR data of the perhydro analogue were also reported ⟨85JOM(294)1⟩. ^{11}B NMR investigations were carried out for other pyrido[1,2-*c*]oxazaborines ⟨86JOC4526, 88JCS(P2)1787⟩.

Characteristic IR data were reported for the pyrido[1,2-*c*][1,3,2]oxazaphosphorine system ⟨63MI 824-01⟩.

8.24.5.3 Thermodynamic Aspects

Ring–chain tautomerism of (**272**) has been reported (Equation (60)). At low temperature the cyclic borinate form is present. The equilibrium constant was also calculated ⟨88JCS(P2)1787⟩.

In the case of 1-[bis(2-chloroethyl)amino]hexahydro-1*H*,3*H*-pyrido[1,2-*c*][1,3,2]oxazaphosphorine-1-oxide, *cis* and *trans* isomers could be identified and separated ⟨63MI824-01⟩.



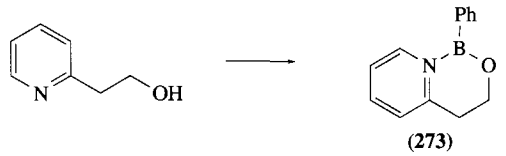
(272a) (272b) (60)

8.24.5.4 Synthesis and Reactivity

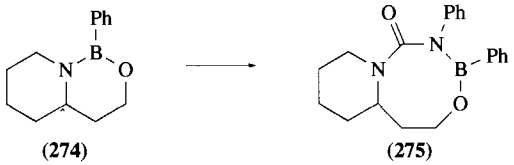
8.24.5.4.1 Pyrido[1,2-c]oxazaborine

Pyridine ethanol was reacted with boranes, affording 2-substituted derivatives ⟨86JOC4526, 88JCS(P2)1787, 92JCS(P2)527⟩. Thus, for example, (**273**) was prepared (Equation (61)). Piperidine ethanol could also be used ⟨85JOM(294)1⟩.

A ring expansion reaction of (**274**) with phenyl isocyanate has been reported to afford (**275**) (Equation (62)) ⟨78JOM(154)C3⟩.



(273) (61)

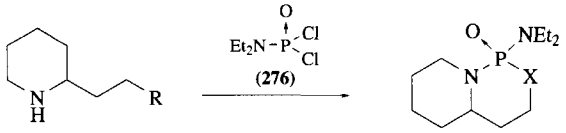


(274) (275) (62)

8.24.5.4.2 Pyrido[1,2-c][1,3,2]oxazaphosphorines and pyrido[1,2-c][1,3,2]diazaphosphorines

The bicyclic oxaza- and diazaphosphorines (**279**) and (**280**) were obtained by the reaction of the phosphoroamidic derivative (**276**) with 2-(2-piperidinyl)ethanol (**277**) or 2-(2-piperidinyl)ethylamine (**278**), respectively (Equation (63)) ⟨63MI824-01⟩. Treatment of (**277**) with bis(2-chloroethyl)-phosphoroamidic dichloride gave the 1-[bis(2-chloroethyl)amino] analogue of (**279**) in excellent yield ⟨83ZN(B)1146⟩.

A cationic derivative of the oxazaphosphorine system has also been prepared ⟨88PS(35)89⟩.



(277) R = OH
(278) R = NH_2

(276) (279) X = O
(280) X = NH (63)

8.24.5.5 Important Compounds and Applications

Remarkable activity of 1-[bis(2-chloroethyl)amino]hexahydro-1*H*,3*H*-pyrido[1,2-*c*][1,3,2]oxazaphosphorine-1-oxide was observed against Walker 256 tumor fragments and P388 leukemia ⟨63JMC82, 83ZN(B)1146⟩.

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8.25
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 1 : 1

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and

PÉTER MÁTYUS
Institute for Drug Research, Budapest, Hungary

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8.25.1 INTRODUCTION

This chapter covers bicyclic ring systems with one bridgehead N atom and with one extra heteroatom in each ring, and their benzo-fused derivatives. Of the 78 theoretically possible bicyclic systems, 33 are known, as are 53 benzo-fused derivatives.

Compounds falling within this chapter are discussed in four groups, according to the nature of the extra heteroatoms:

systems with two extra N atoms (Section 8.25.2),
systems with one extra N and one extra O atom (Section 8.25.3),
systems with one extra N and one extra S atom (Section 8.25.4), and
systems with two extra O atoms; systems with one extra O and one extra S atom; and systems with two extra S atoms (Section 8.25.5).

In the literature, to date, no system has been described with extra heteroatoms other than N, O, or S. Known systems in each of these four groups are listed in Tables 1 to 4, respectively, in the same sequence as they are treated in their sections. For each system, one tautomeric form only is shown. The tables also include those unknown bicycles which have known benzo-fused derivatives. The names and numbers of such unknown systems figure in italics.

Throughout the chapter, *Chemical Abstracts* nomenclature is used.

8.25.2 BICYCLIC 6-6 N-BRIDGEHEAD SYSTEMS WITH TWO EXTRA N ATOMS 1 : 1, AND THEIR BENZO-FUSED DERIVATIVES

8.25.2.1 Introduction

The number of possible bicyclic ring systems containing one bridgehead nitrogen, and two extra nitrogens 1 : 1 in each ring is 10. Of these, eight are known. The pyridazino[2,3-*b*]pyridazine (**1**) and the pyrimido[3,4-*b*]pyridazine (**2**) ring systems have not been reported to date. The number of known tricyclic benzo-fused ring systems falling within the scope of this chapter is 16. Benzologues of (**1**) have not yet been described.

The bicyclic ring systems were previously reviewed ⟨84CHEC-I(3)329⟩; however, none of the benzo-fused systems was the primary subject of *Comprehensive Heterocyclic Chemistry, First Edition* (CHEC-I). Therefore, for the bicyclic systems, we are focusing on material published since 1982, whereas for the benzologues, the full literature is surveyed.

The bicyclic systems, together with the known benzo-fused systems, are listed in Table 1, in the same order as they will be discussed. For any heterocyclic system, only one tautomeric form is shown.

8.25.2.2 Theoretical Methods

Few applications of theoretical methods on ring systems falling within this classification have been reported.

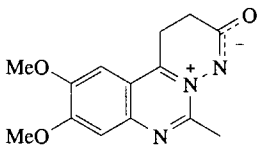
The "orbit molecular building system" has been used for identifying the Fe^{3+}-complexing sites in the siderophore mandurapherrin containing the pyrazino[1,2-*b*]pyridazine ring system ⟨88HCA1528⟩.

Semiempirical PM3 calculations have been performed on a novel alkaloid possessing the pyrazino[2,1-*b*]quinazoline skeleton to assist proton assignment ⟨92JCS(P1)1495⟩.

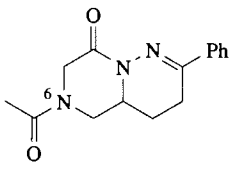
8.25.2.3 Experimental Structural Methods

8.25.2.3.1 Pyridazino[1,6-c]quinazolines

The parent bicyclic system has not yet been described, and one derivative only of the tricyclic benzo-fused system has been reported. Compound (**27**) crystallizes with one molecule of water, and in its mass spectrum the M + 2 and M − 2 ions are identifiable; their relative abundances progressively decrease with the evaporation. Some spectroscopic data of the perchlorate salt of (**27**) have also been described ⟨83ACH43⟩.



(27)



(28)

Table 1 Bicyclic 6-6 nitrogen bridgehead systems with two extra N atoms 1 : 1 and their known benzo-fused derivatives. (Systems which are unreported are named in italic.)

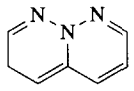
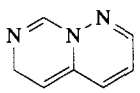
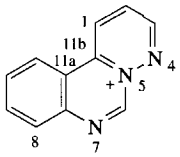
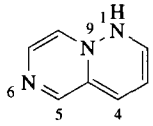
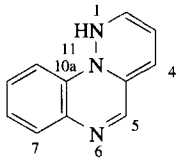
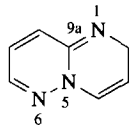
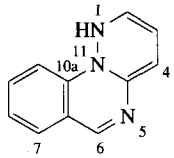
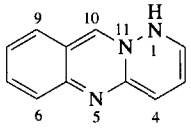
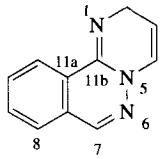
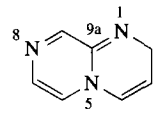
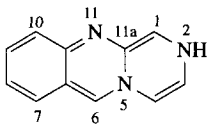
Compound	*Ring system*	*Name and ring file number*
(1)		6H-*Pyridazino[1,6-*b]*pyridazine*
(2)		6H-*Pyrimido[1,6-*b]*pyridazine*
(3)		Pyridazino[1,6-*c*]quinazolin-5-ium, RF 35455
(4)		1*H*-Pyrazino[1,2-*b*]pyridazine, RF 13830
(5)		1*H*-Pyridazino[1,6-*a*]quinoxaline, RF 35460
(6)		2*H*-Pyrimido[1,2-*b*]pyridazine, RF 13842
(7)		1*H*-Pyridazino[1,6-*a*]quinazoline, RF 35451
(8)		1*H*-Pyridazino[6,1-*b*]quinazoline, RF 35453
(9)		2*H*-Pyrimido[2,1-*a*]phthalazine, RF 35463
(10)		2*H*-Pyrazino[1,2-*a*]pyrimidine, RF 13831
(11)		2*H*-Pyrazino[2,1-*b*]quinazoline, RF 35434

Table 1 (continued)

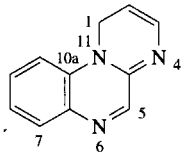
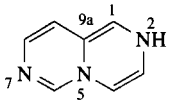
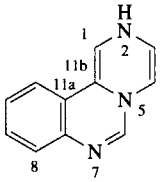
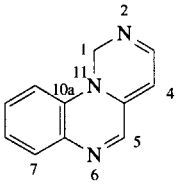
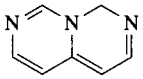
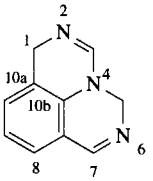
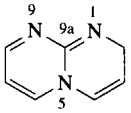
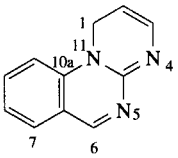
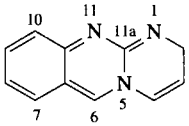
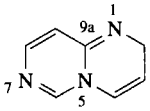
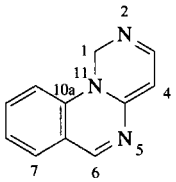
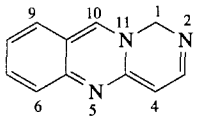
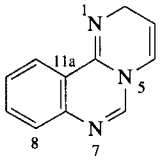
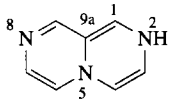
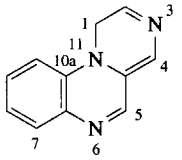
Compound	*Ring system*	*Name and ring file number*
(12)		1*H*-Pyrimido[1,2-*a*]quinoxaline, RF 35478
(13)		2*H*-Pyrazino[1,2-*c*]pyrimidine, RF 13832
(14)		2*H*-Pyrazino[1,2-*c*]quinazoline, RF 35433
(15)		1*H*-Pyrimido[1,6-*a*]quinoxaline, RF 35479
(16)		1*H*-Pyrimido[1,6-*c*]pyrimidine, RF 13846
(17)		1*H*,5*H*-Pyrimido[5,6,1-*ij*]quinazoline, RF 35473
(18)		2*H*-Pyrimido[1,2-*a*]pyrimidine, RF 13847
(19)		1*H*-Pyrimido[1,2-*a*]quinazoline, RF 35469
(20)		2*H*-Pyrimido[2,1-*b*]quinazoline, RF 35476
(21)		2*H*-Pyrimido[1,6-*a*]pyrimidine, RF 13848
(22)		1*H*-Pyrimido[1,6-*a*]quinazoline, RF 35470

Table 1 (continued)

Compound	*Ring system*	*Name and ring file number*
(23)		1*H*-Pyrimido[6,1-*b*]quinazoline, RF 35473
(24)		2*H*-Pyrimido[1,2-*c*]quinazoline, RF 35475
(25)		2*H*-Pyrazino[1,2-*a*]pyrazine, RF 13827
(26)		1*H*-Pyrazino[1,2-*a*]quinoxaline, RF 35439

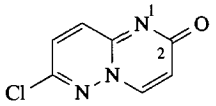
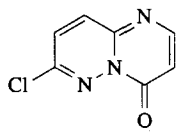
8.25.2.3.2 Pyrazino[1,2-b]pyridazines

The ^{1}H NMR spectrum of **(28)** shows temperature dependence due to restricted rotation around the N(6)—C bond of the amide moiety ⟨87JCS(P1)2517⟩. UV spectral data of the benzologous pyridazino[1,6-*a*]quinoxalines have been reported ⟨72JCS(P1)2182⟩.

8.25.2.3.3 Pyrimido[1,2-b]pyridazines

The 2-oxo and 4-oxo derivatives of this ring system have been extensively studied by spectroscopic methods, since their syntheses do not necessarily prove the position of the carbonyl group. Significant differences have been found in the IR amide-I bands and in the intensity ratios of the two highest extinction coefficients in the UV. The ^{1}H and ^{13}C NMR data can also be of diagnostic value. Data for an isomeric pair are compiled in Table 2 ⟨83H(20)2225, 88JHC1535⟩. The same trends apply for the pyrimido[2,1-*a*]phthalazinones.

Table 2 Some characteristic spectroscopic data of two isomeric pyrimido[2,1-*b*]pyridazinone derivatives.

Derivative	*IR amide-I* (cm^{-1})	*UV* (e_c/e_b)	*^{1}H NMR δ H-3* (ppm)	*^{13}C NMR δ CO* (ppm)
	1640	0.18	6.40	168.8
	1709	0.81	6.70	154.8

A retro-Diels–Alder (RDA) fragmentation process, affording a pyridazinyl isocyanate, has only been observed in the mass spectra of the 2-one isomers. However, this pathway is significantly influenced by electronic properties of the 7-substituent ⟨89OMS(24)195⟩. The principal fragmentation

of the benzologue 3,4-dihydro-2*H*-pyrimido[2,1-*a*]phthalazin-7(6*H*)-one is also a RDA process ⟨76ACH59⟩.

The x-ray analysis of 2-phenylpyrimido[1,2-*b*]pyridazin-4-one has been reported ⟨81MI 825-01⟩.

8.25.2.3.4 Pyrazino[1,2-a]pyrimidines

The structure of 3-chloro-2-methyl-4*H*-pyrazino[1,2-*a*]pyrimidin-4-one, obtained from the reaction of 2-aminopyrazine with ethyl-2-chloroacetoacetate, has been unambigously confirmed by x-ray analysis ⟨87AX(C)1173⟩. The x-ray structures of two derivatives of the benzologue pyrazino[2,1-*b*]quinazoline system have also been reported ⟨82AX(B)1654, 84KGS983⟩. The IR amide-I band of pyrazino[1,2-*a*]pyrimidin-4-ones can be easily identified at ca. 1680 cm^{-1}, whereas in the ^{13}C NMR, the carbonyl carbon appears at ca. δ 158 ppm. The structure of the alkaloid glyantrypine, which contains the pyrazino[2,1-*b*]quinazoline skeleton, has been elucidated by ^{1}H, ^{13}C NMR and MS ⟨92JCS(P1)1495⟩.

8.25.2.3.5 Pyrazino[1,2-c]pyrimidines

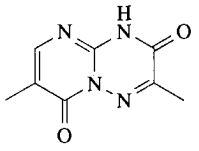
The IR and ^{1}H NMR spectra of a series of 2-aminoethyl derivatives have been briefly discussed ⟨85FES695⟩. High-resolution mass spectral and ^{13}C NMR data as well have been reported for 1,8-dioxopyrazino[1,2-*c*]pyrimidine-6-thiones ⟨89H(29)1601⟩. The UV data of a perhydro derivative (centperazine) have been described ⟨81MI 825-02⟩.

8.25.2.3.6 Pyrimido[1,6-c]pyrimidines

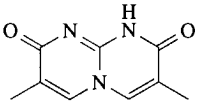
A benzologous derivative, the *peri*-fused 2,6-di-*p*-tolyl-1*H*,5*H*-pyrimido[5,6,1-*ij*]quinazoline, has been fully characterized by ^{1}H and ^{13}C NMR as well as IR data ⟨93JMC3202⟩.

8.25.2.3.7 Pyrimido[1,2-a]pyrimidines

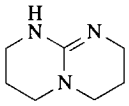
The structures of (**29**) and (**30**) have been determined by x-ray crystallography. Both compounds exist in the keto forms ⟨91JHC231⟩.



(**29**)



(**30**)

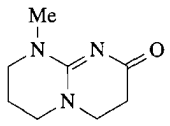
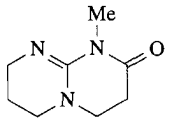


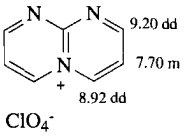
(**31**)

Achiral and chiral derivatives of hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (1,5,7-triazabicyclo-[4.4.0]dec-5-ene, TBD) (**31**) have been used as selective hosts for anionic guests. Structures of the complexes with acetate, nitrate, α-nitrotoluene, and nitrite have been analyzed by x-ray crystallography. The counterion is typically bound by two hydrogen bonds to the protonated nitrogens ⟨90CC55, 92CC239, 92CC629, 92AX(C)1874, 93ACS122⟩. Proton NMR spectroscopy has been used for studying these complexes in solutions ⟨88AG1574, 89JA4994, 89TL4493, 90CC55, 91LA539, 91TL1827, 92JA1511, 92AG58, 92CC239⟩. IR, UV, and ^{13}C NMR spectroscopy are powerful diagnostic tools for distinguishing the through-conjugated and cross-conjugated species, such as (**32**) and (**33**). Typical data are shown in Table 3 ⟨85JCS(P2)1255, 85JCS(P2)1265⟩.

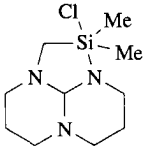
The regio- and stereochemistry of arylpyrimido[1,2-*a*]pyrimidinium salts have been investigated by ^{1}H NMR ⟨83M717⟩; Proton NMR assignment of the parent aromatic pyrimido[1,2-*a*]pyrimidinium perchlorate (**34**) has also been reported ⟨84KGS704⟩. A temperature-dependent ^{29}Si NMR study of (**35**) reveals that increasing temperature causes a reversible shift to pentacoordination of silicon ⟨93JOM(446)51⟩. On the basis of a ^{15}N NMR measurement, the regioisomeric (**36**) and (**37**) could be easily distinguished. The chemical shift of δ 95 ppm supports the structure (**36**) and (**37**) could be excluded ⟨76MI 825-01⟩.

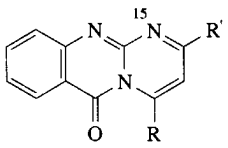
Table 3 Some characteristic IR, UV, and ^{13}C NMR data of compounds (**32**) and (**33**).

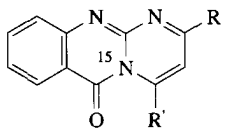
	IR		*UV* (λ_{max}/*nm*)	*^{13}C NMR*		
	ν(C=O)	*ν(C=N)*	*BH$^+$*	*δ(C=O)*	*δ(C=N)*	*δ(Me—N)*
	(cm^{-1})			(ppm)		
 (**32**)	1633	1568 1554	207 230	176.6	157.7	36.9
 (**33**)	1682	1636	209 235	167.8	146.8	27.3



(**34**)


(**35**)


(**36**)


(**37**)

8.25.2.3.8 Pyrimido[1,6-a]pyrimidines

The MS fragmentation patterns of the isomeric 2-alkoxy-4-oxo and 4-alkoxy-2-oxo derivatives of this ring system have been discussed ⟨86JHC335, 86JHC1063⟩.

The 2-oxo- and 4-oxopyrimido[1,2-*c*]quinazolines can be distinguished by ^1H NMR; in the 2-oxo isomers, only the H-3 signal is deshielded on adding Eu(DPM)$_3$ shift reagent ⟨74JHC603⟩.

8.25.2.3.9 Pyrazino[1,2-a]pyrazines

Proton NMR data of some octahydro derivatives have been reported ⟨81JMC1329, 91S318⟩.

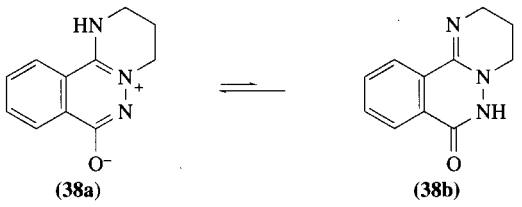
8.25.2.4 Thermodynamic Aspects

8.25.2.4.1 Pyrazino[1,2-b]pyrazines

Two rotamers of (**28**) could be observed by ^1H and ^{13}C NMR due to the restricted rotation about the N(6)—C amide bond ⟨87JCS(P1)2517⟩.

8.25.2.4.2 Pyrimido[1,2-b]pyridazines

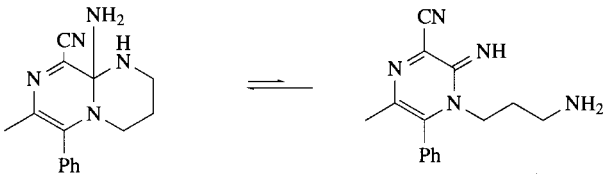
Prototropic tautomerism of the pyrimido[2,1-*a*]phthalazine derivative (**38**) has been studied ⟨84ACH363⟩. The zwitterionic form (**38a**) predominates both in solution and in the solid state (Equation (1)).



(38a) (38b) (1)

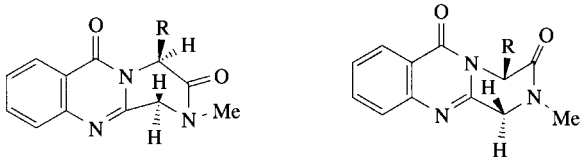
8.25.2.4.3 Pyrazino[1,2-a]pyrimidines

A ring-chain tautomerism for (**39**) has been postulated. However, in the solid state and in solutions only (**39a**) could be detected (Equation (2)) ⟨86HCA1025⟩.



(39a) (39b) (2)

Conformational studies on the pyrazino[2,1-*b*]quinazolones (**40**), incorporating the cyclodipeptide Sar-Gly, have shown that the methyl derivative (R = Me) exists in the (**40a**) conformation, whereas the analogue with hydrogen (R = H) is conformationally flexible ⟨74JCS(P1)2122, 82AX(B)1654⟩.



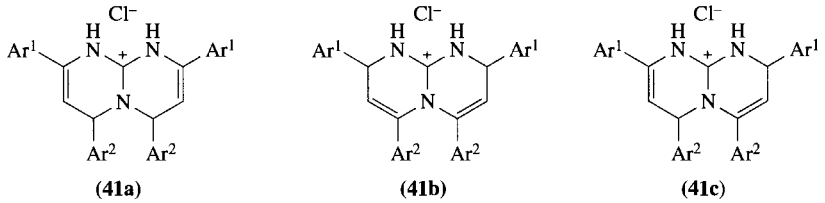
(40a) (40b)

8.25.2.4.4 Pyrazino[1,2-c]pyrimidines

The pK_a of centperazine [7-ethyl-2-methyl-1,2,3,4,8,9-hexahydropyrazino[1,2-*c*]pyrimidin-6(7*H*)-one] by a titration method is 7.1 ⟨82MI 825-01⟩.

8.25.2.4.5 Pyrimido[1,2-a]pyrimidines

Structures (**41a**)–(**41c**) have been considered as possible tautomeric structures of aryldihydropyrimido[1,2-*a*]pyrimidines and (**41a**) is thought to be the most stable ⟨83M717⟩.



(41a) (41b) (41c)

Tautomerism of a tetrahydropyrimido[2,1-*b*]quinazoline was studied by ^{1}H NMR ⟨73JMC407⟩. Proton affinities larger than 1000 kJ mol^{-1} were measured for the "superbases" TBD (**31**) and its methylated analog (MTBD) ⟨93RCM599⟩. Studies on acylguanidines have shown a large tautomeric

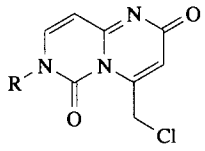
preference for the through-conjugated forms (the carbonyl and the imine nitrogen are conjugated) vs. cross-conjugated ones. Thus, a hexahydro derivative exists in the form (**42**) in solution and in the solid state (Equation (3)) ⟨85JCS(P2)1255, 85JCS(P2)1265⟩.



(42) (43) (3)

8.25.2.4.6 Pyrimido[1,6-a]pyrimidines

The acidity constant of the nucleoside analogue (**44**) has been reported. The $pK_a = 1$ was obtained by the spectroscopic method. The high-pressure liquid chromatographic (HPLC) retention parameter for this compound has also been determined ⟨92JOC1579⟩.



(**44**) R = β-D-ribosyl

8.25.2.5 Reactivity

8.25.2.5.1 Pyridazino[1,6-c]quinazolines

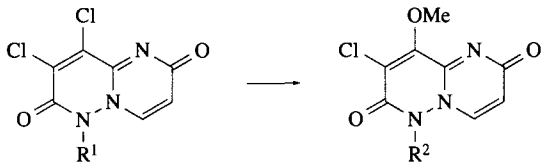
The photochemical behavior of (**27**) has been studied in different solvents. Using a Pyrex filter, no reaction took place, whereas complex mixtures were obtained with a quartz filter ⟨83ACH43⟩.

8.25.2.5.2 Pyrazino[1,2-b]pyridazines

A few derivatives only of this ring system have been described. Removal of the acetyl group from (**28**) by acid catalysis has been reported ⟨87JCS(P1)2517⟩.

8.25.2.5.3 Pyrimido[1,2-b]pyridazines

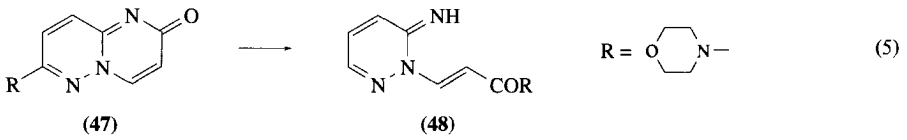
The halo substituted derivatives of this ring system have been studied most. 7-Chloropyrimido[1,2-*b*]pyridazin-2- and -4-ones undergo nucleophilic displacement reactions with amines to afford the 7-amino derivatives ⟨83MI 825-01, 88JHC1535⟩. In the 8,9-dichlorobenzoyl-protected nucleoside derivative (**45**), the 9-chloro substituent could be selectively exchanged for methoxide ion in methanol. The debenzoylation of the sugar moiety also took place, and (**46**) was formed (Equation (4)). The 4,7-dioxo isomer reacted analogously ⟨92JHC1409⟩.



(45) (46) (4)

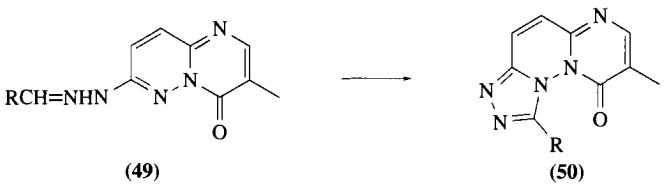
The 2-chloro substituent in the linear benzologue pyridazino[6,1-*b*]quinazoline is also exchangeable with amines or KSH ⟨70M303, 76IJC(B)879⟩.

Opening of the pyrimidine ring of the bicyclic system and that of the pyrimido[2,1-*a*]phthalazine could also be achieved by nucleophilic attack. Thus, (**47**) afforded the pyridazinimine (**48**) on heating with morpholine (Equation (5)) ⟨85JHC1535⟩.

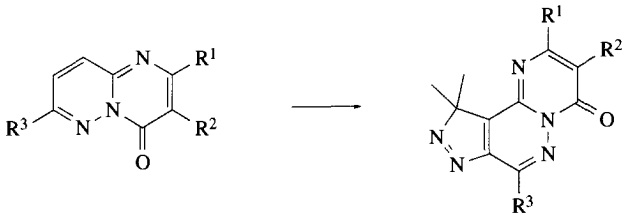


(47) (48) (5)

N-(3-Aminopropyl)phthalazines were formed by treatment of (**38**) with hot 10% KOH or Ac_2O ⟨83ACH65, 88ACH99⟩. Oxidative cyclization of the 7-hydrazones (**49**) onto the pyridazine nitrogen afforded the tricyclic compound (**50**) (Equation (6)). Bromine or $Pb(OAc)_4$ could be used as oxidizing agents ⟨83H(20)749, 83MI 825-01, 87PHA304⟩. A regiospecific 1,3-dipolar cycloaddition reaction of the pyrimido[1,2-*b*]pyridazin-4-ones with 2-diazopropane has been reported. Starting from (**51**), the tricyclic compounds (**52**) were formed in 32–52% yields, via dihydro intermediates (Equation (7)) ⟨85H(23)1⟩.



(49) (50) (6)

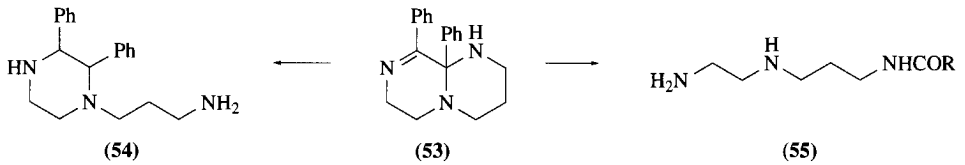


(51) (52) (7)

An interesting rearrangement reaction of the pyrimido[1,2-*a*]phthalazine derivative (**38**) to triazaindenoindenes in boiling carboxylic anhydrides has been reported ⟨86ACH15⟩.

8.25.2.5.4 Pyrazino[1,2-a]pyrimidines

The diphenyl derivative (**53**) may undergo different ring opening reactions depending on the reactants. The pyrazine derivative (**54**) was formed upon hydrogenolysis, whereas the terminal monoacylated triamines (**55**) could be obtained in good yields by acylation followed by hydrolysis (Scheme 1) ⟨90CC1385, 92JCR(S)264⟩.

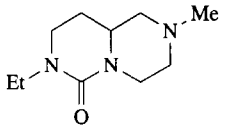


(54) (53) (55)

Scheme 1

8.25.2.5.5 Pyrazino[1,2-c]pyrimidines

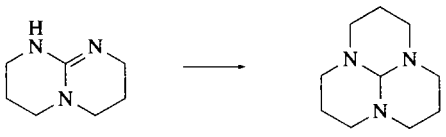
The enantiomers of centperazine (**56**) have been prepared. Resolution of the desmethyl centperazine followed by methylation of the desmethyl enantiomers by the Eschweiler–Clark method afforded the enantiomers of (**56**) ⟨88IJC(B)394⟩. Demethylation of (**56**) has been observed by incubating it with rat liver microsomes ⟨85MI 825-01⟩. Exchange of the side-chain chloro substituent of a 2-chloroethyl derivative of this ring system with aliphatic and aromatic amines has been reported. The 2-aminoethyl derivatives were obtained in moderate-to-high yields ⟨85FES695⟩.



(**56**)

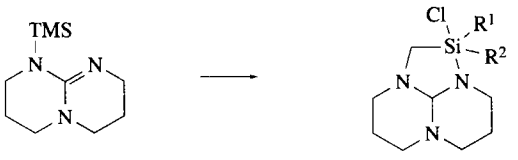
8.25.2.5.6 Pyrimido[1,2-a]pyrimidines

Alkylation reactions of TBD (**31**) have been studied. Treatment with sodium hydride followed by the reaction with 1,3-dibromopropane gave the *peri*-fused (**57**) which can be isolated as a tetrafluoroborate in 65% yield (Equation (8)) ⟨92CC507⟩. Benzylation of (**31**) has also been described. A "polymer-supported TBD" has been prepared by the reaction of (**31**) with chloromethylated polystyrene resin ⟨92JMAS(A)249⟩.



(**31**) (**57**) (8)

The trimethylsilyl derivative (**58**) could be smoothly obtained with TMS-Cl. This compound reacted with chloromethyl(methyl)chlorosilanes to afford compounds (**59**) in almost quantitative yields (Equation (9)) ⟨93JOM(446)51⟩.

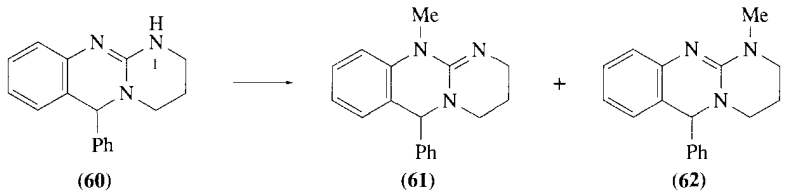


(**58**) (**59**) (9)

R^1, R^2 = Me, Cl

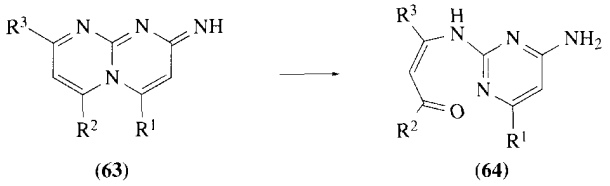
The regiochemistry of methylation of oxo derivatives has been investigated extensively. Treatment of (**42**) with MeI afforded the 1-methyl-2-oxo derivative (**33**) as its iodide salt in 80% yield ⟨85JCS(P2)1255⟩.

The 2,6-dioxo compound (**29**) gave a mixture of *N*(1)-methyl and 2-methoxy derivatives on reaction with dimethyl sulfate. Reaction of the 2,8-dioxo regioisomer (**30**) with diazomethane, dimethyl sulfate, or MeI gave the *N*(1)-methyl derivative predominantly together with some 2-methoxy derivative ⟨91JHC231⟩. The nucleophilic substitution reaction of (**30**) with chloride has been reported. The bicyclic lactam could be converted smoothly to the 2-chloro compound by reacting with thionyl chloride. Treatment of this compound with NaOMe afforded the corresponding 2-methoxy derivative in good yield ⟨91JHC231⟩. Methylation of the sodio salt of the linear benzologue (**60**) with MeI gave a mixture of (**61**) and (**62**) (Equation (10)), whereas acylation took place exclusively at N-1 ⟨79CPB880⟩.

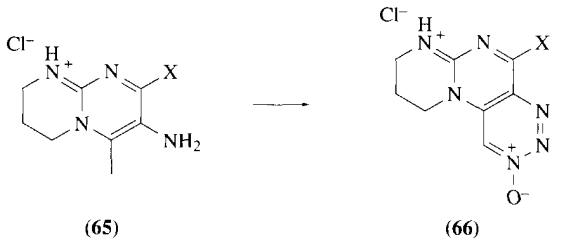


(60) (61) (62) (10)

Hydrolysis of (**63**) (formed from 2-aminopyridines and allenic nitriles) under mild basic conditions afforded (**64**) (Equation (11)) ⟨89JCS(P1)609⟩. Two ring substituents of bicyclic (**65**) participated in a transformation with nitrous acid. Diazotation followed by cyclization afforded the tricyclic compound (**66**) (Equation (12)) ⟨86JCS(P1)711⟩.



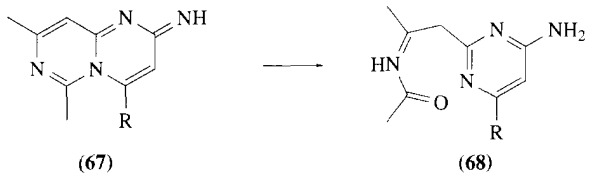
(63) (64) (11)



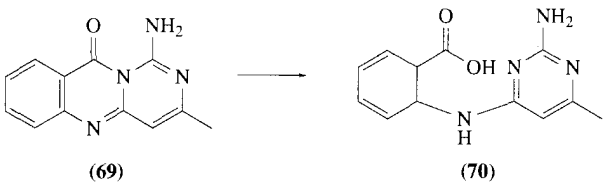
(65) (66) (12)

8.25.2.5.7 Pyrimido[1,6-a]pyrimidines

This ring system and its benzologues are particularly sensitive to nucleophilic attack. Compounds (**67**) underwent *in situ* hydrolysis, analogously to (**63**), to afford (**68**) by ring opening (Equation (13)) ⟨89JCS(P1)609⟩. The benzologue pyrimido[6,1-*b*]quinazolone (**69**) also underwent rapid acidic or basic hydrolysis affording the *N*-substituted anthranilic acid (**70**) (Equation (14)) ⟨66T227⟩.

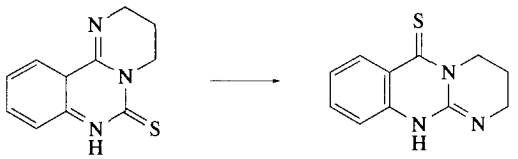


(67) (68) (13)



(69) (70) (14)

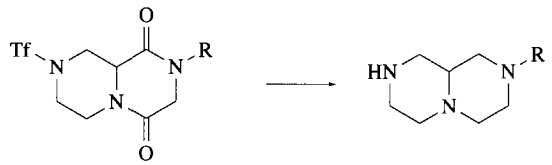
The angular pyrimido[1,2-*c*]quinazoline derivative (**71**) could be transformed into the pyrimido[2,1-*b*]quinazoline (**72**) by treatment with diaminopropane (Equation (15)) ⟨80ZC143⟩. Reaction of (**71**) with H_2O_2 afforded the 6-oxo derivative smoothly ⟨73ZC428⟩.



(71) (72) (15)

8.25.2.5.8 Pyrazino[1,2-a]pyrazines

Reduction of the 8-triflyl-1,4-dioxo derivatives (**73**) with LAH gave the fully saturated compounds (**74**) (Equation (16)) ⟨91S318⟩.

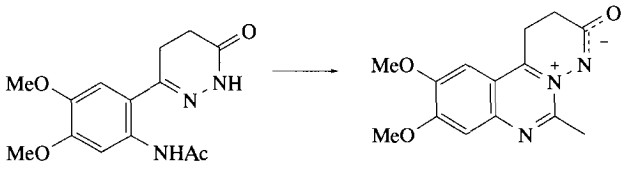


(73) (74) (16)

8.25.2.6 Synthesis

8.25.2.6.1 Synthesis of pyridazino[1,6-c]quinazolines

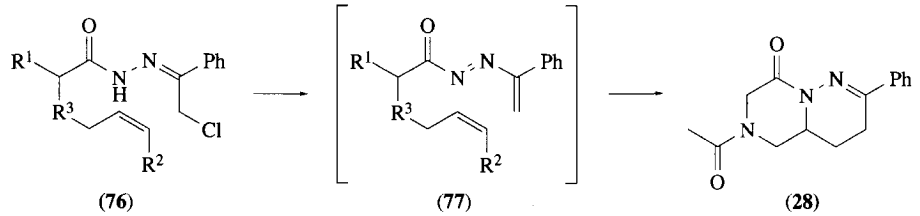
The parent bicyclic system has not yet been reported, and for the benzologue (**27**) one synthesis has been described. Treatment of (**75**) with perchloric acid afforded the perchlorate salt of (**27**) in quantitative yield (Equation (17)). The mesoionic (**27**) could be obtained from this salt with aqueous Na_2CO_3 ⟨83ACH43⟩.



(75) (27) (17)

8.25.2.6.2 Synthesis of pyrazino[1,2-b]pyridazines

One synthesis has been reported for this bicyclic ring system. The intramolecular Diels–Alder reaction of the azoalkene (**77**); $R^1 = R^2 = H$, $R^3 = NAc$) generated *in situ* from the hydrazone (**76**) with sodium carbonate, afforded (**28**) in good yield (Scheme 2) ⟨87JCS(P1)2517⟩.



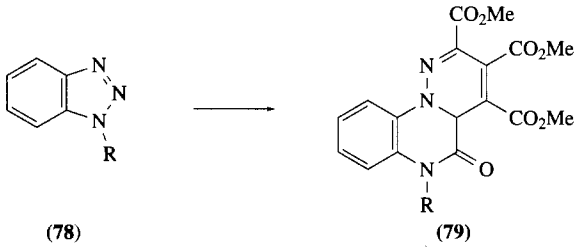
(76) (77) (28)

$R^1 = R^2 = H$, $R^3 = NAc$

Scheme 2

The pyridazino[1,6-*a*]quinoxaline ring system, which is the only known benzologue, can be prepared from 1-substituted benzotriazoles (**78**) with two moles of DMAD (Equation (18)). The reaction presumably proceeds via pyridazino[1,2-*a*]benzotriazoles, which undergo ring scission by N—N bond cleavage followed by recyclization to (**79**). The reaction is sensitive to the solvent: in

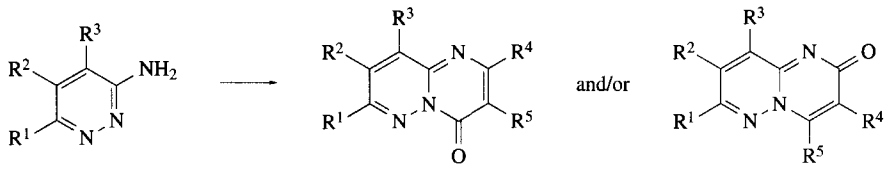
acetonitrile, only (**79**) could be isolated, whereas in THF, the pyridazino[1,2-*a*]benzotriazoles were also obtained ⟨72JCS(P1)2182⟩.



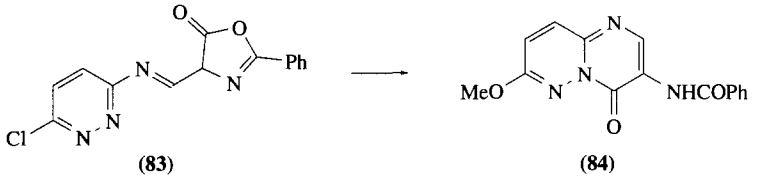
(78) (79) (18)

8.25.2.6.3 Synthesis of pyrimido[1,2-b]pyridazines

Pyrimido[1,2-*b*]pyridazines are most conveniently prepared in a [3 + 3] pathway, reacting 3-aminopyridazines (**80**) as N—C—N fragments with bifunctional electrophiles (Equation (19)). Depending on the electrophile and reaction conditions, the intermediate can be isolated (e.g., when using alkoxymethylenemalonates) and subsequently cyclized. The 4-oxo isomers (**81**) are obtained with methyl-2-benzoylamino-3-dimethylaminopropenoate and ethoxymethylenemalonates, whereas a mixture of (**81**) and (**82**) may be formed with ethyl acetoacetate ⟨90JHC359, 92JHC1409⟩. The 2-oxo isomers are generally formed with DMAD; one exception has been described ⟨88JHC1535⟩. The rearrangement reaction of the aminomethyleneoxazole (**83**), induced by NaOMe in methanol, resulted in the 4-oxo derivative (**84**) ⟨88H(27)903⟩.

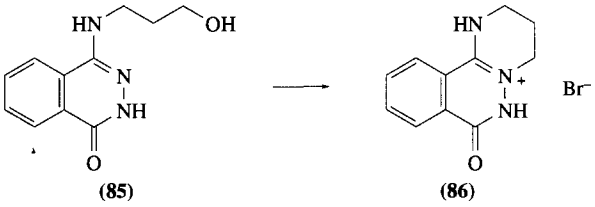


(80) (81) and/or (82) (19)

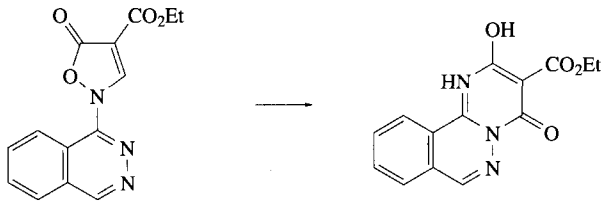


(83) (84) (20)

N-Phenylaminopyridazine underwent cyclization with bis(trichlorophenyl)butylmalonate to afford a mesoionic product ⟨91AP(324)863⟩. The three benzo-fused systems are prepared in different ways. The pyrimidine ring is usually elaborated onto the phthalazine ring in the syntheses of pyrimido[2,1-*a*]phthalazines. Aminophthalazine reacted, analogously to 3-aminopyridazines, with ethoxymethylenemalonate to afford the 4-oxo derivative. With ethyl acetoacetate or acrylic ester, the 2-oxo compounds were formed ⟨74CR(C)209⟩. Another efficient route for the preparation of this ring system involved the cyclization of 3-hydroxypropylaminophthalazines. Thus (**85**) cyclized to (**86**) in a few minutes on heating with 48% HBr (Equation (21)). A number of other derivatives have been prepared in this way ⟨83ACH65, 90T6895, 91T4457⟩. The phthalazinylisoxazolone (**87**) could be rearranged into (**88**) in 95% yield (Equation (22)) ⟨92AJC1825⟩.

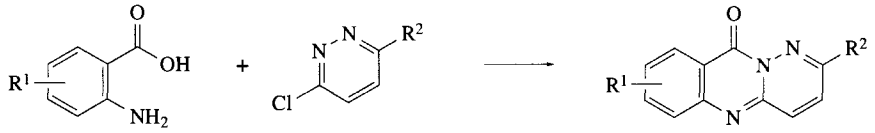


(85) (86) (21)



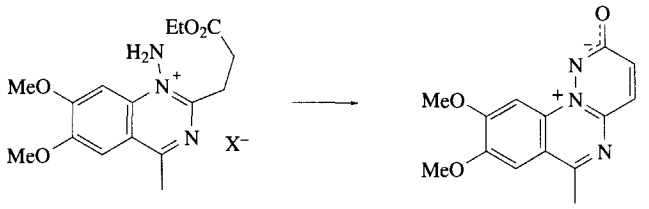
(87) (88) (22)

The linear pyridazino[6,1-*b*]quinazoline system can be conveniently prepared from anthranilic acid derivatives. In a [3 + 3] pathway, 3-chloropyridazines (**89**) reacted with (**90**) to afford the 10-oxo derivatives (**91**) (Equation (23)). The reaction proceeded in hot AcOH or on heating without solvent ⟨77IJC(B)250, 80JMC964, 93BCJ477⟩.



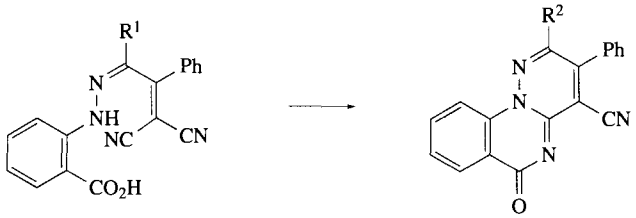
(90) (89) (91) (23)

In another route, the B and C rings were formed in one reaction by treatment of anthranil hydrazide with succinic or maleic anhydrides ⟨74MI 825-02, 78EJM296, 92KFZ32⟩. In a multistep approach, *N*-succinoyl anthranilic ester was converted into the tricyclic system ⟨88IJC(B)906⟩. The pyridazino[1,6-*a*]quinazoline system has been obtained in two ways. The *N*-aminoquinazolinium salt (**92**) cyclized easily on treatment with alkali at room temperature to give (**93**) (Equation 24) ⟨83ACH43⟩.



(92) (93) (24)

In the other route, the activated nitriles (**94**) were transformed to (**95**) in good yields on refluxing in AcOH or by treatment with alkali (Equation (25)). The compounds (**94**) were prepared from ethylidenemalonitriles with diazotized anthranilic acid ⟨87JHC227, 88AQ(C)22, 93BCJ1722⟩.

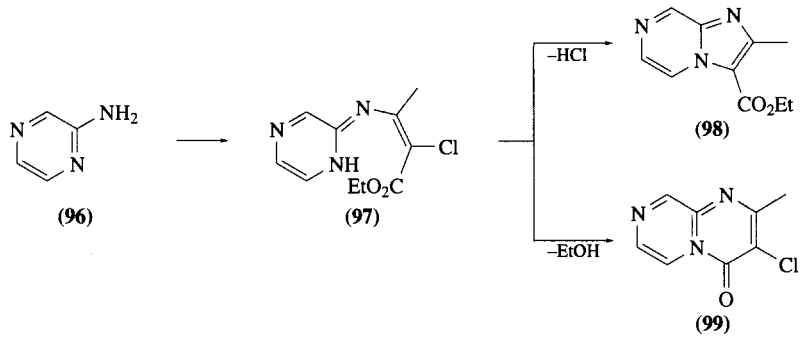


(**94**) R^1 = H, SCN (**95**) R^2 = H, SH (25)

8.25.2.6.4 Synthesis of pyrazino[1,2-a]pyrimidines

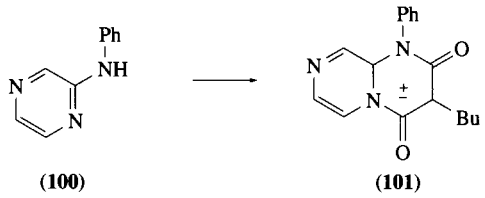
The [3 + 3] pathway has also been efficiently employed for preparation of this ring system. 3-Alkoxy-2-aminopyrazines reacted with alkoxymethylenemalonates in two steps to afford 9-alkoxypyrazino[1,2-*a*]pyrimidin-4(4*H*)-ones ⟨90JHC1639⟩. Methyl 2-benzoylamino-3-dimethylaminopropenoate also condensed with 2-aminopyrazine to give 3-benzoylaminopyrazino[1,2-*a*]pyrimidin-4(4*H*)-one in 30% yield ⟨90JHC359⟩. The reaction of (**96**) with ethyl 2-chloroacetoacetate in refluxing ethanol gave two bicyclic products, (**98**) and (**99**), in ca. 1 : 1 ratio, together with the intermediate

(**97**) (Scheme 3). The presence of an electron donor substituent in the 3-position of (**96**) shifted the reaction completely to the formation of (**98**) ⟨85EJM79⟩.

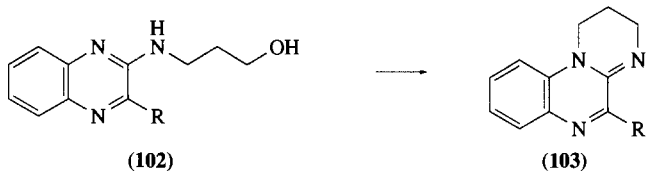


Scheme 3

The mesoionic product (**101**) could be obtained in 68% yield by treatment of 2-phenylaminopyrazine (**100**) with bis(trichlorophenyl)butylmalonate (Equation (26)) ⟨91AP(324)863⟩. Two benzo-fused ring systems of pyrazino[1,2-*a*]pyrimidine are known. The angularly annelated pyrimido[1,2-*a*]quinoxalines are conveniently synthesized from aminoquinoxaline precursors. Reaction with ethoxymethylenemalonate followed by thermal cyclization at 250 °C in Dowtherm afforded the 1-oxo derivative of this ring system ⟨77JCS(P1)789⟩. The 2-(3-hydroxypropylamino) derivatives (**102**) were cyclized to (**103**) on heating with $POCl_3$ (Equation (27)) ⟨70YZ1391⟩.

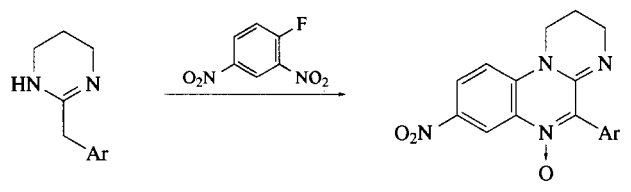


(26)

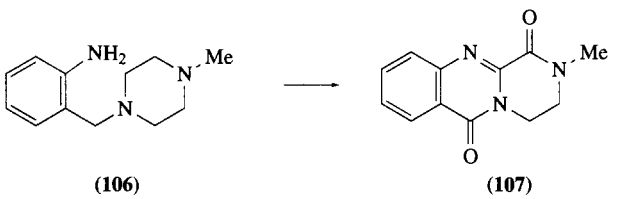


(27)

Another type of synthesis involved the cyclocondensation of (**104**) with 1-fluoro-2,4-dinitrobenzene in refluxing acetonitrile to give the *N*-oxide (**105**) in moderate yield (Equation (28)) ⟨83IJC(B)1250⟩. In the known syntheses of the linear benzologue, the B or C ring was closed in the final step. Oxidation of (**106**) with MnO_2 in benzene at room temperature, afforded dioxopyrimido[2,1-*b*]quinazoline (**107**) in 35% yield (Equation (29)) ⟨68JCS(C)1722⟩.

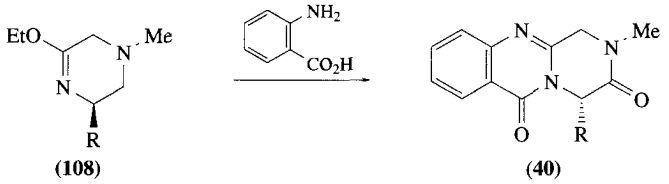


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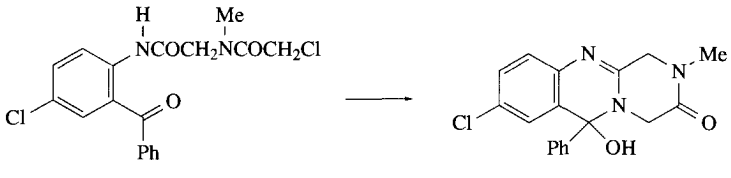


(29)

The imino ethers (**108**) obtained from cyclo(Sar-Gly), underwent cyclocondensation with anthranilic acid at 150 °C to afford (**40**) in moderate yield (Equation (30)) ⟨74JCS(P1)2122⟩. The *o*-aminobenzophenone derivative (**109**) could be converted to (**110**) in 66% yield (Equation (31)) by treatment with ammonia at room temperature ⟨81JOC4489⟩. The 3-oxo-6-phenyl derivative has been prepared by acidic cyclization of the (*o*-glycylamino)benzhydrylglycine ⟨84KGS983⟩. Starting with anthranilamide, the quinazolines (**111**) could be synthesized in several steps. Intramolecular alkylation in hot dioxane in the presence of Et_3N afforded (**112**) in excellent yields (Equation (32)) ⟨91SC173⟩.



(108) (40) (30)



(109) (110) (31)



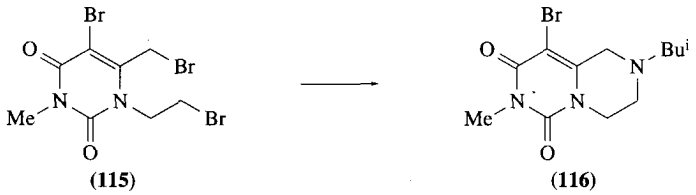
(111) (112) (32)

8.25.2.6.5 Synthesis of pyrazino[1,2-c]pyrimidines

Two syntheses use pyrimidine precursors. Thus, (**113**) and (**115**) were easily cyclized to the bicyclic derivatives (**114**) and (**116**) by treatment with $SOCl_2$ and isobutylamine, respectively (Equations (33) and (34)) ⟨85FES695, 92JHC741⟩.

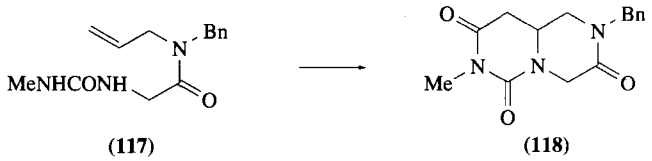


(113) R = NHCOPh (114) (33)

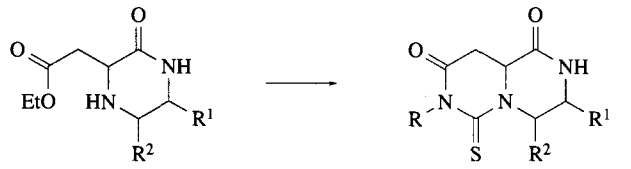


(115) (116) (34)

Another reported preparation uses the acyclic urea (**117**) (Equation (35)). The Pd^{2+}-catalyzed aminocarbonylation of this compound (1 atm CO/AcOH/$CuCl_2$/NaOAc) afforded (**118**) in good yield ⟨88JA3994⟩. The 3-ethoxycarbonylmethylpiperazines (**119**) reacted with isothiocyanates to give (**120**) (Equation (36)). In this way, the perhydropyrimido[1,6-*a*]quinoxalines ($R^1 + R^2 = —(CH_2)_4$) could also be prepared ⟨89H(29)1601⟩. The other known benzo-fused system has also been obtained from a hydrogenated pyrazine. Reduction of (**121**) with H_2 (PtO_2/AcOH) resulted in the formation of the pyrazino[1,2-*c*]quinazoline (**122**) in 73% yield (Equation (37)) ⟨82LA794⟩.



(117) (118) (35)



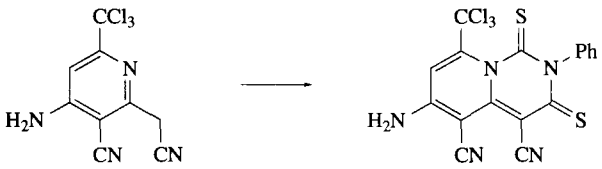
(119) (120) (36)



(121) (122) (37)

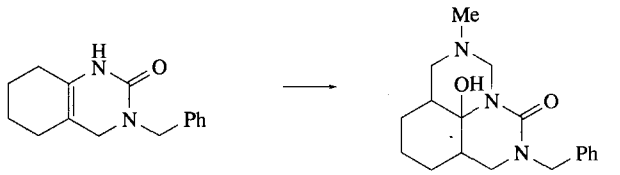
8.25.2.6.6 Synthesis of pyrimido[1,6-c]pyrimidines

In the first step of this synthesis, the pyrimidine derivative (**123**) was prepared from an enaminonitrile and trichloroacetonitrile, then this compound was treated with phenylisothiocyanate to give (**124**) in 75% yield (Equation (38)) ⟨82JCS(P1)2667⟩.

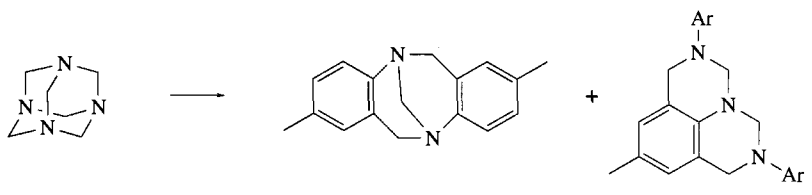


(123) (124) (38)

The benzo-fused system and its fully saturated analogue have also been reported. The first synthesis started with the saturated quinazoline (**125**), the reaction of which with formaldehyde and $MeNH_2$–HCl in refluxing ethanol gave (**126**) (Equation (39)) ⟨70M1745⟩. In a modified preparation of the Tröger's base (**128**), the pyrimido[5,6,1-*ij*]quinazoline derivative (**129**) could also be separated. In this reaction, hexamethylenetetramine (**127**) was treated with *p*-toluidine in TFA, and (**128**) and (**129**) were obtained in 41% and 26% yields, respectively (Equation (40)) ⟨93JMC3202⟩.



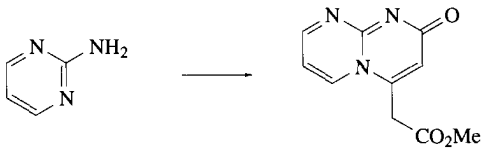
(125) (126) (39)



(127) (128) (129) (40)

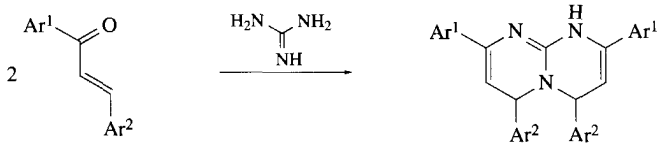
8.25.2.6.7 Synthesis of pyrimido[1,2-a]pyrimidines

These compounds are most frequently prepared by a [3 + 3] pathway. 2-Aminopyrimidines or their hydrogenated analogues can be used as starting materials, as in the reaction of (**130**) with allenedicarboxylic ester to give (**131**) in 58% yield (Equation (41)) ⟨88JCS(P1)2993⟩. The cyclocondensation could also be carried out with ethylacetoacetate or ethylacrylate to give 4-oxo or 2-oxo derivatives, respectively ⟨84S152, 85JCS(P2)1255⟩. Controversial results have, however, been reported for the reaction of (**130**) with DMAD ⟨86MI 825-02⟩. A mesoionic dioxo derivative was obtained from 2-phenylaminopyrimidine with bis(2,4,6-trichlorophenyl) malonates ⟨91AP(324)863⟩. 2-Aminopyrimidine with benzylidenacetophenones afforded 2,4-diarylpyrimido[1,2-*a*]pyrimidines, whereas 3-alkoxycarbonyl-2-methyl-4-phenyl derivatives were formed with benzylidenacetoacetates ⟨83M717, 91BMC291⟩. Partially or fully hydrogenated derivatives of this ring system were mostly prepared from acyclic precursors, with or without isolation of monocyclic intermediates. Guanidine reacted with 2 moles of chalcones affording (**132**) in moderate yields (Equation (42)), whereas several products were obtained with acrylonitrile ⟨84M309, 84M445⟩. In a multistep approach to compounds of type (**134**), the synthesis started with *N*-tosyl bis(iodoethyl)amine. The cyclization of (**133**) was carried out in the final step by treatment with MeI (Equation (43)) ⟨91LA539⟩.



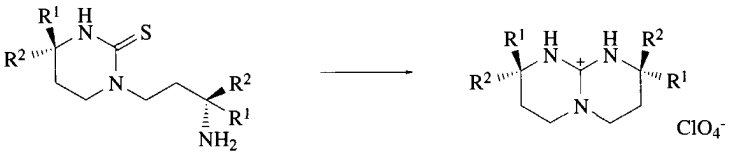
(41)

(130) (131)



(42)

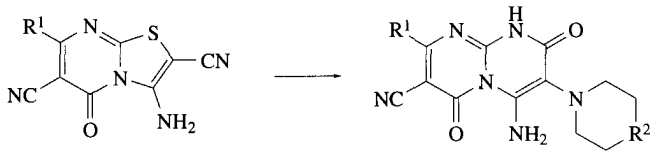
(132)



(43)

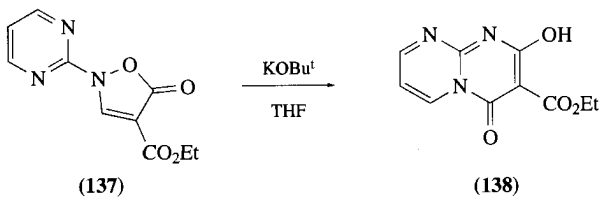
(133) (134)

The 2,8-bis(hydroxymethyl) derivatives have been synthesized from L-asparagine ⟨88HCA685, 90TL2269, 90CB907⟩. Pyrimido[1,2-*a*]pyrimidines have also been prepared by base-induced ring transformations. Reaction of (**135**) with cyclic secondary amines in boiling ethanol afforded (**136**) (Equation (44)) ⟨92MI 825-01⟩. The pyrimidinylisoxazolone (**137**) could be converted into (**138**) in 72% yield (Equation (45)) ⟨89AJC2161⟩.



(44)

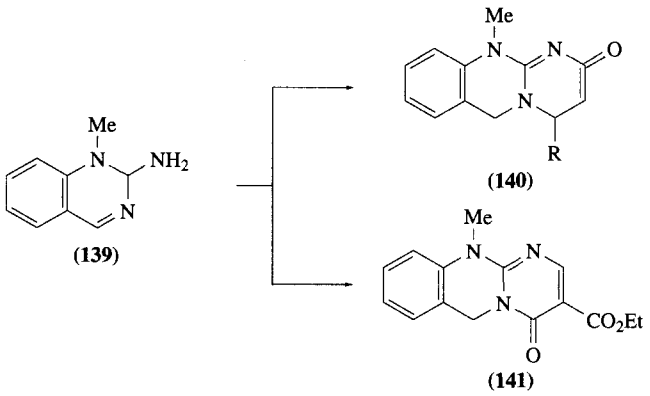
(135) (136)



(45)

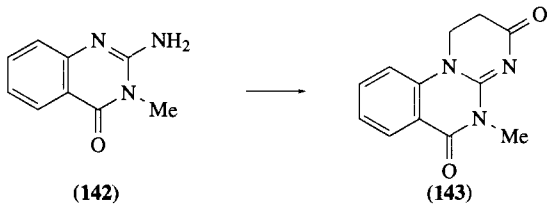
(137) (138)

Both benzo-fused ring systems can be prepared from 2-aminoquinazolines by cyclocondensation with a variety of bifunctional electrophiles ⟨78KGS105⟩. Using 2-amino-1-methylquinazoline (**139**), the 2-oxopyrimido[2,1-*b*]quinazolines (**140**) were obtained with propiolic ester or ethylacetoacetate, whereas the 4-oxo derivative (**141**) was formed with ethoxymethylenemalonate (Scheme 4). A mixture of 2-oxo and 4-oxo isomers was produced with acryloyl chloride ⟨70JCS(C)2134⟩. An 11-cyano derivative could be prepared by ring-opening of a *peri*-fused triazolo ring system ⟨86JHC833⟩. Intramolecular ring closures of *N*-benzoyltetrahydropyrimidines also gave this tricyclic ring system ⟨89JHC257⟩. The reaction of 2-amino-3-methylquinazolin-4(3*H*)-one (**142**) with acryloyl chloride afforded the pyrimido[1,2-*a*]quinazoline (**143**) (Equation (46)) ⟨87KGS1527⟩.



(139) (140) (141)

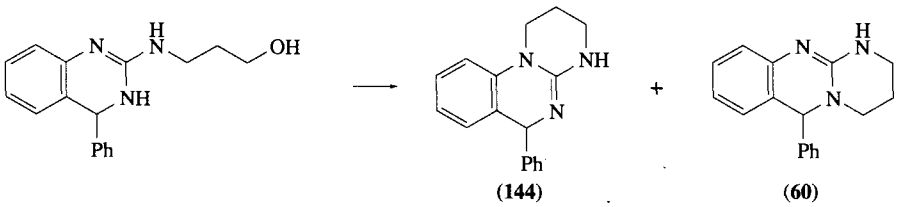
Scheme 4



(142) (143) (46)

An angularly fused product was obtained from 2-aminoquinazolin-4(1*H*)-one with ethoxymethylenemalonate, whereas linearly fused products were formed with ethoxymethylenemalonitrile or ethoxymethylenecyanoacetate ⟨89JHC161⟩.

The 1- and 3-(hydroxypropyl)-2-aminodihydroquinazolines are also cyclized to the angular and linear benzologue, respectively, by treatment with $SOCl_2$. However, from 2-(3-hydroxypropylamino)quinazoline a mixture of (**144**) and (**60**) was formed in which (**144**) predominated (Equation (47)) ⟨79CPB880⟩. Only the angular derivative was obtained from 6-chloro-2-(3-hydroxypropylamino)-4-phenylquinazoline ⟨73NKK1944⟩.



(144) (60) (47)

Anthranilic acid derivatives are also appropriate starting materials for the synthesis of the linearly fused benzologues. Reaction of (**145**) in AcOH gave (**36**) in good yields (Equation (48)) ⟨68ZC103, 76MI 825-01⟩. Treatment of (**146**) with 1,3-diaminopropane produced (**147**) in excellent yield (Equation (49)) ⟨82JHC1117⟩.

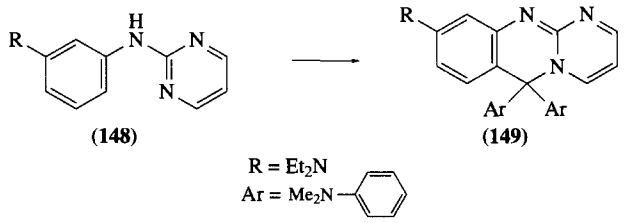


(145) (36) (48)



(146) (147) (49)

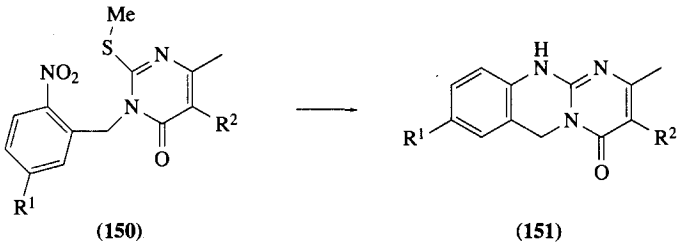
This ring system could also be prepared by cyclization of 2-phenylaminopyrimidines (**148**) with a diaryl ketone in hot $POCl_3$ to afford (**149**) in 53% yield (Equation (50)) ⟨88HCA33⟩. Reduction of (**150**) with $SnCl_2$ followed by cyclization with AcOH in methanol gave 4-oxopyrimido[2,1-*b*]quinazolines (**151**) in good yields (Equation (51)) ⟨78JHC77⟩. Isatoic anhydrides can serve as starting materials for both benzologues.



(148) (149) (50)

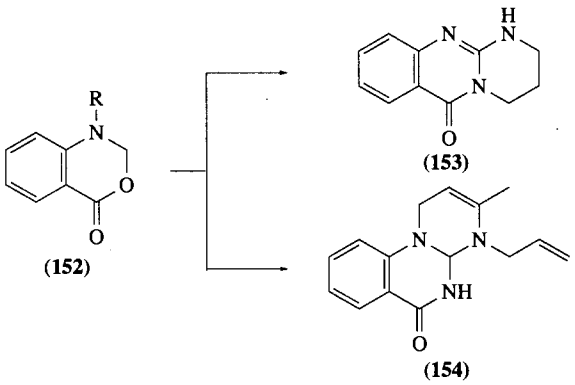
$R = Et_2N$

$Ar = Me_2N$—C$_6$H$_4$—



(150) (151) (51)

Reaction of (**152**; R = H) with 2-methylthiotetrahydropyrimidine afforded (**153**), whereas the treatment of the *N*-propargyl derivative of (**152**) with allyl-*S*-methylisothiourea gave the angular (**154**), probably via an allene (Scheme 5) ⟨68M1499, 75JMC447, 76JOC825⟩.

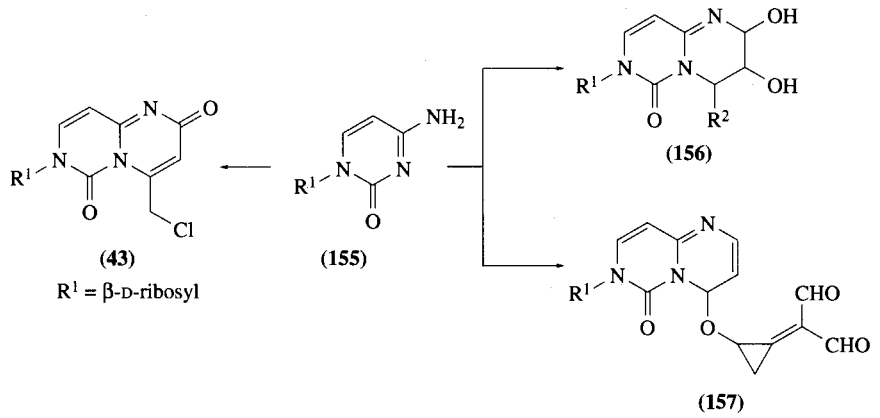


(152) (153) (154)

Scheme 5

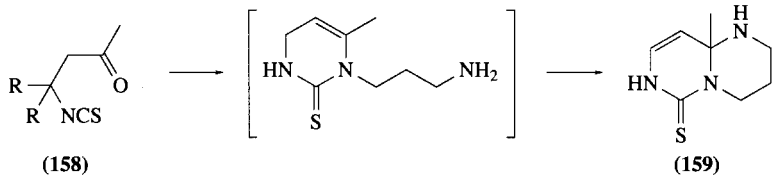
8.25.2.6.8 Synthesis of pyrimido[1,6-a]pyrimidines

Such bicyclic systems are readily formed from 4-aminopyrimidines in a [3 + 3] pathway. Cytidine (**155**) reacted with *p*-nitrophenyl-4-chlorotetrolate in DMF to afford (**43**) in 50% yield (Scheme 6); the 2-chloromethyl-4-oxo regioisomer was formed when a single strained polynucleotide poly(C) was used ⟨87MI 825-01, 92JOC1579⟩.



Scheme 6

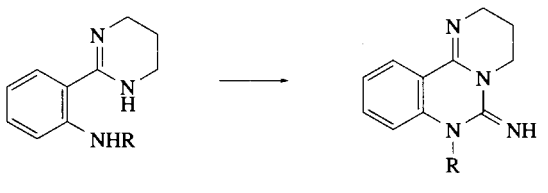
Cytidine and 1-methylcytosine also underwent cyclocondensation with epoxyaldehydes in aqueous buffers to give (**156**) in 30–45% yields depending on the pH of the reaction medium. However, with epoxybutanone imidazopyrimidines were formed ⟨85JOC5627⟩. Reaction of 4-amino-2,6-dihydroxypyrimidine with methyl 2-benzoylamino-3-dimethylaminopropenoate afforded a 3-benzoylaminopyrimido[1,6-*a*]pyrimidine derivative ⟨90JHC359⟩. Treatment of (**155**) with malondialdehyde formed the 4-cyclopropyloxy derivatives (**157**) ⟨84JA3370⟩. Malonic acids also readily give pyrimido[1,6-*a*]pyrimidinones with 4-aminopyrimidines. Some new examples have been described ⟨86JHC1063, 90JHC1963⟩. The acyclic isothiocyanate (**158**; R = H) serves as a precursor for a pyrimidinethione, which reacted with 1,3-diaminopropane to give (**159**) in 20% yield (Scheme 7) ⟨87JCS(P1)261⟩.



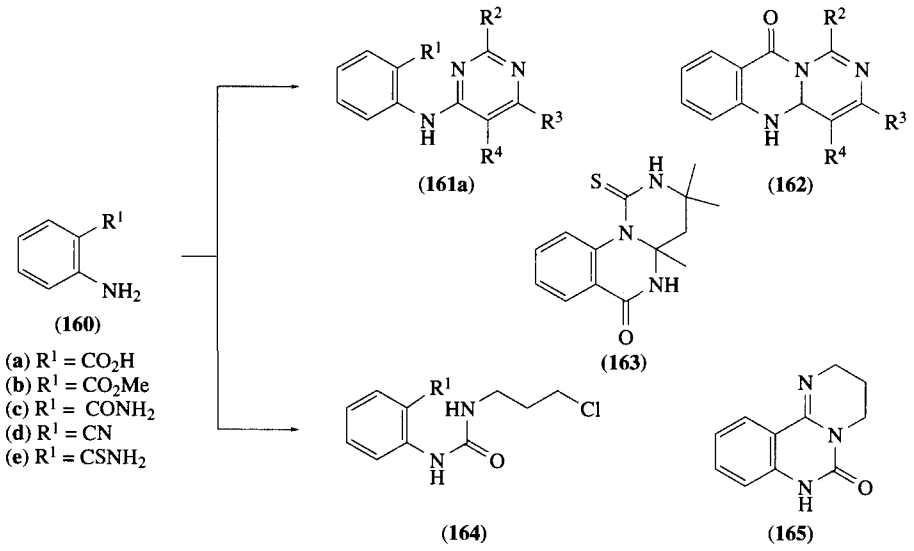
Scheme 7

All three benzo-fused systems can be prepared from anthranilic acid derivatives. 4-Chloropyrimidines with (**160a**) gave the intermediates (**161a**) which readily cyclized to pyrimido[6,1-*b*]quinazolines (**162**) on treatment with Ac_2O or $SOCl_2$ (Scheme 8). The reaction can be carried out without isolation of (**161**), when using (**160b**) or (**160c**) ⟨66T227, 68ZC103, 86JIC(B)914, 89JHC313, 91PHA26⟩. The isothiocyanate (**158**; R = Me) with (**160c**) or with the hydrochloride of (**160e**) formed the angular pyrimido[1,6-*a*]quinazoline derivative (**163**) ⟨76M183, 78M113⟩. 3-Chloropropyl-isocyanate converted (**160d**) or (**160e**) into the intermediate urea (**164**) which with ammonia or 10% NaOH solutions cyclized to (**165**) in excellent yield (Scheme 8) ⟨84JHC1411, 89JHC595⟩.

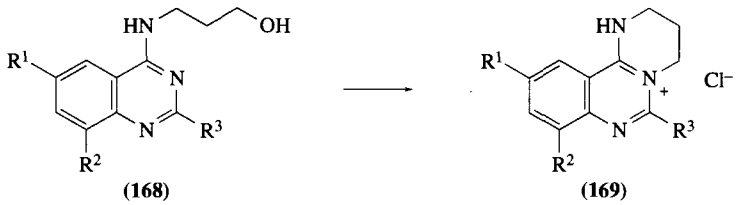
The angular pyrimido[1,2-*c*]quinazoline ring system has also been prepared in other ways. Thus (**166**) reacted with cyanogen bromide in refluxing 1-propanol to afford the 6-imino derivatives (**167**) in 35–60% yields (Equation (52)) ⟨78JHC877⟩. The ring closure to 6-oxo derivatives can be analogously performed with formic acid ⟨74JHC603⟩. The 4-(3-hydroxypropylamino)quinazolines (**168**) were cyclized to (**169**) in moderate yields by heating with $POCl_3$ (Equation (53)) ⟨74YZ417, 84MI 825-01⟩. The 6-thione derivatives were also described ⟨75BSF1411, 76BSF1857⟩



(52)



Scheme 8

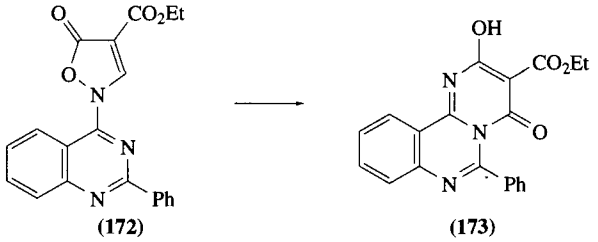


(53)

Two ring transformation reactions also led to pyrimido[1,2-*c*]quinazolines. The benzothiazines (**170**) with 1,3-diaminopropane gave (**171**) in 25–75% yields (Equation (54)); however, quinazoline dimers may also be formed in this reaction ⟨73ZC428⟩. The quinazolinylisoxazolone (**172**) can be rearranged, as can other hetarylisoxazolones, to the tricyclic compound (**173**) by base catalysis (Equation (55)) ⟨89AJC2161⟩.



(54)

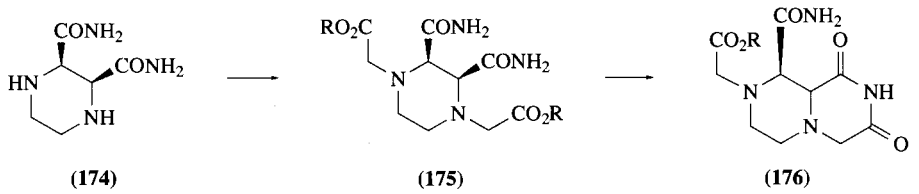


(55)

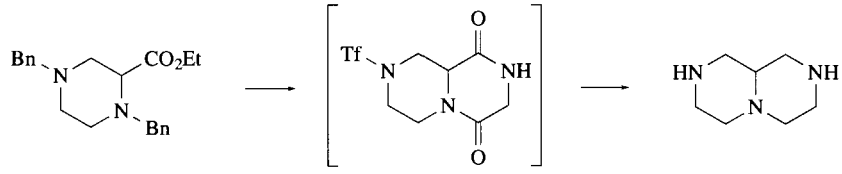
8.25.2.6.9 Synthesis of pyrazino[1,2-a]pyrazines

The usual precursor is a piperazine. The dicarboxamide (**174**) with bromoacetates in DMSO at room temperature afforded the *N*-alkoxycarbonylalkylated derivatives (**175**) in high yields (Equation (56)), which were quantitatively converted to (**176**) during chromatography (silica gel/MeOH) ⟨81JMC1329⟩. The perhydro compound (**178**) has been prepared from (**177**) through (**73**) in several

steps (Equation (57)) ⟨91S318⟩. The pyrazino[1,2-*a*]quinoxaline (**180**) has been prepared from (**179**) by treatment with diethyl oxalate followed by reduction with LAH (Equation (58)) ⟨79IJC(B)244⟩.



(174) (175) (176) (56)



(177) (73) (178) (57)



(179) (180) (58)

8.25.2.7 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Of bicyclic systems surveyed in this chapter, the pyrimido[1,2-*b*]pyridazine (**6**), pyrazino[1,2-*a*]pyrimidine (**10**), pyrimido[1,2-*a*]pyrimidine (**18**), and the pyrimido[1,6-*a*]pyrimidine (**21**) ring systems have been most investigated.

These systems uniformly have at least one pyrimidine ring, and they are readily formed from aminodiazines, incorporating the amidine moiety, with bifunctional electrophiles serving as three-carbon fragments. In this way, most frequently, oxo derivatives are obtained. Alkoxymethylenemalonates and 2-benzoylamino-3-dimethylaminopropenoate convert the amines into 4-oxo isomers via, sometimes isolable, intermediates; 2-oxo and/or 4-oxo isomers may be formed with acetylenecarboxylic or acrylic acid derivatives or with ethyl acetoacetate. The decisive factors for the regiochemistry have not yet been fully explored. The base-induced rearrangement of ethyl 2-diazanyl-5-oxo-2,5-dihydroisoxazole-4-carboxylates is also a powerful approach to the bicyclic systems. It gives 3-ethoxycarbonyl-2-hydroxy-4-oxo derivatives which present a versatile substitution pattern for further functionalization. A further important aspect of the synthetic methods discussed above is their wide applicability for preparation of the benzo-fused derivatives.

8.25.2.8 Important Compounds and Applications

Many members of these ring systems have been shown to possess interesting properties; however, only a few compounds have gained practical applications.

8.25.2.8.1 Pyrazino[1,2-c]pyrimidine

7-Ethyl-2-methyl-octahydropyrazino[1,2-*c*]pyrimidin-6(6*H*)-one (centperazine) (**56**) exhibits a very strong antifilarial activity. This compound has been undergoing Phase II clinical trials ⟨93LA437⟩.

8.25.2.8.2 Pyrimido[1,2-a]pyrimidine

The commercially available 3,4,6,7,8,9-hexahydropyrimido[1,2-*a*]pyrimidine (other name: TBD) is currently used in many organic syntheses as an exceptionally strong base. Some recent applications have been reported ⟨92DP91, 93ACS122⟩. 2,8-Disubstituted derivatives of this compound have been widely used as synthetic receptors for the host–guest complexation of biologically important compounds ⟨91JA9424, 92JA1511, 93TL2449⟩. Some mesoionic 2,4-dioxopyrimido[1,2-*a*]pyrimidines possess remarkable antihypertensive and antianginal activities ⟨91AP(324)863⟩.

8.25.2.8.3 Pyrimido[1,6-a]pyrimidine

A pyrimido[1,2-*c*]quinazoline-4-carboxylic acid derivative (FR50948) exhibits excellent anti-allergic effects ⟨88MI 825-01⟩.

8.25.3 BICYCLIC 6-6 N-BRIDGEHEAD SYSTEMS WITH ONE EXTRA N ATOM AND ONE EXTRA O ATOM 1 : 1, AND THEIR BENZO-FUSED DERIVATIVES

8.25.3.1 Introduction

This group of compounds covers N-bridgehead pyridazino-, pyrimido- and pyrazino-oxazines and their benzo derivatives. Theoretically, 16 bicyclic systems are possible, and 10 of them are known, with 19 benzo-fused derivatives (see Table 4).

None of the above groups of compounds was considered in CHEC-I, and therefore the whole of the literature has been surveyed. The only previous review of this field is that by Mosby ⟨B-61MI 825-02⟩, who lists one reference ⟨53ACS1017⟩ on the preparation of a pyrimido[6,1-*c*][1,4]oxazine and/or pyrazino[2,1-*c*][1,4]oxazine derivative. No further indication has been found in the literature as to which structure was formed.

In the bicyclic system pyrazino[1,2-*c*][1,3]oxazine, only one compound has been described: hexahydro-2′-methylspiro[cyclohexane-1,8′(6*H*)-oxazino[3,4-*a*]pyrazine], a convulsant, named COP ⟨63MI 825-01, 64MI 825-01⟩. No information has been found in the literature, however, as concerns its chemistry and preparation.

For the tricyclic system [1,4]oxazino[4,3-*a*]quinoxaline, only one reference, a patent has been found, where the structure falls within a very broad general formula, and no specific example of it is given ⟨92EUP509398⟩.

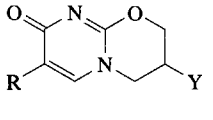
8.25.3.2 Theoretical Methods

Calculations with the Hückel Molecular Orbital (HMO) method were carried out for the pyrimido[2,1-*b*][1,3]oxazinones (**214**) to rationalize their formation and ring opening (see also in Section 8.25.3.6.6, Scheme 16). π-Electron charge (Δp) and reactivity indices for the positions influencing the ring opening are given ⟨89JCS(P2)1209⟩.

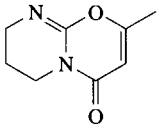
8.25.3.3 Experimental Structural Methods

8.25.3.3.1 X-ray diffractometry

Crystallographic parameters were determined for the pyrimido[2,1-*b*][1,3]oxazine (**215**) ⟨67RS970⟩. The 1*H*-[1,4]oxazino[3,4-*b*]quinazolin-(4*H*)3-one (tricyclic lactone) skeleton was demonstrated for the methanolysis product of triptoquivaline, a metabolite of *Aspergillus clavatus* ⟨75JA663⟩.



(214) R = H, Br, Me; Y = H



(215)

Table 4 Bicyclic 6-6 nitrogen bridgehead systems with one extra *N* and one extra *O* atom 1 : 1 and their known benzo-fused derivatives. (Systems which are unreported are named in italic.)

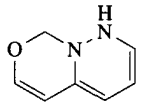
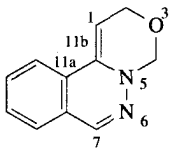
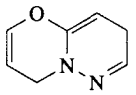
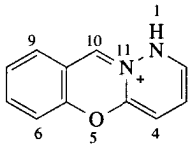
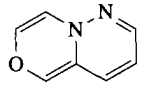
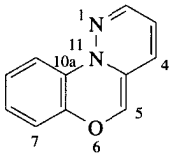
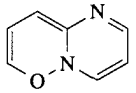
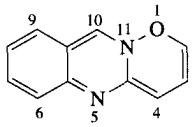
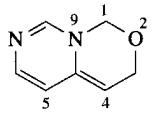
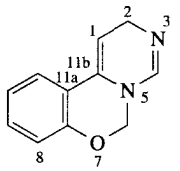
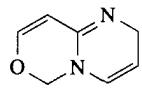
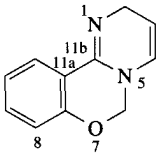
Compound	*Ring system*	*Name and ring file number*
(181)		*1*H,*8*H-*Pyridazino*[*2*,*3*-c][*1*,*3*]*oxazine*
(182)		2*H*,4*H*-[1,3]Oxazino[4,3-*a*]phthalazine, RF 34924
(183)		*2*H,*6*H-*Pyridazino*[*3*,*2*-b][*1*,*3*]*oxazine*
(184)		1*H*-Pyridazino[6,1-*b*][1,3]benzoxazin-11-ium, RF 34942
(185)		Pyridazino[6,1-*c*][1,4]oxazine, RF 13595
(186)		Pyridazino[6,1-*c*][1,4]benzoxazine, RF 34939
(187)		*Pyrimido*[*1*,*2*-b][*1*,*2*]*oxazine*
(188)		[1,2]Oxazino[3,2-*b*]quinazoline, RF 34925
(189)		1*H*,3*H*-Pyrimido[1,6-*c*][1,3]oxazine, RF 13607
(190)		2*H*,6*H*-Pyrimido[1,6-*c*][1,3]benzoxazine, RF 34951
(191)		*2*H,*6*H-*Pyrimido*[*1*,*2*-c][*1*,*3*]*oxazine*
(192)		2*H*,6*H*-Pyrimido[1,2-*c*][1,3]benzoxazine, RF 34950

Table 4 (continued).

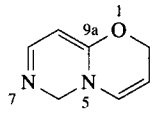
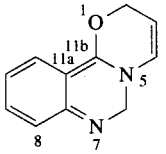
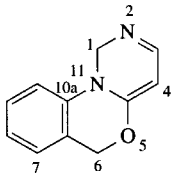
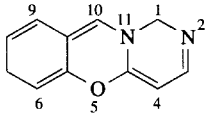
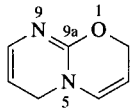
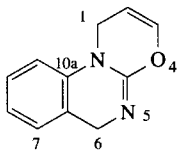
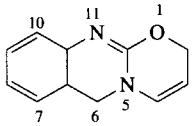
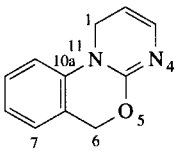
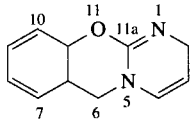
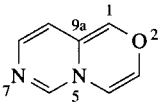
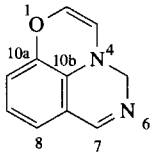
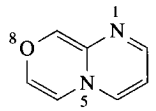
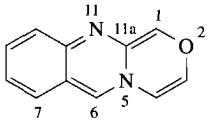
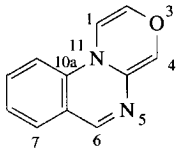
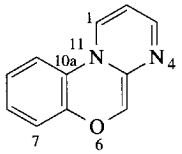
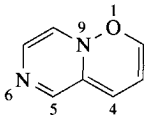
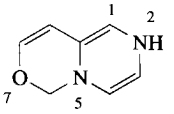
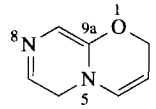
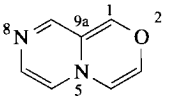
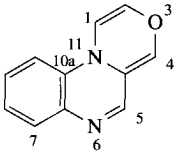
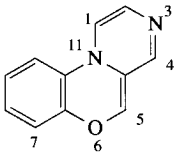
Compound	*Ring system*	*Name and ring file number*
(193)		2*H*,6*H*-Pyrimido[6,1-*b*][1,3]oxazine, RF 13614
(194)		2*H*,6*H*-[1,3]Oxazino[3,2-*c*]quinazoline, RF 34930
(195)		1*H*,6*H*-Pyrimido[1,6-*a*][3,1]benzoxazine, RF 34945
(196)		1*H*,7*H*-Pyrimido[6,1-*b*][1,3]benzoxazine, RF 34946
(197)		2*H*,6*H*-Pyrimido[2,1-*b*][1,3]oxazine, RF 13613
(198)		1*H*,6*H*-[1,3]Oxazino[3,2-*a*]quinazoline, RF 34928
(199)		2*H*,6*H*-[1,3]Oxazino[2,3-*b*]quinazoline, RF 34929
(200)		1*H*,6*H*-Pyrimido[1,2-*a*][3,1]benzoxazine, RF 34944
(201)		2*H*,6*H*-Pyrimido[2,1-*b*][1,3]benzoxazine, RF 34952
(202)		Pyrimido[6,1-*c*][1,4]oxazine, RF 13603
(203)		5*H*-Pyrimido[1,6,5-*de*]-1,4-benzoxazine, RF 34953

Table 4 (continued).

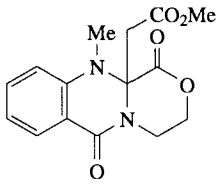
Compound	*Ring system*	*Name and ring file number*
(204)		Pyrimido[2,1-*c*][1,4]oxazine, RF 13602
(205)		[1,4]Oxazino[3,4-*b*]quinazoline, RF 34926
(206)		[1,4]Oxazino[4,3-*a*]quinazoline, RF 34927
(207)		Pyrimido[2,1-*c*][1,4]benzoxazine, RF 34943
(208)		Pyrazino[1,2-*b*][1,2]oxazine, RF 13588
(209)		2*H*,6*H*-Pyrazino[1,2-*c*][1,3]oxazine, RF 13592
(210)		2*H*,6*H*-Pyrazino[2,1-*b*][1,3]oxazine, RF 13594
(211)		Pyrazino[2,1-*c*][1,4]oxazine, RF 13589
(212)		[1,4]Oxazino[4,3-*a*]quinoxaline, RF 34931
(213)		Pyrazino[2,1-*c*][1,4]benzoxazine, RF 34934

8.25.3.3.2 NMR spectroscopy

Owing to the diversity of the structures discussed in this section, a description and comparison of their spectral behavior is not attempted here. Proton and ^{13}C NMR spectroscopy have been widely used to characterize compounds of the types discussed in this chapter, and to elucidate their structures. ^{15}N NMR investigations have not been reported. Several more specialized studies applied to solve certain structural problems are mentioned below.

(i) Proton NMR

Assignments have been accomplished for four structural isomers and stereoisomers with pyrimido[1,6-*c*][1,3]benzoxazine and pyrimido[1,2-*c*][1,3]benzoxazine structures ⟨75S802⟩. The [1,4]oxazino[3,4-*b*]quinazoline structure (**216**), rather than a possible seven-membered ring structure, was established for the cyclization product of (**305**; $R^1 = CH_2CO_2Me$, $R^2 = H$) (see Section 8.25.3.6.8) ⟨80JHC1169, 80JHC1163⟩.



(**216**)

The ring–chain tautomerism between (**217a**) and (**217b**) (Equation (59)) ⟨85CPB2395⟩ and between (**218a**) and (**218b**) (Equation (60)) ⟨86HCA1025⟩ (see Section 8.25.3.4.3) were investigated by means of ^1H NMR.

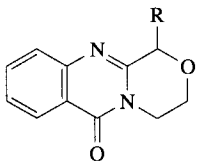


(**217a**) (**217b**) (59)

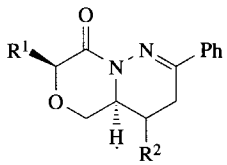


(**218a**) X = 0, *n* = 3 (**218b**) (60)

Detailed conformational analyses were carried out for the 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones (**219**). The oxazine ring of (**219**) assumes two equally populated, rapidly interconverting half-chair conformations. Substitution at position 1 resulted in the predominance of one of the conformers ⟨93JHC1413⟩. The orientations of the hydrogens and the half-chair and chair-like conformations of the oxazinone moieties were demonstrated for the [1,4]oxazino[3,4-*b*]quinazoline (**216**) ⟨80JHC1169⟩ and the pyridazino[6,1-*c*][1,4]oxazinone (**220**) ⟨87JCS(P1)2517⟩.



(**219**) R = H, Me, OH, OAc, OEt



(**220**)

(ii) Carbon-13 NMR

For compounds (**219**), the pseudoaxial orientation of the substituent at position 1 was shown ⟨93JHC1413⟩. Detailed ^{13}C NMR investigations were also carried out on compound (**216**) ⟨80JHC1169⟩, its 11a-methyl analogue ⟨80JHC1163⟩ and compound (**220**) ⟨87JCS(P1)2517⟩.

8.25.3.3.3 IR and UV Spectroscopy

IR and UV spectroscopy have widely been used to characterize the present range of compounds and to support their structures. Lactones have been characterized by their IR lactone band. For a series of compounds (**219**) both data have been given ⟨93JHC1413⟩. The ring-chain tautomers (**218a**)⇌(**218b**) (Section 8.25.3.4.3) were investigated via their UV λ_{max} values ⟨86HCA1025⟩.

8.25.3.3.4 Mass spectrometry

Mass spectral characteristics have been frequently given for the investigated compounds, most of which produce strong molecular ions. No specific discussions on fragmentation patterns are to be found.

8.25.3.4 Thermodynamic Aspects

Almost all compounds described in this section are solids with crystalline structures.

8.25.3.4.1 Chromatographic behavior

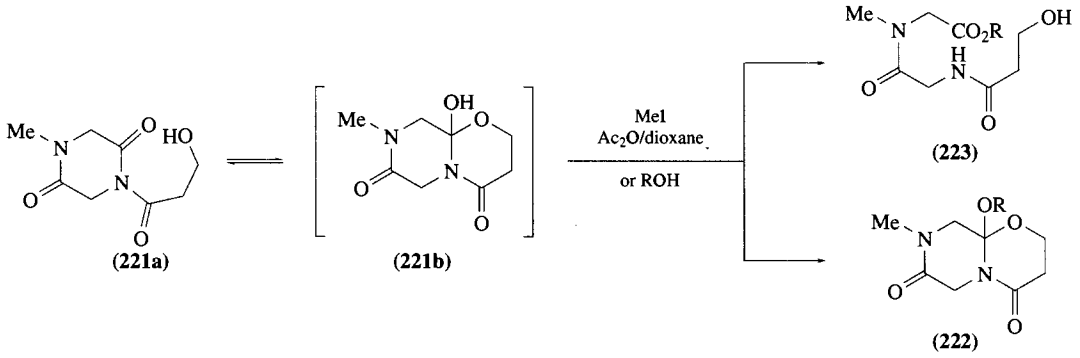
There are very few data and no specific study has been performed to establish the chromatographic behavior of the compounds in this section. Several products have been purified or separated by thin-layer chromatography or column chromatography.

8.25.3.4.2 Conformations

The few conformational studies that have been carried out are mentioned in Section 8.25.3.3.2 under NMR spectroscopy.

8.25.3.4.3 Tautomerism

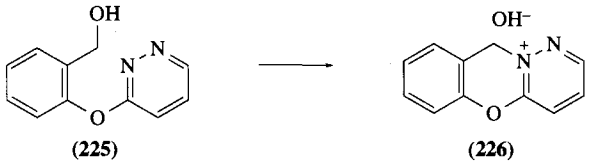
Ring–chain tautomerism was revealed between the *N*-(formylethyl)pyrimidinedione (**217a**) and its cyclic hemiacetal, the pyrimido[2,1-*b*][1,3]oxazine, (**217b**). In $CDCl_3$ the cyclic, and in DMSO-d_6 the acyclic form predominates ⟨85CPB2395⟩. The pyrazino[2,1-*b*][1,3]oxazine (**221b**) is formed from the *N*-(hydroxypropyl)diketopiperazine (**221a**) in an equilibrium reaction (Scheme 9). The equilibrium strongly favors the monocyclic form, but the *O*-alkylated bicycle (**222**) was obtained in good yield, beside an open-chain dipeptide (**223**) ⟨67ZOB2225⟩.



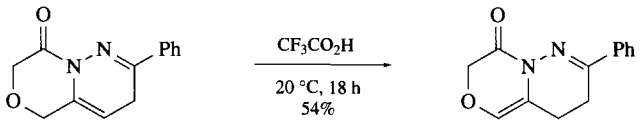
Scheme 9

Another tautomeric equilibrium postulated in this series is that between the bicyclic amine (**218b**) and the monocyclic imine (**218a**). The equilibrium is dependent upon the nature of X, the value of

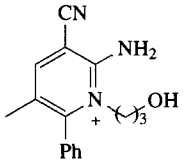
n, the solvent, and the pH (cf. the equilibrium between the pyrazinopyrimidine (**39b**; X = N) and (**39b**) in Section 8.25.2.4.3). With X = O, *n* = 3, only the monocyclic form (**218a**) could be separated as crystal. In ethanolic solution (**218a**) and (**218b**) were present in a ratio of 41.5 : 58.5. In acidic medium, the equilibrium was shifted towards the open-chain cation (**224**) ⟨86HCA1025⟩. The pyridazino[6,1-*b*][1,3]benzoxazinium salt (**226**) was formed from the hydroxy derivative (**225**) during storage in the solid phase or in solution (Equation (61)) ⟨77ABC1975⟩. Prototropic isomerism has been revealed for the pyridazino[6,1-*c*][1,4]oxazinone (**227**), which converted into the 3,4-dihydro form (**228**) on the action of strong acid (Equation (62)) ⟨87JCS(P1)2517⟩.



(225) (226) (61)



(227) (228) (62)



(224)

8.25.3.5 Reactivity

8.25.3.5.1 Unimolecular thermal and photochemical reactions

No reaction of this type has been described.

8.25.3.5.2 Electrophilic attack at heteroatoms

(i) Protonation

Stable proton acid salts were frequently prepared, but pK_a values have not been reported. Proton-induced isomerizations are mentioned in Section 8.25.3.4.3.

(ii) N-*Alkylation*, N-*acylation*

N-Alkylation with substituted alkyl halides and *N*-acylation with acyl chlorides is described for compound (**322**; X = H_2) ⟨75IJC462⟩.

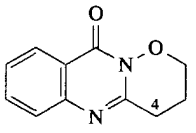
(iii) Oxidation

Cyclic tertiary amines formed by the oxidative cyclization route always suffer further oxidation, resulting in unsaturation (see the formation of (**229**) from (**298**) in Section 8.25.3.6.8.). Further oxidation and nucleophilic attack by the hydroxide anion on the α-carbon results in lactams ⟨68JCS(C)1722⟩ or, depending on the structure, in ring opening and formation of monocyclic lactams ⟨80PHA389⟩.

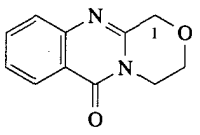
8.25.3.5.3 Electrophilic attack at carbon atoms

(i) Active methylene group reactions

The methylene groups of saturated oxazino moieties, next to the amidine carbon are active enough to react with electrophiles. The [1,2]oxazino[3,2-*b*]quinazoline (**229**) reacts with benzaldehyde to furnish the 4-benzylidene derivative ⟨87JHC175, 91JHC2071⟩. The [1,4]oxazino[3,4-*b*]quinazoline (**230**) can be selectively monobrominated at position 1 with NBS ⟨91MI 825-01, 93JHC1413⟩. The bromo group may then be variously replaced (see Section 8.25.3.5.7); (**230**) also reacts at position 1 with aromatic aldehydes, Vilsmeier–Haack reagent, sodium nitrite, phenyldiazonium chloride, and diethyl oxalate ⟨93JHC1413⟩.



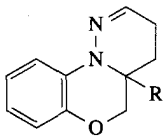
(**229**)



(**230**)

(ii) Oxidation

The 3,4,4a,5-tetrahydropyridazino[6,1-*c*][1,4]benzoxazine (**231**) was oxidized to the 4a,5-dihydro derivative by ddq ⟨91MIP9117983⟩.

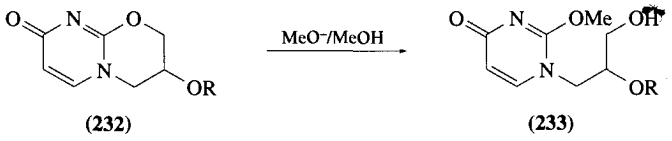


(**231**)

8.25.3.5.4 Nucleophilic attack at carbon atoms

(i) Ring-opening reactions

The oxazino group, as a cyclic ether, tends to undergo ring fission. Pyrimido[2,1-*b*][1,3]oxazines and their benzologues are attacked by anions at C-9a; thus, (**232**) with methoxylate anion gives the lactim ether (**233**) (Equation (63)) ⟨82JCS(P1)223⟩ and (**214**) gives the lactam (**270**) in sodium hydroxide solution (see Scheme 16 in Section 8.25.3.6.6) ⟨89JCS(P2)1209⟩. In acid-catalyzed ring opening the nucleophilic attack takes place at C-2; thus, (**234**) gives (**235**) (Equation (64)) ⟨84JHC1411⟩. Ring opening may be reversed by the action of bases ⟨88JHC1103⟩; see also the formation of (**280**) from (**278**) and that of (**283**) from (**281**) in Section 8.25.3.6.6 ⟨79CPB880⟩.



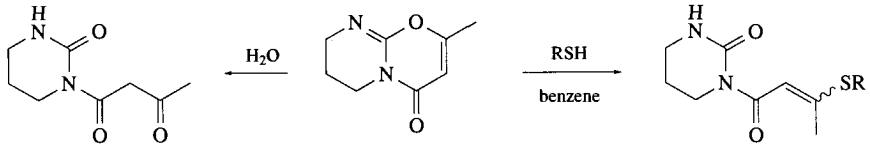
(232) (233) (63)



(234) (235) (64)

X = Cl, Br, OH, OMe, OAc, NHPh

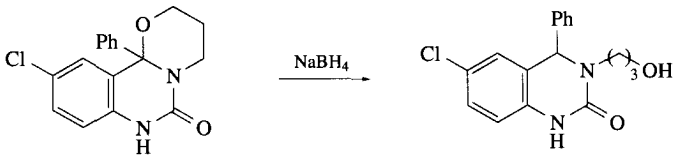
Ring opening at C-2 takes place in (**215**) by the action of thiols or water to give (**236**) or (**237**) (Scheme 10) ⟨69G1000⟩.



(237) (215) (236) *E* and *Z* isomers

Scheme 10

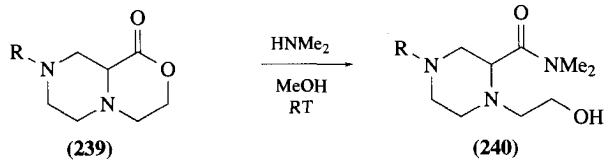
For other ring systems, the acid-catalyzed, reversible ring opening of the pyrimido[1,6-*c*][1,3]benzoxazine (**252**) (see Section 8.25.3.6.3) ⟨61M278, 65M1943⟩ and the fission of the [1,3]oxazino-[3,2-*c*]quinazoline (**238**) by the action of hydride anion ⟨81CPB2135⟩ have been described (Equation (65)).



(238) (65)

(ii) Lactone ring opening

Oxazinone moieties with a lactone structure undergo ring opening on attack by bases. Thus, (**239**) gives the amide (**240**) (Equation (66)) ⟨78MI 825-01⟩. There are further examples of lactone ring opening ⟨70JCS(C)1651, 71IJC1077⟩. Compound (**216**) reacts with ammonia to give the bicyclic amide, with amines to give the diamide and with benzylamine to give a spiro-derivative ⟨84H(22)2815⟩. Lactone ring opening is followed by decarboxylation of the *N*-carboxylic acid resulting from (**253**) (see Section 8.25.3.6.4) ⟨83JHC1159⟩, and by water elimination from the hydroxy derivative resulting from (**265**; X = S) (see Section 8.25.3.6.5) ⟨76M183⟩.



(239) (240) (66)

(iii) Oxo group reduction

The oxo groups of the 1,2-dioxo analogue of (**322**) (see Section 8.25.3.6.9) were reduced with LAH/THF ⟨75IJC462⟩.

8.25.3.5.5 Electrophilic attack on substituents

(i) Oxidations

The thioxo group of (**265**; X = S) ⟨76M183⟩ and of (**266**; X = S) ⟨76M171⟩ (see Section 8.25.3.6.5) was oxidized to the oxo group with hydrogen peroxide solution.

An hydroxy group was oxidized to an oxo group with the Jones reagent for (**219**; R = OH) ⟨93JHC1413⟩ and with pyridinium dichromate in DMF for (**291**; R = H) (see Section 8.25.3.6.7) ⟨92CPB2668⟩.

(ii) O-*Alkylation*

The hydroxy group of aminocarbinol (**221**) was *O*-alkylated with methyl iodide ⟨67ZOB2225⟩.

(iii) S-*Alkylation*

The thioxo group of (**265**; X = S) (see Section 8.25.3.6.5) was alkylated with MeI in ethanol ⟨76M183⟩. *S*-Methylation on a phase-transfer catalyst, however, resulted in the cleavage of the lactone ring ⟨82S1073⟩.

8.25.3.5.6 Nucleophilic attack on substituents

(i) O-*Desalkylation*

O-Desalkylation was effected by reaction with hydrobromic acid at 150°C for compound (**291**; R = Me) (see Section 8.25.3.6.7) ⟨92CPB2668⟩.

8.25.3.5.7 Nucleophilic substitution

The 6-methoxy substituent of (**250**) (see Section 8.25.3.6.3) was exchanged for the amino group by NH_3 in methanol at 120°C, and for the hydroxy group by NaOH in dioxane ⟨92JOC3354⟩.

The 4-chloro group of (**268**; X = Cl) (see Section 8.25.3.6.5) was hydrolyzed ⟨70LA(734)155⟩. The 1-bromo group of (**219**; R = Br) was exchanged for the ethoxy group by sodium ethoxide and for the acetoxy group by sodium acetate in acetic acid ⟨93JHC1413⟩.

8.25.3.6 Synthesis

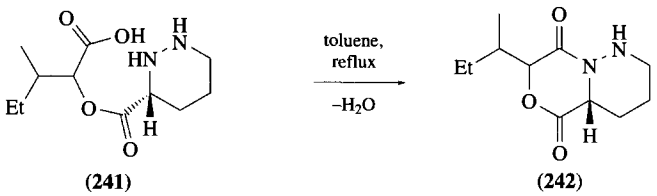
8.25.3.6.1 Pyridazino-oxazines and their benzo derivatives

Only a few representatives of these systems have been prepared.

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

The fully saturated pyridazino[6,1-*c*][1,4]oxazine (**242**) was obtained by lactamization from the acid (**241**), which is a degradation product of the antibiotic monoamicin (Equation (67)) ⟨71JCS(C)522⟩. The only representative of pyridazino[6,1-*b*][1,3]benzoxazines, (**226**), is formed by

intramolecular quaternization from the credazine metabolite (**225**), during storage (see Equation (61)) ⟨77ABC1975⟩.

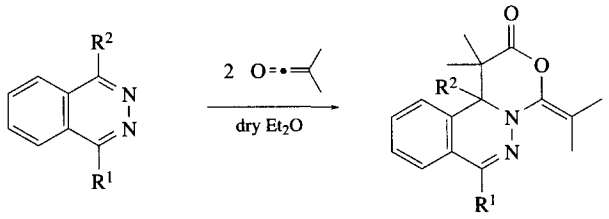


(241) (242) (67)

(ii) By cycloaddition

A route to tetrahydropyridazino[6,1-*c*][1,4]oxazines (**220**) is by the spontaneous intramolecular Diels–Alder cycloaddition of the azoalkanes (**77**; X = O), formed *in situ* from the hydrazones (**76**; X = O) (see Section 8.25.6.1.6). If R^1 was not H, considerable stereoselectivity was observed. This has been ascribed to steric effects in the transition state of the azoalkane ⟨87JCS(P1)2517⟩.

Compound (**227**) ⟨87JCS(P1)2517⟩ and the pyridazino[6,1-*c*][1,4]benzoxazine (**231**) ⟨91MIP9117983⟩ were synthesized in a similar fashion. Compounds (**244**), representatives of [1,3]oxazino[4,3-*a*]phthalazines, were synthesized by 1 : 2 cycloaddition of (**243**) and dimethylketene (Equation (68)) ⟨70JCS(C)1651⟩.

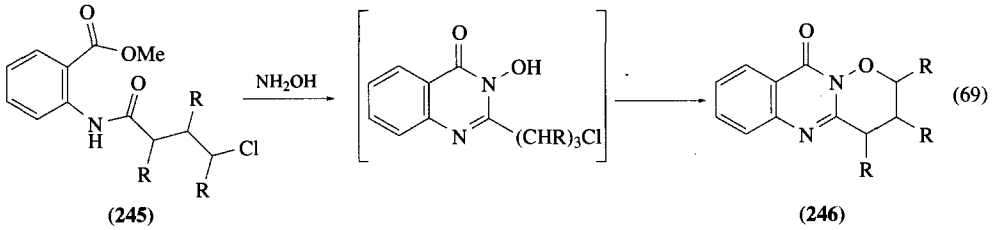


(243) (244) (68)

8.25.3.6.2 *[1,2]Oxazino[3,2-b]quinazolines (benzo derivatives of the unknown pyrimido [1,2-b][1,2]oxazines*

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

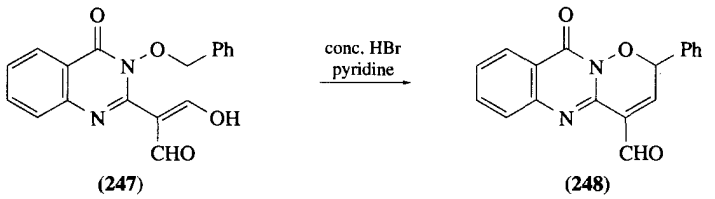
The reaction of *N*-acyl anthranilates (**245**) and hydroxylamine is a general method to prepare compounds of type (**246**). The reaction involves an *N*-hydroxyquinazoline intermediate (Equation (69)) ⟨77AF766, 87JHC175, 91JHC2071⟩.



(245) (246) (69)

(ii) By formation of one bond β to a heteroatom [6 + 0(β)]

The quinazoline (**247**) was condensed to (**248**) in 30% yield (Equation (70)) ⟨86IJC(B)709⟩.

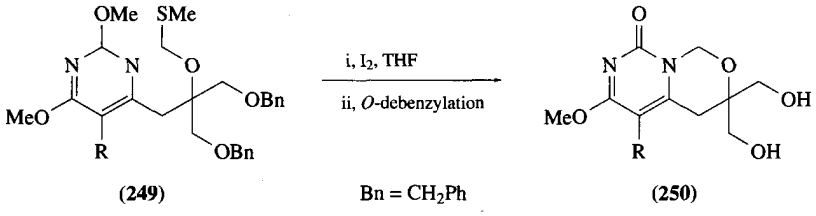


(70)

8.25.3.6.3 Pyrimido[1,6-c][1,3]oxazines and pyrimido[1,6-c][1,4]benzoxazines

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

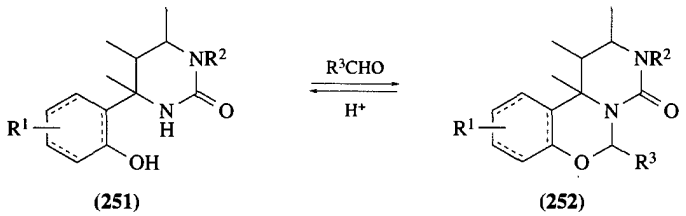
Only one bicyclic derivative, (**250**) has been described; this was formed by *O*-demethylation and cyclization of (**249**) in the same step (Equation (71)) ⟨92JOC3354⟩.



(71)

(ii) By formation of two bonds from [5 + 1] atom fragments

A number of derivatives of type (**252**) were synthesized by the condensation of 4-(*o*-hydroxyphenyl)pyrimidines or their partly or fully saturated analogues (**251**) with aldehydes (Equation (72)) ⟨61M31, 61M278, 65M1943, 79JHC21⟩; 4-thioxo ⟨65M1943⟩ and 4-aryl derivatives ⟨75S802⟩ were prepared similarly.

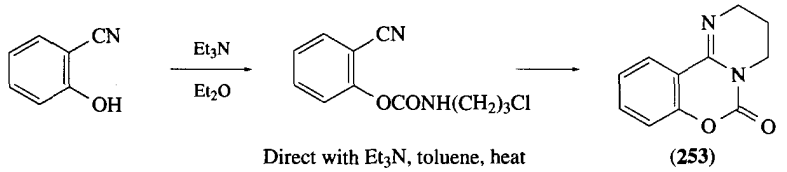


(72)

8.25.3.6.4 Pyrimido[1,2-c][1,3]benzoxazines (benzo derivatives of the unknown pyramide[1,2c][1,3]oxazines)

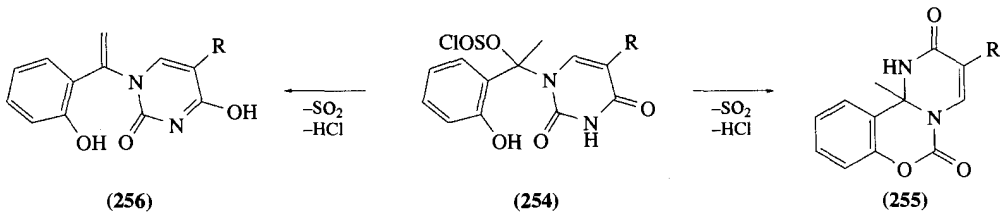
(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

The simple preparation of compound (**253**) from 2-hydroxybenzonitrile involves a benzoxazine intermediate (Scheme 11) ⟨83JHC1159⟩.



Scheme 11

The adduct (**254**), obtained from 2-hydroxyacetophenone and *N*-chlorosulfinylpyrimidone, may stabilize in two ways, affording (**256**) or, via rearrangement and double [6 + 0(α)] cyclizations, the tricycle (**255**) (Scheme 12) ⟨82CI(L)200⟩.

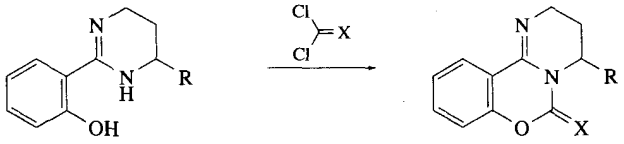


(256) (254) (255)

Scheme 12

(ii) By formation of two bonds from [5 + 1] atom fragments

Condensation of (**257**) with phosgene (yield 89%) or thiophosgene (yield 38%) gives (**258**) ⟨78CB314, 79GEP(O)2811163⟩. Condensation also takes place with aldehydes (Equation (73)) ⟨75S802⟩.

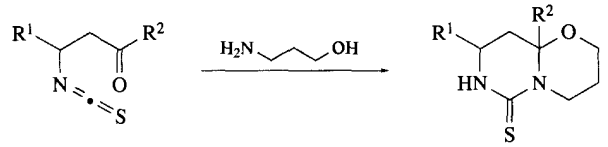


(257) (258) (73)

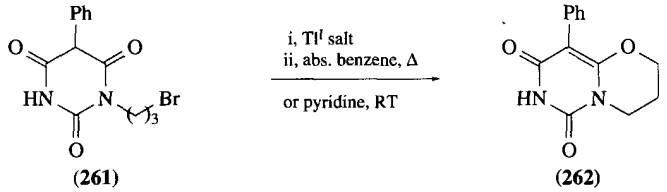
8.25.3.6.5 Pyrimido[6,1-b][1,3]oxazines and their benzo derivatives

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

The dihydropyrimidine formed from isothiocyanate (**259**) undergoes *in situ* intramolecular nucleophilic addition, giving rise to (**260**) in good yield (Equation (74)) ⟨76M171, 87JCS(P1)261⟩. The phenylbarbituric acid (**261**) in pyridine undergoes intramolecular *O*-4-alkylation to yield compound (**262**) (Equation (75)) ⟨71JOC2407⟩. The Tl^I salt of (**261**) also gives (**262**) when it is heated in anhydrous benzene (yield 49%); in aqueous benzene, however, intramolecular *O*-2-alkylation to (**275**) takes place (see Section 8.25.3.6.6) ⟨72JOC3486⟩.



(259) (260) (74)

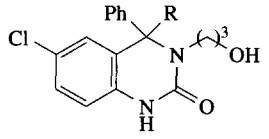


(261) (262) (75)

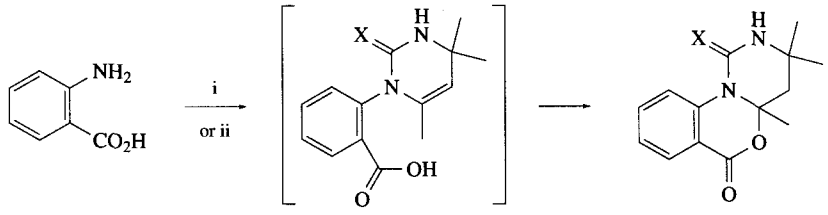
The [1,3]oxazino[3,2-*c*]quinazoline (**238**) was prepared in good yield from (**263**), when there is a leaving group at position 4 ⟨70YZ629, 81CPB2135⟩. A similar synthesis was carried out from a dihydroquinazoline analogue of (**263**) with R = OH ⟨80PHA256⟩.

The pyrimido[1,6-*a*][3,1]benzoxazine (**265**) was prepared in a one-pot reaction from anthranilic acid with reagents and conditions (i) ⟨76M183⟩ or (ii) ⟨82S1073⟩. The intermediate (**264**) was assumed

(Scheme 13). In a similar sequence, *o*-aminobenzyl alcohol under conditions (i) yields the appropriate tricyclic derivative ⟨76M171⟩. The pyrimido[6,1-*b*][1,3]benzoxazine (**266**) can be prepared by treating *o*-hydroxybenzylamine under conditions (i) (Scheme 14) ⟨76M171⟩.



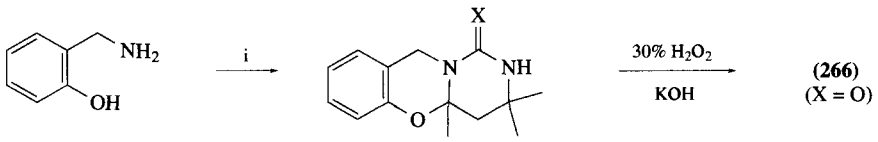
(**263**) R = CCl_3, OH



(**264**) (**265**)

i, SCN-C(Me)$_2$CH$_2$COMe, in boiling xylene
ii, NH_4SCN, Me_2C=CHCOMe, H_2O, H^+

Scheme 13



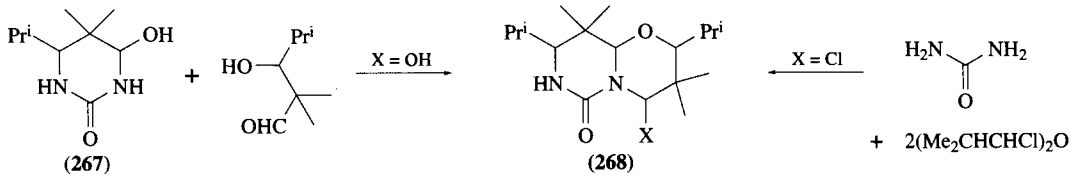
(**266**) X = S

i, SCN-C(Me)$_2$CH$_2$COMe, in boiling xylene

Scheme 14

(ii) By formation of two bonds from [3 + 3] atom fragments

The perhydro derivative (**268**) was prepared by condensing (**267**) with isobutyraldol, or by reacting urea with dichlorodiisobutyl ether (Scheme 15) ⟨70LA(734)155⟩.



(**267**) (**268**)

Scheme 15

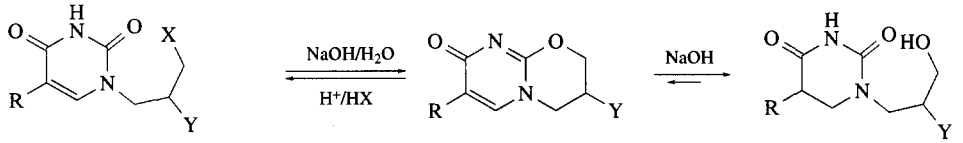
8.25.3.6.6 Pyrimido[2,1-b][1,3]oxazines and their benzo derivatives

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

In the most common syntheses in this group, an *N*-(γ-substituted-propyl)barbituric acid or uracil, bearing a nucleophilic γ-substituent, undergoes ring closure via intramolecular *O*-alkylation, condensation or a nucleophilic substitution onto C-2 of the pyrimidine ring. In the ring closure of the uracils (**269**), the cyclic ethers (**214**) are formed under kinetic control (Scheme 16) ⟨89JCS(P2)1209⟩. For the bifunctional (**271**), both the pyrimido-oxazine and the pyrimido-oxazole derivatives were

formed in an equilibrium reaction ⟨72JOC3486⟩. Condensation of the uracil (**272**) by the action of triphenylphosphine in diethyldiazodicarboxylate (DEAD) yielded the appropriate (**214**) ⟨85CPB2395⟩. The *N*-formyl ethyl derivative of (**272**),(**217a**), was found to be in equilibrium with its cyclic hemiacetal (**217b**) ⟨85CPB2395⟩ (see Equation (59) in Section 8.25.3.3.2).

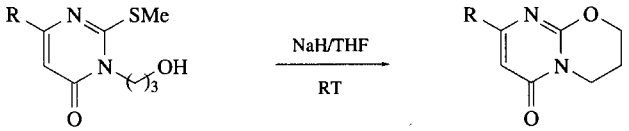
The 2-thioalkylpyrimidone (**273**) is cyclized to (**274**) in good yield (Equation (76)) ⟨87JCR(S)158, 87JCR(M)1286⟩. Compound (**273**), prepared by the alkylation of *S*-methyl-2-thiouracil, was earlier described as the bicyclic (**274**) on the basis of the IR data ⟨78IZV2079, 80IZV2568⟩. The structure was corrected later ⟨87JCR(M)1286⟩.



(**269**) R = H, Br, Me; X = Br, Cl; Y = H
(**271**) X = Y = *O*-mesyl;
(**272**) R = F; X = OH, Y = H;

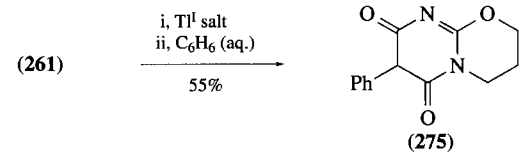
(**214**) (**270**)

Scheme 16



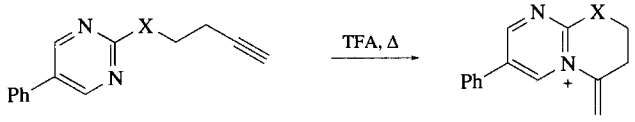
(**273**) (**274**) (76)

The phenylbarbituric acid (**261**) in aqueous benzene yields (**275**) by intramolecular *O*-2-alkylation (Equation (77)) (cf. Section 8.25.3.6.5) ⟨72JOC3486⟩.

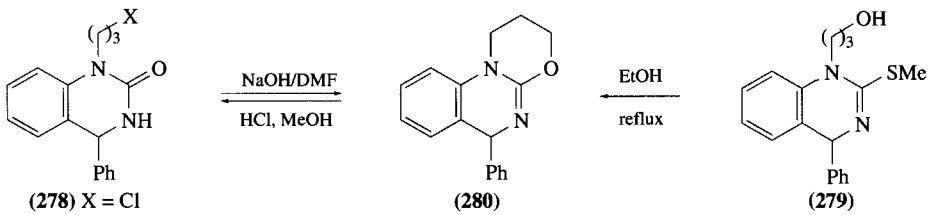


(**261**) (**275**) (77)

The pyrimido[2,1-*b*][1,3]oxazinium salt (**277**) was formed in moderate yield from the protonated (**276**) (Equation (78)); (**276**) underwent cycloamination rather than formation of the expected Diels–Alder product ⟨90T595⟩. Representative of the benzo derivatives, [1,3]oxazino[3,2-*a*]quinazolines (**280**) and [1,3]oxazino[2,3-*b*]quinazolines (**283**) were prepared in moderate yields from the appropriate *N*-1- and *N*-3-substituted quinazolines (**278**), (**279**), and (**281**), (**282**), respectively ⟨79CPB880⟩ (see Schemes 17 and 18).

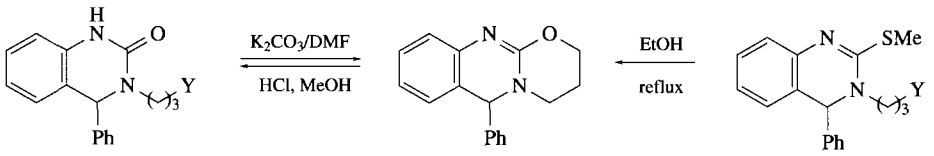


(**276**) X = O (**277**) X = O (78)



(**278**) X = Cl (**280**) (**279**)

Scheme 17

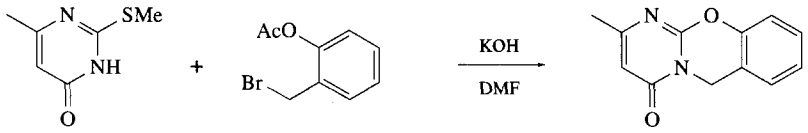


(281) Y = Cl (283) (282)

Scheme 18

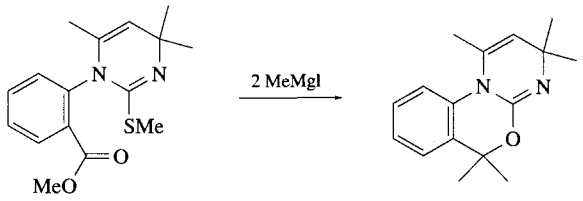
In a similar manner, the 6-oxo analogue (**234**) was obtained from (**235**) ⟨84JHC1411, 88JHC1103⟩ (Section 8.25.3.5.4).

The only known representative of the pyrimido[2,1-*b*][1,3]benzoxazine system, (**285**), was formed from *S*-methyl-2-thiouracil (**284**) and 2-acetoxybenzyl bromide in a one-pot reaction (Equation (79)) ⟨87JCR(M)1286⟩.



(284) (285) (79)

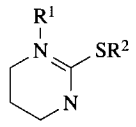
The pyrimido[1,2-*a*][3,1]benzoxazine (**287**), the only known representative of this ring system, was synthesized by treating (**286**) with a Grignard reagent (Equation (80)) ⟨88JHC1713⟩.



(286) (287) (80)

(ii) By formation of three bonds from [2 + 4] atom fragments

2-Methylthiotetrahydropyrimidine (**288**) reacted with diketene under mild conditions to yield the bicyclic derivative (**215**), whereas at higher temperature the *E*- and *Z*-isomers of the ring-opened compound (**236**) were obtained. From (**288**; R^1 = Me, or R^2 = benzyl) only the appropriate (**236**) was formed. This was explained by the intermediate formation of an adduct, which stabilizes either via SR^2H elimination, or by ring opening ⟨69G1000⟩.



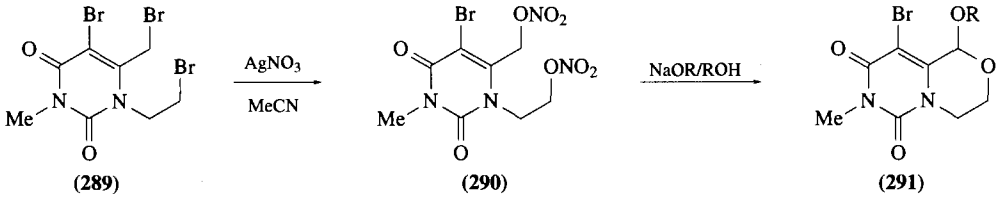
(**288**) R^1 = H; R^2 = Me

8.25.3.6.7 Pyrimido[6,1-c][1,4]oxazines and their benzo derivatives

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

Reaction of the uracil derivative (**289**) with sodium alkoxide/2-nitropropane gives the dinitrate (**290**) which, with sodium alkoxide, provides a convenient route to (**291**) (Scheme 19) ⟨92CPB2668⟩.

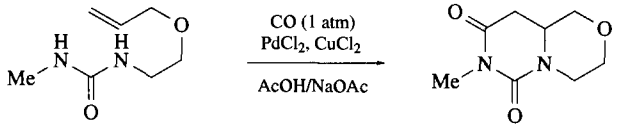
Lactonization of 2-hydroxyethylorotic acid derivatives resulted in (**292**) ⟨86MI 825-01⟩. The general method applied to prepare the pyrazinopyrimidine (**118**) from the urea (**117**) (see Section 8.25.2.6.5)



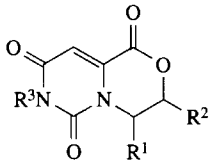
(289) (290) (291)

Scheme 19

was likewise applied to pyrimido-oxazines. The urea (**293**) undergoes Pd^{2+}-catalyzed aminocarbonylation and cyclization to a morpholine intermediate, via nucleophilic attack by the ureido nitrogen on the alkene carbon atom, this being followed by another [6 + 0(α)] cyclization step, resulting in (**294**) in excellent yield (Equation (81)) ⟨88JA3994⟩.



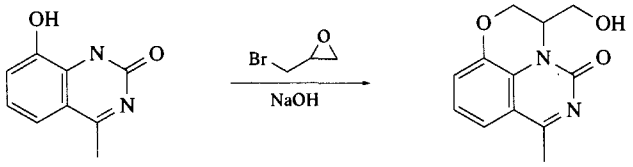
(293) (294) (81)



(292)

(ii) By formation of two bonds [4 + 2] atom fragments

The only known benzo derivative (**296**) was formed from the 8-hydroxyquinazoline (**295**) by reaction with epibromohydrin (Equation (82)) ⟨79JHC623⟩.



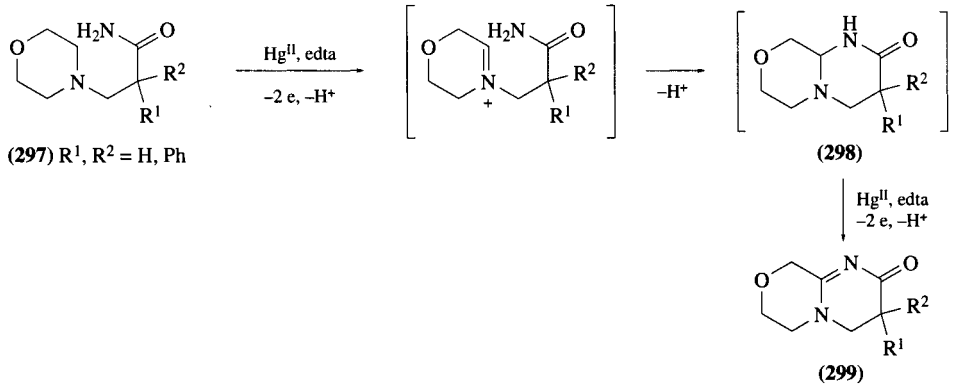
(295) (296) (82)

8.25.3.6.8 Pyrimido[2,1-c][1,4]oxazines and their benzo derivatives

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

The bicyclic compounds were synthesized (Scheme 20) from *N*-substituted morpholine intermediates (**297**). Oxidative cyclization is an obvious route to produce compounds of type (**299**) ⟨77AP(310)200⟩, but yields are moderate because of by-product formation (cf. Section 8.25.3.5.2).

Cyclodehydration of the lactam (**300**) results in (**301**) in good yield (Equation (83)) ⟨73AP(306)325⟩. [1,4]Oxazino[3,4-*b*]quinazoline derivatives, representatives of the linear tricyclic system, were synthesized from quinazoline intermediates. Thus, (**219**) was obtained from the *N*-hydroxyethylquinazoline (**303**) by intramolecular *O*-alkylation (Scheme 21) ⟨93JHC1413⟩ and when (**304**) was treated with ethanolamine and then aqueous potassium hydroxide (Equation (84)) ⟨93JHC1413⟩.

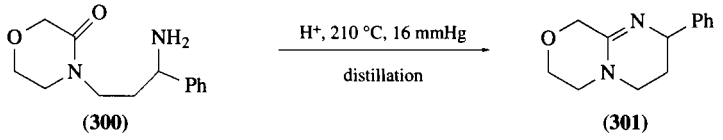


(297) R^1, R^2 = H, Ph

(298)

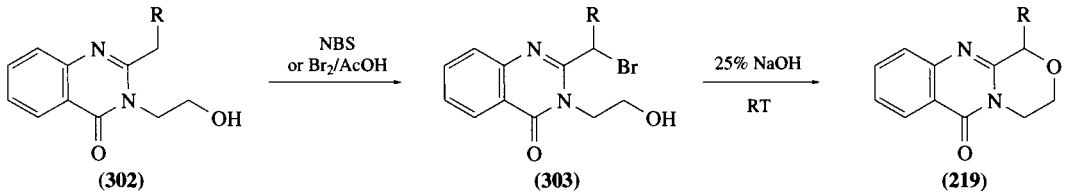
(299)

Scheme 20



(83)

(300) (301)

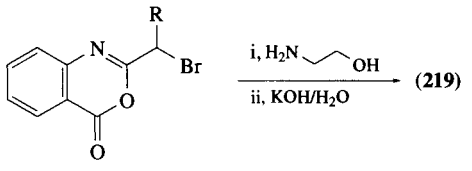


(302) (303) (219)

(**a**) R = H; (**b**) R = Me; (**c**) R = Br

(**a**) R = H; (**b**) R = Me; (**c**) R = OH

Scheme 21

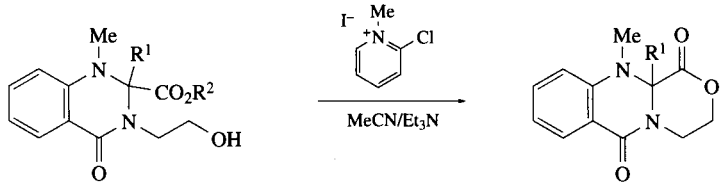


(219) (84)

(304)

(**a**) R = H, X = Cl; (**b**) R = Me, X = Br

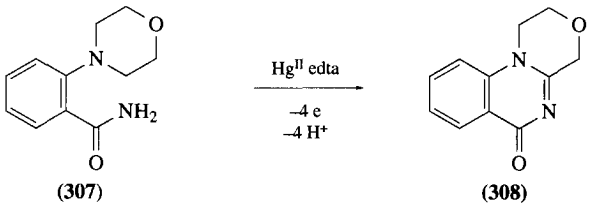
[1,4]Oxazino[3,4-*b*]quinazolines were prepared by the oxidative cyclization of *N*-(2-aminobenzyl)morpholine with MnO_2 ⟨68JCS(C)1722⟩ or with Hg^{II}OAc ⟨80PHA389⟩. Yields were low because of further oxidation and ring opening. Derivatives with lactone structures were obtained from the appropriate hydroxy acids, for example, (**306**) from (**305**), in excellent yields (Equation (85)) ⟨80JHC1163⟩. Further examples of lactonization are illustrated in the references ⟨71IJC1077, 81TL4969⟩. The [1,4]oxazino[4,3-*a*]quinazoline (**308**) was obtained in 57% yield by oxidative cyclization of the morpholinobenzamide (**307**) (Equation (86)) ⟨78AP(311)586⟩. Pyrimido[2,1-*c*][1,4]benzoxazines (**310**) and (**311**) were synthesized from the 3-aminobenzoxazine (**309**) (Scheme 22) ⟨81USP4254118, 81USP4254121⟩.



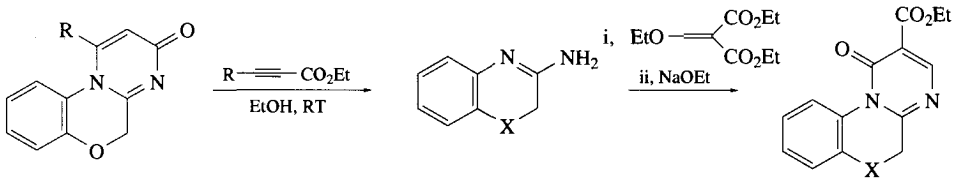
(85)

(305) R^1 = Me, CH_2CO_2Me; R^2 = H, Me

(306)



(307) (308) (86)



(310) R = H, CH_2OH, CO_2Et (309) X = O (311) X = O

Scheme 22

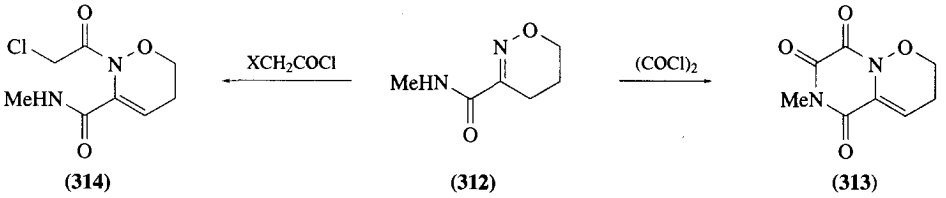
(ii) By formation of two bonds from [4 + 2] atom fragments

Condensation of 3-oxomorpholine or its lactim ether with 2-sulfinylaminobenzoyl chloride prepared *in situ* afforded the [1,4]oxazino[3,4-*b*]quinazoline (**230**) in good yield ⟨79IJC(B)107⟩.

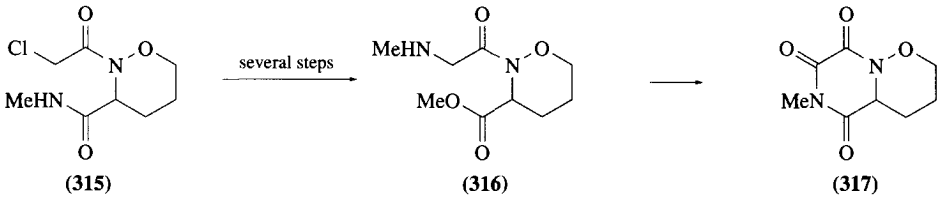
8.25.3.6.9 Pyrazino-oxazines and their benzo derivatives

(i) By formation of one bond adjacent to a heteroatom [6 + 0(α)]

The pyrazino[1,2-*b*][1,2]oxazine (**313**) was formed in excellent yield by acylating the amide (**312**) with oxalyl chloride (Scheme 23). Reaction with chloroacetyl chloride gave only the monocyclic (**314**). Neither (**314**) nor its saturated analogue (**315**) could be cyclized. (**317**) was obtained through the ester (**316**) ⟨79JOC2487⟩.



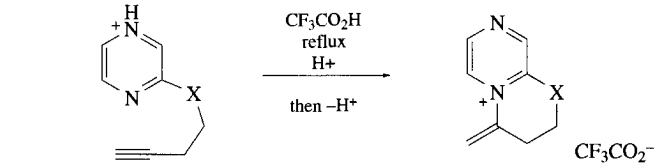
(314) (312) (313)



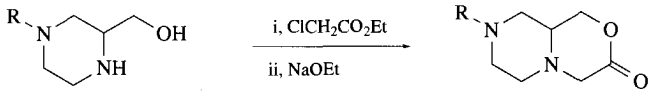
(315) (316) (317)

Scheme 23

The pyrazino[2,1-*b*][1,3]oxazinium trifluoroacetate (**319**) is formed in good yield from the protonated pyrazine derivative (**318**) by intramolecular cycloamination, together with a small amount of the expected Diels–Alder product (Equation (87)) ⟨89T6519⟩. Saturated pyrazino[2,1-*c*][1,4]oxazinones (**320**) and (**239**) were prepared by lactone formation, in good yields (Equation (88)) ⟨75IJC468, 78MI 825-01⟩.

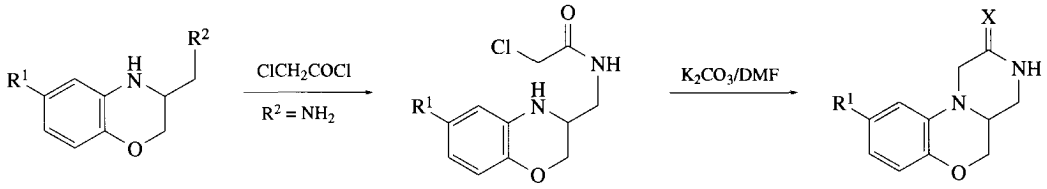


(318) X = O (319) (87)



(320) (88)

The pyrazino[2,1-*c*][1,4]benzoxazine (**322**; X = O) was synthesized from 3-(aminomethyl)-benzoxazine (**321**; $R^2 = NH_2$) (Scheme 24). The piperazine ring was constructed by alkylation with chloroacetyl chloride and subsequent cyclization ⟨75IJC462, 83JHC139⟩. In a similar sequence, (**323**) reacted with diethyl oxalate to yield the 1,2-dioxo analog, whereas (**324**) reacted with ethylene oxide to furnish the 1,2-dihydro analogue of (**322**; $X = H_2$) under suitable reaction conditions ⟨75IJC462⟩.



(**321**) $R^2 = NH_2$
(**323**) R^2 = *N*-benzyl
(**324**) R^2 = succinimido

(**322**)

Scheme 24

8.25.3.7 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Compounds surveyed in this chapter vary greatly as regards their degree of saturation, the number of oxo groups, and the nature of substitution. None of the parent systems has been prepared. In almost all derivatives, the oxazino moiety is saturated.

The methods most frequently used to synthesize these compounds are [6 + 0(α)] cyclizations. Ring closures may take place via intramolecular alkylation, condensation, or nucleophilic substitution. The starting materials for the cyclizations in the case of pyrazino-oxazines are always pyrazine derivatives. Only a few representatives of these systems have been prepared. Pyrimido-oxazines are the most explored group of compounds. In the bicyclic series, cyclizations have been carried out in most cases from pyrimidine intermediates and only rarely from morpholino intermediates. For the preparation of benzo-fused derivatives, both benzoxazine and quinazoline intermediates have been used. Pyrazino-oxazines represent a small group of compounds. For cyclizations, both pyrazino and oxazino intermediates have been used. There are many lactone structures among these compounds. For their preparation, the usual methods of lactone formation have been applied.

8.25.3.8 Important Compounds and Applications

The use of these groups of compounds seems as yet to be marginal. Some exert weak CNS activity: thus, [1,2]oxazino[3,2-*b*]quinazolines of type (**246**) have antiinflammatory, antipyretic, and analgesic activities ⟨77AF766⟩; pyrimido[1,2-*c*][1,3]benzoxazines of type (**258**) have antiinflammatory and antipyretic activities ⟨79GEP(O)2811163⟩, and pyrazino[2,1-*c*][1,4]benzoxazines of type (**322**) have weak CNS depressant and hypotensive activity ⟨75IJC462⟩. Antiallergic activity is exhibited by pyrimido[1,2-*c*][1,4]benzoxazines of types (**310**) ⟨81USP4254118⟩ and (**311**) ⟨81USP4254121⟩. Antitumor activity has been demonstrated for pyrimido[2,1-*b*][1,3]oxazines of type (**217**) ⟨85CPB2395,

85JAP(K)163883〉. 6-Aminopyrimido[1,6-*c*][1,3]oxazines of type (**250**) exert slight activity against HIV and herpes virus 〈92JOC3354〉. Hypoglycemic activity has been described for [1,3]oxazino[3,2-*a*]quinazolines (**280**) 〈79CPB880〉. Insecticidal activity is displayed by pyridazino[6,1-*c*][1,4]benzoxazines of type (**231**) and their more saturated analogues 〈91MIP9117983〉. Pyrazino[2,1-*c*][1,4]oxazines of type (**320**), as cyclic analogues of diethylcarbamazine, were tested for antifilarial activity, but they proved inactive 〈75IJC(B)468, 77JMC1327〉. Metabolic products of the fungi *Aspergillus clavatus* and *Aspergillus fumigatus* were found to possess the 3,4-dihydro[1,4]oxazino[3,4-*b*]quinazolin-3-one structural moiety 〈75JA663, 76TL2861〉.

8.25.4 BICYCLIC 6,6 N-BRIDGEHEAD SYSTEMS WITH ONE EXTRA N ATOM AND ONE EXTRA S ATOM 1 : 1, AND THEIR BENZO-FUSED DERIVATIVES

8.25.4.1 Introduction

The systems falling within this group are N-bridgehead pyridazino-, pyrimido- and pyrazinothiazines and their benzo-fused derivatives. Theoretically, 16 bicyclic systems are possible, but only seven of them are known with 13 benzo-fused derivatives (see Table 5). None of the groups of compounds were considered in CHEC-I and therefore the whole of the literature has been surveyed. The only previous review of this field is that by Mosby 〈61MI 825-01〉 who lists a few references on pyrimido[2,1-*b*][1,3]thiazines. That ring system still remains the most extensively studied.

8.25.4.2 Theoretical Methods

No work appears to have been published in this field.

8.25.4.3 Experimental Structural Methods

8.25.4.3.1 X-ray diffractometry

The molecular structures of six pyrimido[2,1-*b*][1,3]thiazines (**349**)–(**354**), one pyrimido[2,1-*c*][1,4]thiazine (**355**), and one pyrazino[2,1-*c*][1,4]thiazine (**356**) have been determined by single crystal x-ray diffractometry. In the 8-amino-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-ones (**349**)–(**352**), the thiazine ring is half-chair-shaped. In (**349**)–(**351**), five of the six atoms of the thiazine ring and those of the pyrimidine ring are nearly coplanar, whereas C-3 is displaced out of the mean plane 〈91AX(C)2413, 91AX(C)2638, 92JHC1449〉. In (**352**), there is strong conjugation between the amino and nitroso groups, which causes a significant distortion of the pyrimidine ring from planarity 〈91JHC891〉. In the 8-oxo derivative (**353**), the thiazine ring has an envelope-like conformation, probably due to the considerable double-bond character of the C(10)—S(1) bond 〈74ACS(A)903〉. In (**354**), six atoms are nearly coplanar, while C-3, C-4, and C-8 are situated below the plane, and C-6 above the plane 〈89JHC55〉. In (**355**), the thiazine ring has a distorted half-chair, the hexahydropyrimidine ring has a distorted chair conformation, and the N(5)—C(6)—C(7)—S(8) segment is planar 〈88MI 825-02〉. In the *trans*-D,L-cyclic dipeptide (**356**; R = H), the thiazine ring is in a chair conformation and the *trans*-fused dioxopiperazine ring is puckered 〈82CSC853〉.

8.25.4.3.2 NMR spectroscopy

Proton and ^{13}C NMR spectroscopy have been widely used to elucidate the structures of the compounds discussed in this chapter. Nitrogen-15 NMR investigations have not been reported. Several specialized studies are mentioned below.

*(i) Pyrimido[2,1-*b*][1,3]thiazine derivatives*

Detailed conformational analyses were performed on the cycloalkane and -ene-fused derivatives (**357**)–(**359**). The structures and stereostructures of (**360**)–(**362**) have been elucidated 〈89MRC959〉.

Table 5 Bicyclic 6-6 nitrogen bridgehead systems with one extra *N* and one extra *S* atom 1 : 1 and their known benzo-fused derivatives. (Systems which are unreported are named in italic.)

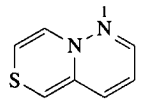
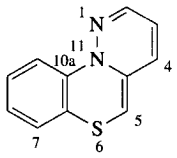
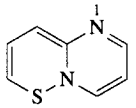
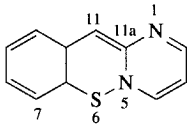
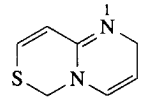
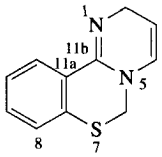
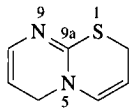
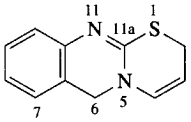
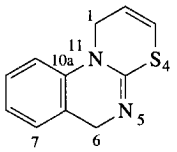
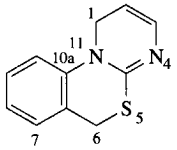
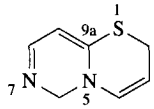
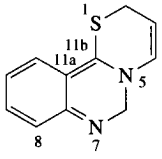
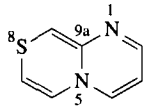
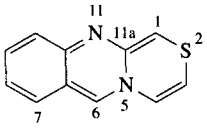
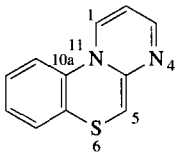
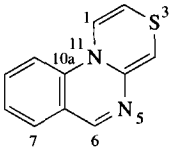
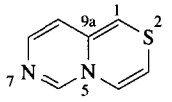
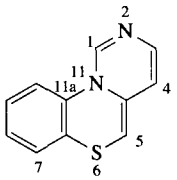
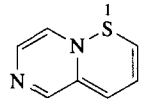
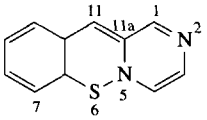
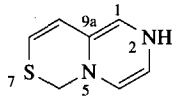
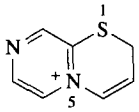
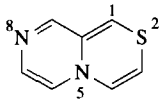
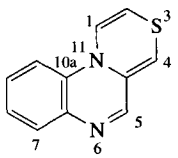
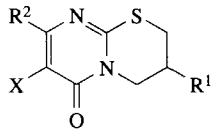
Compound	*Ring system*	*Name and ring file number*
(325)		*Pyridazino[6,1-c][1,4]thiazine*
(326)		Pyridazino[6,1-*c*][1,4]benzothiazine, RF 35177
(327)		*Pyrimido[1,2-*b*][1,2]thiazine*
(328)		Pyrimido[1,2-*b*][1,2]benzothiazine, RF 35181
(329)		2H,6H-*Pyrimido[1,2-*c*][1,3]thiazine*
(330)		2*H*,6*H*-Pyrimido[1,2-*c*][1,3]benzothiazine, RF 35188
(331)		2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazine, RF 13744
(332)		2*H*,6*H*-[1,3]Thiazino[2,3-*b*]quinazoline, RF 35196
(333)		1*H*,6*H*-[1,3]Thiazino[3,2-*a*]quinazoline, RF 35195
(334)		1*H*,6*H*-Pyrimido[1,2-*a*][3,1]benzothiazine, RF 35185
(335)		2*H*,6*H*-Pyrimido[6,1-*b*][1,3]thiazine, RF 13744
(336)		2*H*,6*H*-[1,3]Thiazino[3,2-*c*]quinazoline, RF 35197

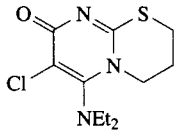
Table 5 (continued).

Compound	*Ring system*	*Name and ring file number*
(337)		Pyrimido[2,1-*c*][1,4]thiazine, RF 13735
(338)		[1,4]Thiazino[3,4-*b*]quinazoline, RF 35193
(339)		Pyrimido[2,1-*c*][1,4]benzothiazine, RF 35182
(340)		[1,4]Thiazino[4,3-*a*]quinazoline, RF 35194
(341)		Pyrimido[6,1-*c*][1,4]thiazine, RF 13736
(342)		Pyrimido[6,1-*c*][1,4]benzothiazine, RF 35183
(343)		[*1,4*]*Pyrazino*[*1,2*-b][*1,2*]*thiazine*
(344)		Pyrazino[1,2-*b*][1,2]benzothiazine, RF 35175
(345)		2*H*,6*H*-Pyrazino[1,2-*c*][1,3]thiazine, RF 13731
(346)		2*H*-Pyrazino[2,1-*b*][1,3]thiazin-5-ium, RF 13732
(347)		Pyrazino[2,1-*c*][1,4]thiazine, RF 13729
(348)		[1,4]Thiazino[4,3-*a*]quinoxaline, RF 35199

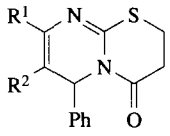


$R^2 = NH_2$

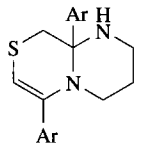
(349) X = R^1 = H
(350) X = $NHSO_3Na$; R^1 = H
(351) X = Br; R^1 = Me
(352) X = NO; R^1 = OH



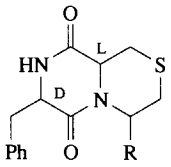
(353)



(354)
R^1 = Me, R^2 = CO_2Et

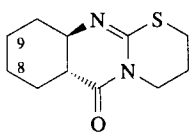


(355)

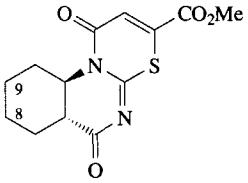


(356)

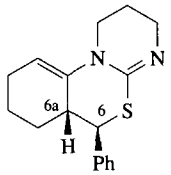
The angular constitution of (**363**) was revealed by ^{13}C NMR and DNOE measurements. The coupling constants of the protons at positions 6 and 6a indicated the *trans*-annelation of the rings ⟨87CB1449⟩.



(357)
(358) *cis*-fused isomer
(359) 8,9-dehydro analogue



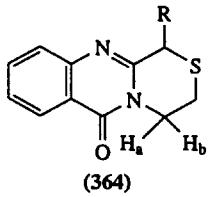
(360)
(361) *cis*-fused isomer
(362) 8,9-dehydro analogue



(363)

(ii) [1,4]Thiazino[3,4-b]quinazoline derivatives

In (**364**), the presence of a substituent at position 1 caused nonequivalence at position 4. The difference between the chemical shifts of H_a and H_b increased with increase in the size of R, indicating that only one of the protons experienced the deshielding effect of the carbonyl group, due to an energy barrier in flipping ⟨87JPR321⟩.



(364)

R	δH_a (ppm)	δH_b
H	4.42	
OH	5.20	4.14
OAc	5.54	3.94

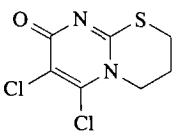
(iii) Pyrazino[2,1-c][1,4]thiazines

The solution conformations of cyclic dipeptides have been investigated by ^1H NMR. The *cis*-L,L isomer of (**356**; R = H) always assumed a folded conformation, whereas the *trans*-D,L isomer did so only in hydrophilic solvents ⟨79BSB683⟩. The folded conformation of (**356**; R = CO_2Me) and of its *cis*-L,L isomer in $CDCl_3$ has been demonstrated ⟨90JHC1661⟩. The degree of folding was investigated for cyclic dipeptides derived from L-γ-thiapipecolic acid with glycine or sarcosine ⟨85BSB413⟩.

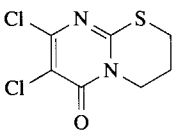
8.25.4.3.3 IR spectroscopy

(i) Pyrimido[2,1-b][1,3]thiazine derivatives

It has been reported that, as in several other systems ⟨72ACS947⟩ (see also Section 8.25.2.3.3) the pyrimidothiazinone (**365**) with a *p*-quinonoidal structure exhibits an amide-I band in a lower absorption region than that for the *o*-quinonoidal isomer (**366**) ⟨68KGS918, 72ACS947⟩.



(**365**)



(**366**)

The characteristic amide-I bands were frequently used to determine the position of the carbonyl group in cases where the synthesis was ambiguous (Table 6).

Table 6 IR amide-I band of pyrimido[2,1-*b*][1,3]thiazinone derivatives.

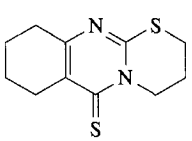
Compound	*IR amide-I band* ν (cm^{-1})	*Ref.*
(**365**)	1638	75ACS(B)1092
(**366**)	1686	75ACS(B)1092
(**349**) X = H; $R^1 = R^2 = H$	1673	91T7673
(**349**) X = H; R^1 = H, R^2 = Me	1680	68KGS918
(**349**) X = H; R^1 = OH, R^2 = Me	1665	67IZV1841

On the basis of the strong ν_{CO} band at 1680 cm^{-1}, the mesoionic enolate, and not the dioxo structure, was assigned to (**370**) (see in Section 8.25.4.3.5) ⟨77ZN(B)1204⟩. The thiazino[3,2-*a*]quinazoline structures (**360**)–(**362**), and not a possible thiazolo structure, were supported by the appearance of ν_{CO} bands in a relatively low region ⟨89MRC959⟩.

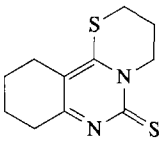
8.25.4.3.4 UV spectroscopy

(i) Pyrimido[2,1-b][1,3]thiazine derivatives

The UV spectra of a series of compounds (**349**; R^1 = OH) have been studied. Introduction of a substituent (X) into position 7 induced a bathochromic shift in the highest λ_{max} values, in the following sequence: X = H < Br < NH_2 < NO. No effect was caused by a 3-OH substituent ⟨91JHC891⟩. The UV characteristics of the linear and angular isomers (**367**) and (**368**) have been investigated ⟨77ZC444⟩.



(**367**) λ_{max} = 342–352 nm



(**368**) λ_{max} = 371–378 nm

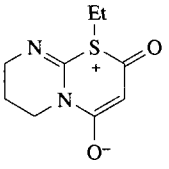
8.25.4.3.5 Mass spectrometry

The compounds discussed in this section usually produce strong molecular ions. The fragmentation patterns of a few compounds have been described.

*(i) Pyrimido[2,1-*b*][1,3]thiazines and their benzo derivatives*

(**354**; R^2 = H; R^1 = CH=CH—Ph) exhibited a base peak due to the expulsion of (CH=CH—Ph); further peaks arose due to the loss of Ph, followed by the CO—CH_2—CH_2 group ⟨91MI 825-02⟩. (**369**) exhibits the base peak due to (M^+—CO) and a further peak from (M^+—$C_3H_2O_2$) fragment ⟨74ZN(B)258⟩ while (**437**; R = H) exhibits a peak due to the *o*-C_6H_4(NSC)CO^+ fragment ⟨67HCA1440⟩. The pyrimido[1,2-*a*][3,1]benzothiazine (**363**) exhibited a strong molecular ion peak and characteristic fragmentation involving selective cleavage of the pyrimidine and thiazine rings ⟨87CB1449⟩.

Compounds (**360**)–(**362**) gave fairly similar mass spectra owing to their favored RDA fragmentation accompanied by the migration of one or two hydrogen atoms. Base peaks arose from the RDA-H process ⟨91OMS(26)493⟩.



(**369**)

8.25.4.4 Thermodynamic Aspects

8.25.4.4.1 Melting points

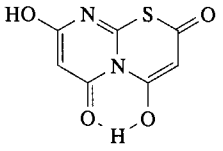
8-Oxopyrimido[2,1-*b*][1,3]thiazines with *p*-quinonoidal structure have higher melting points than their *o*-quinonoidal 6-oxo isomers (see (**365**) and (**366**)) ⟨72ACS947⟩.

8.25.4.4.2 Chromatographic behavior

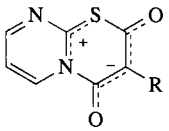
The HPLC behavior of cyclic dipeptides with a dioxopyrazino[2,1-*c*][1,4]thiazine structure and of their sulfoxide analogues has been investigated ⟨80CCC2927⟩.

8.25.4.4.3 Aromaticity, stability

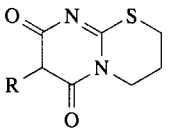
The pyrimido[2,1-*b*][1,3]thiazine-diones (**369**)–(**372**) can be described only by a series of mesomeric forms. For (**370**) ⟨77ZN(B)1204⟩ and (**369**) ⟨74ZN(B)258⟩ the IR spectrum supports the mesoionic enolate/enol forms. Compounds (**371**) have poor stability, (**371**; R = H) decomposes above its melting point with the expulsion of C_3O_2; in water or alcohols it undergoes ring fission to malonic acid/esters ⟨72S312⟩.



(**370**)



(**371**)



(**372**)

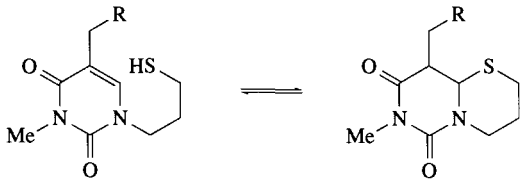
Compounds (**372**) have poor solubility in apolar solvents, but they dissolve in alkalies, indicating the participation of the mesomeric enol forms in their structures ⟨70LA(742)85⟩.

8.25.4.4.4 Conformations

The conformational studies that have been carried out are mentioned in Section 8.25.4.3.2 under NMR spectroscopy.

8.25.4.4.5 Ring–chain tautomerism

The pyrimido[6,1-*b*][1,3]thiazines (**373b**) were shown to exist in protic solvents in equilibrium with the open-chain 1-(3-thiolpropyl)uracils (**373a**) (Equation (89)) ⟨88TL5445⟩.



(89)

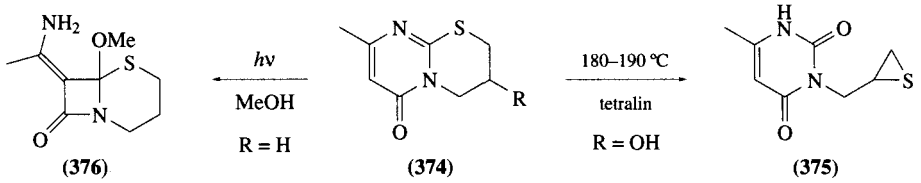
(**373a**) R = H, F, Me, $CH_2N(Ph)Me$ (**373b**)

8.25.4.5 Reactivity

8.25.4.5.1 Unimolecular thermal and photochemical reactions

(i) Pyrimido[2,1-b][1,3]thiazines

When heated in inert solvents, the 3-hydroxy derivative (**374**; R = OH) transformed into (**375**) with fission of the thiazine and formation of a thiirane ring (Scheme 25). The process is probably initiated by nucleophilic attack of the hydroxy group on C-9a ⟨86IZV1634⟩. Compound (**374**; R = H) was photochemically ring-contracted to the β-lactam (**376**) in a yield of 66% ⟨81H(15)399⟩.



(**376**) (**374**) (**375**)

Scheme 25

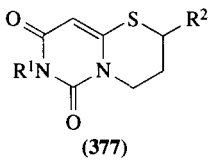
8.25.4.5.2 Electrophilic attack at heteroatoms

(i) Protonation

Stable proton acid salts were frequently prepared. pK_a values have not been reported.

(ii) N-Alkylation

The pyrimido[6,1-*b*][1,3]thiazine (**377**; R^1 = H) was *N*-alkylated at position 7 ⟨90EUP404525⟩.



(**377**)

(iii) O-Acylation

(**374**; R = OH) was *O*-acylated with benzoyl chloride ⟨86IZV1634⟩.

(iv) S-Oxidation

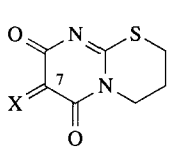
The pyrimido[6,1-*b*][1,3]thiazine (**377**; R^2 = H) was oxidized with *m*-chloroperbenzoic acid to the sulfoxide and the sulfone ⟨90EUP404525⟩. The [1,4]thiazino[3,4-*b*]quinazoline (**379**) underwent

oxidation only to the sulfoxide on the action of *m*-chloroperbenzoic acid. Under more vigorous conditions ($AcOH/H_2O_2$), ring opening and oxidation to the sulfonic acid took place instead of giving the sulfone ⟨87JPR321⟩.

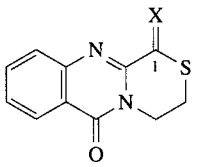
8.25.4.5.3 Electrophilic attack at carbon atoms

(i) CH-acidic reactions

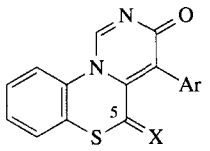
Compounds (**378**)–(**380**) contain an activated methylene group showing typical reactions.



(**378**) X = H_2
(**381**) X = NNHPh
(**382**) X = NOH



(**379**) X = H_2
(**383**) X = CHPh
(**384**) X = $CHCO_2Et$
(**385**) X = C(OH)Me
(**386**) X = $C(SMe)_2$
(**387**) X = C(SMe)NHPh



(**380**) X = H_2
(**388**) X = $CHNMe_2$

The pyrimido[2,1-*b*][1,3]thiazine-dione (**378**) reacted at position 7 with phenyldiazonium chloride to give (**381**) and with isoamyl nitrite to give (**382**) ⟨70LA(742)85⟩. The [1,4]thiazino[3,4-*b*]quinazoline (**379**) (the thio analogue of the oxazinoquinazoline (**230**)) (see Section 8.25.3.5.3) reacted at position 1 with benzaldehyde to give (**383**) ⟨87JPR321⟩, with ethyl chloroformate to give (**384**) and with acetic anhydride to give the *E* isomer of (**385**) stabilized by an intramolecular H-bond ⟨89ZC137⟩. The carbanion derived from (**379**) with NaH in DMSO reacted with CS_2 and PhNCS to give (following methylation) (**386**) and the *E*–*Z* isomers of (**387**), respectively ⟨89ZC101⟩, whereas in DMF with alkyl or aralkyl halides it underwent dialkylation, with activated halopyridines monoarylation, and with acrylonitrile Michael addition ⟨90ZC211⟩. The pyrimido[6,1-*c*][1,4]benzothiazine (**380**) reacted at position 5 with bis(dimethylamino)methoxymethane to give (**388**) ⟨87JOC1366⟩. The 6,8-dioxopyrimido[2,1-*b*][1,3]thiazine (**372**; R = Et, Ph) was alkylated at position 7 with ethyl iodide in the NaOEt/EtOH system ⟨70LA(742)85⟩. The 6-oxo-8-amino derivatives (**349**; R^1 = H; X = H, OH, Me) reacted at position 7 with Br_2 in AcOH and with $NaNO_2$ ⟨89JHC1701, 91JHC891, 91AX(C)2638⟩. The 8-methyl analog of (**349**; X = H, R^1 = OH) was halogenated at position 7 by NBS or NCS ⟨86IZV1634⟩.

The 6,8-dioxopyrimido[6,1-*b*][1,3]thiazine (**377**) was formylated at position 9 with the Vilsmeier–Haack reagent ⟨90EUP404525⟩.

8.25.4.5.4 Nucleophilic attack at carbon atoms

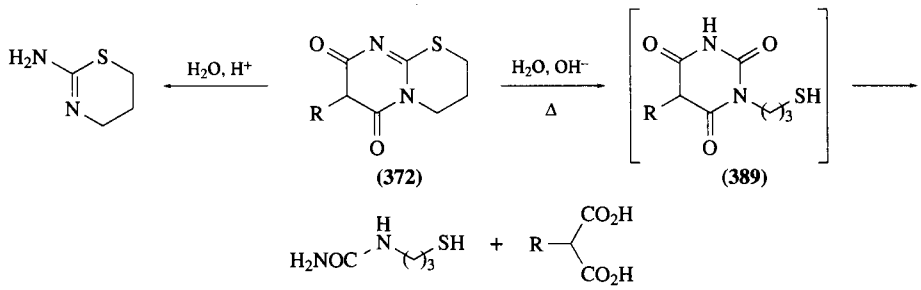
(i) Nucleophilic attack at ring carbon α to a heteroatom

By the action of acetic anhydride in an organic solvent the sulfoxide of (**377**; R^2 = H) rearranged to the 2-acyloxy derivative (**377**; R^2 = OAc) ⟨90EUP404525⟩, while the sulfoxide of the thiazinoquinazoline (**379**) yielded the 1-acyloxy derivative ⟨87JPR321⟩. The former reaction in the presence of excess triethylamine resulted in the hydroxy derivative (**377**; R^2 = OH) ⟨90EUP404525⟩.

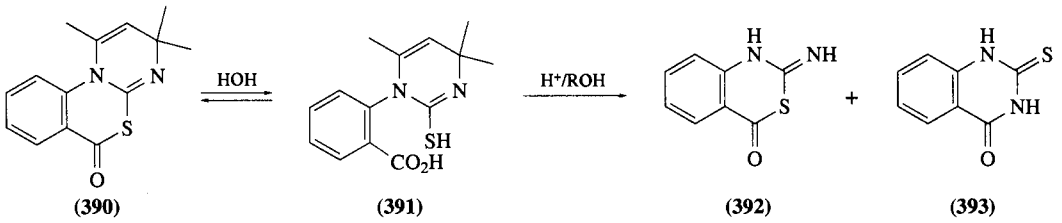
(ii) Nucleophilic attack at ring carbon α to a heteroatom, followed by ring opening

The dioxopyrimidothiazines (**372**) were attacked by aqueous alkali at C-9a, and suffered cleavage through (**389**) (Scheme 26). In aqueous acidic media only the amide bonds were cleaved ⟨70LA(742)85⟩. The monooxo derivatives of type (**349**) were attacked by alkali at position 9a, with cleavage of the thiazine ring ⟨89JHC1701⟩. The [1,3]thiazino[2,3-*b*]quinazolin-6-one (**437**; R = H) cleaved both in alkaline and in acidic media at the amide bond ⟨67HCA1440⟩. The pyrimido[1,2-*a*][1,3]benzothiazines (**390**) in aqueous solution suffered reversible ring opening to (**391**) (Scheme

27). In alcoholic hydrogen chloride, further decomposition took place, leading to (**392**) and (**393**), the latter being formed from (**391**) ⟨63JOC740⟩.

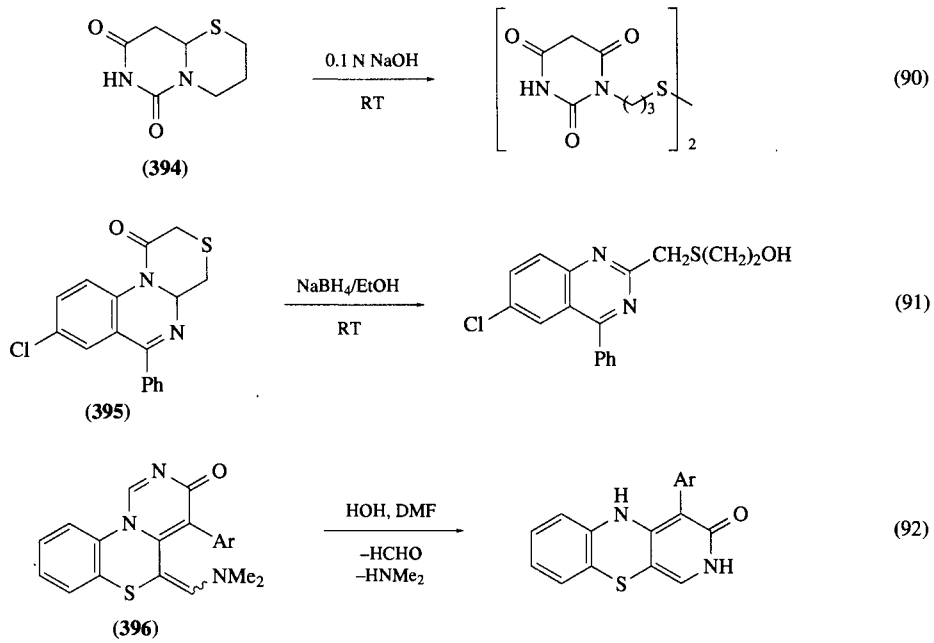


Scheme 26



Scheme 27

Ring opening of the pyrimido[6,1-*b*][1,3]thiazine-dione (**394**) in diluted alkali was followed by dimerization (Equation (90)) ⟨72JCS(P1)2385⟩. Reductive ring opening of the [1,4]thiazino[4,3-*a*]quinazoline (**395**) took place on the action of hydride anion (Equation (91)) ⟨73IJC1051⟩. The pyrimido[6,1-*c*][1,4]benzothiazine (**396**) in aqueous DMF suffered hydrolytic cleavage, which was followed by recyclization onto the exocyclic carbon (Equation (92)) ⟨87JOC1366⟩.



(iii) Nucleophilic substitution

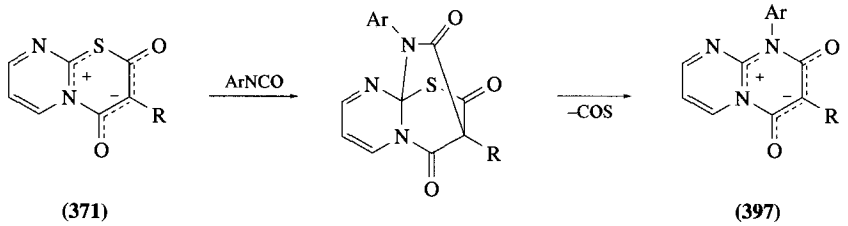
The 2-hydroxy group of (**377**; $R^2 = OH$) was substituted by an SPh group on the action of thiophenol in the presence of BF_3 in dichloromethane ⟨90EUP404525⟩.

The 6-chloro group of (**365**) was exchanged for a hydroxy group in boiling water. The 7-chloro group of (**365**) and the chloro groups of (**366**) could not be exchanged ⟨72ACS947⟩.

8.25.4.5.5 Intermolecular reactions with cyclic transition states

(i) Heterocycle as 4π component in [2 + 4] cycloaddition

The 1,3-thiazine betaine (**371**) forms a cycloadduct with aryl isocyanate, which fragments to compound (**397**) to restore aromaticity (Scheme 28) ⟨76CB3668⟩.



(**371**) (**397**)

Scheme 28

8.25.4.5.6 Epimerization

Racemization of cyclic dipeptides with pyrazino[1,2-*c*][1,3]thiazine and pyrazino[2,1-*c*][1,4]-thiazine structures has been studied ⟨81TL3101⟩.

8.25.4.5.7 Reactions of substituents

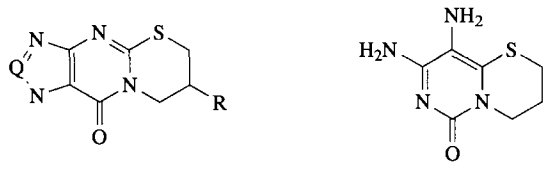
The 8-amino-7-nitrosopyrimido[2,1-*b*][1,3]thiazine (**352**; R^1 = Me, OH) was reduced to the diamino derivative (**398**) with Pd/C, H_2, or sodium hydrosulfite. In the latter reaction, the sulfamic acid (**350**; R^1 = Me, OH) and the thiadiazolo derivative (**399**) were also obtained as by-products ⟨91JHC891, 92JHC1449⟩.

The *o*-amino groups of (**398**) reacted with PhNSO to give (**399**) (Equation (93)) ⟨93FES427⟩ and with $NaNO_2$, carbamide or thiocarbamide to give (**400**; Q = N, COH and CSH, respectively) ⟨91FES899⟩. Similar reactions were carried out starting from the 8,9-diamino-pyrimido[6,1-*b*][1,3]thiazine (**401**) ⟨92FES1315⟩. The pyrazino[1,2-*b*][1,2]benzothiazine sulfonate ester (**402**) reacted with various *N*- and *S*-nucleophiles through the oxazino derivative (**403**) (Equation (94)). $NHMe_2$ and Et_3N gave (**403**) itself, water gave (**404**; X = OH), and NaSMe gave (**404**; X = SMe), while with ammonia and primary amines as proposed, the 1-amino-11-oxo derivative of (**404**; X = OH) was formed through (**403**) by Michael addition, followed by opening of the oxazole ring ⟨74JOC1560⟩.

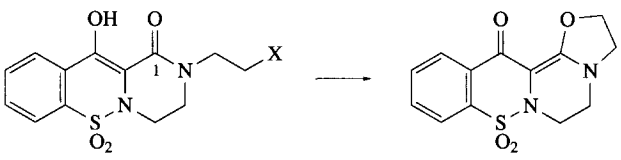


(93)

(**398**) (**399**)



(**400**) (**401**)



(94)

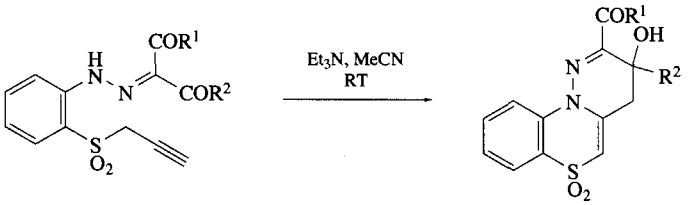
(**402**) X = OSO_2Me
(**404**) X = OH, SMe

(**403**)

8.25.4.6 Synthesis

8.25.4.6.1 Pyridazino[6,1-c][1,4]benzothiazines (benzo derivatives of the unknown pyridazino [6,1-c][1,4]thiazines)

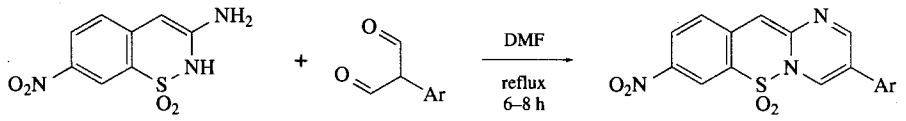
Compound (**406**) and its 3,4-anhydro derivative were synthesized from the propynylsulfonyl derivative (**405**) (Equation (95)). The synthesis involves initial allenization and subsequent Michael addition. Dehydration of (**406**) took place either directly or in a separate step, in the presence of acids ⟨87JCR(S)346⟩.



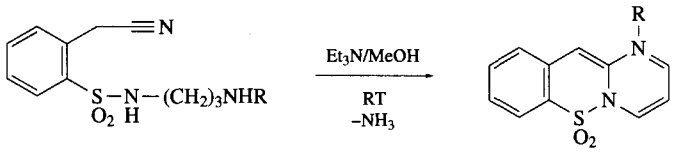
(405) (406) (95)

8.25.4.6.2 Pyrimido[1,2-b][1,2]benzothiazines (benzo derivatives of the unknown pyrimido [1,2-b][1,2]thiazines)

Two representatives have been described. The heteroaromatic (**408**) was synthesized from [3 + 3] atom fragments by condensing the 3-aminobenzothiazine (**407**) with malonaldehydes (Equation (96)) ⟨91IJC(B)655⟩. The tetrahydro derivatives (**410**) were formed from (**409**) via addition and condensation (Equation (97)) ⟨79CPB2372⟩.



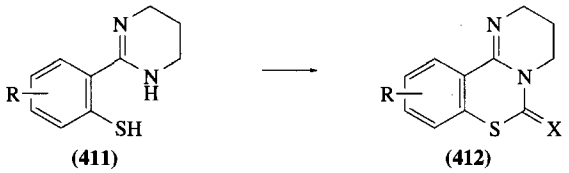
(407) (408) (96)



(409) (410) (97)

8.25.4.6.3 Pyrimido[1,2-c][1,3]benzothiazines (benzo derivatives of the unknown pyrimido [1,2-c][1,3]thiazines)

Compounds (**412**) were formed from the thiophenols (**411**) with phosgene or thiophosgene (X = O, S) ⟨79GEP(O)2811163⟩ or with BrCN (X = NH) ⟨79GEP(O)2811131⟩. (In a similar [5 + 1 fragment] synthesis, the analogous benzoxazines were obtained from the appropriate phenols; see Section 8.25.3.6.4.)



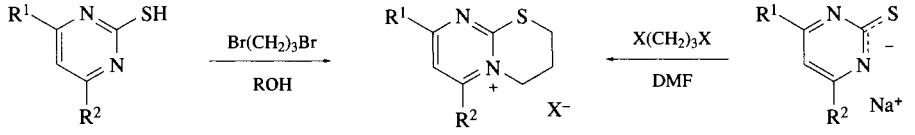
(411) (412) (98)

8.25.4.6.4 Pyrimido[2,1-b][1,3]thiazines

(i) From [3 + 3] atom fragments by bond formation adjacent to heteroatom

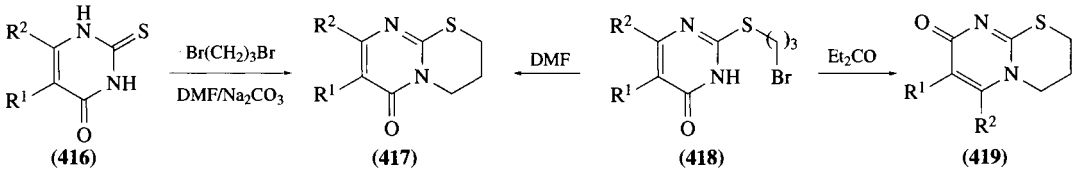
In the most frequently used version, a pyrimidine-2-thione or -thiol (often a 2-thiouracil) was reacted with a bifunctional electrophile containing three carbon atoms. 1,3-Dihalopropane, epichlorohydrin, malonyl chloride, or propargyl bromide served as bifunctional electrophiles. In a few cases, *S*-alkylated intermediates were isolated.

The pyrimidine-2-thiones (**413**) reacted with dibromopropane to give the quaternary salts (**414**) in low yields (Scheme 29) ⟨67DOK(171)874⟩. The yields were enhanced by using the sodium salts (**415**) of the thiols ⟨67IZV1841, 68KGS918, 84IZV1396, 86IZV1634⟩. 2-Thiouracils (**416**) with DMF/Na_2CO_3 furnished 6-oxopyrimidothiazines of type (**417**) in good yields ⟨89JHC1701⟩. A number of compounds (**417**; R^1 = CN; R^2 = aralkyl, aryl, hetaryl) have been prepared ⟨84JHC1307, 87LA797, 89IJC(B)159, 89JPR893, 90AP(323)895, 90IJC(B)1129, 90EJM533, 91AP(324)837, 91IJC(B)962, 92EJM851⟩. The reaction of tetrahydropyrimidine-2-thiol with dibromopropane also proceeded with good yield ⟨82JIC1170⟩. The isolated *S*-alkylated intermediate (**418**; $R^1 = R^2$ = Cl) gave both the 6-oxo and the 8-oxo isomers, (**417**) and (**419**), their ratio being dependent on the reaction conditions ⟨72ACS947, 75ACS(B)1092⟩.



(**413**) (**414**) X = Br, Cl (**415**)

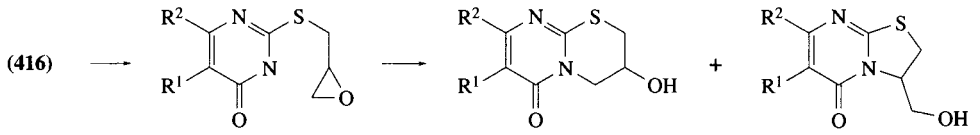
Scheme 29



(**416**) (**417**) (**418**) (**419**)

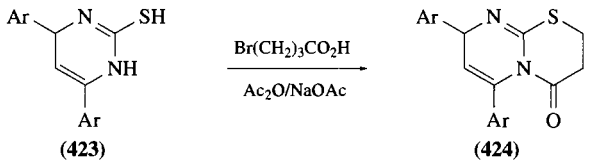
Scheme 30

Epibromohydrin, 2-hydroxy-1,3-dibromopropane, or 2,3-dibromopropanol reacted with (**416**) to furnish both pyrimidothiazines (**421**) and thiazoles (**422**), probably through a common oxirane intermediate (**420**) (Scheme 31) ⟨91JHC891⟩. With malonyl chloride or carbon suboxide, pyrimidine-2-thiones formed the mesoionic betaine (**371**) in excellent yield ⟨72S312⟩. When reacted with 3-bromopropanoic acid, 1,4-dihydropyrimidine-2-thiols (**423**) gave (**424**) in excellent yields (Equation (99)) ⟨87MI375⟩. The 1,6-dihydropyrimidines (**425**) yielded (**354**) (Equation (100)) ⟨81JCED99, 89JHC55, 91MI 825-02⟩.

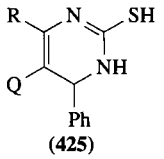


(**416**) → R^1 = H, Me, R^2 = NH_2 (**420**) → (**421**) + (**422**)

Scheme 31

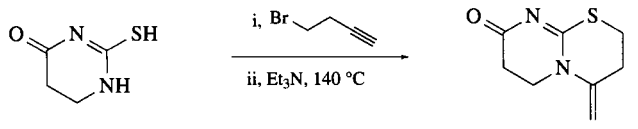


(**423**) (**424**) (99)

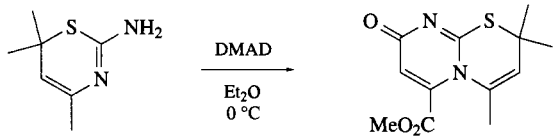


(425) → (354) (100)

The reaction between 2-thiolethyl-1,4,5,6-tetrahydropyrimidine and carbon suboxide resulted in (**370**) ⟨77ZN(B)1204⟩. With propargyl bromide, (**426**) gave (**427**) via *S*-alkylation and intramolecular addition (Equation (101)) ⟨84H(22)1225⟩. In the other version of [3 + 3] fragment syntheses, a 2-amino-1,3-thiazine was reacted with bifunctional electrophiles. Thus, (**428**) reacted with DMAD to yield (**429**) (Equation (102)) ⟨74MI 825-01⟩.

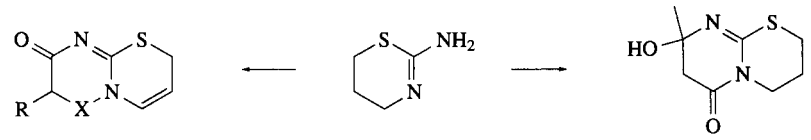


(426) (427) (101)



(428) (429) (102)

Compound (**430**) reacted with methyl acrylate or 3-bromopropionate to give (**431**), with malonyl chlorides to give (**432**) (Scheme 32) ⟨70LA(742)85⟩, and with diketene to give (**433**) ⟨81H(15)399⟩. The first reported synthesis of this ring system was the reaction of (**430**) with diethyl malonate to give (**432**; R = H) ⟨50BRP638504⟩. The perchlorate salt of (**277**; X = S) was obtained via the cycloamination of (**276**; X = S), as shown in Section 8.25.3.6.6 ⟨90T595⟩.

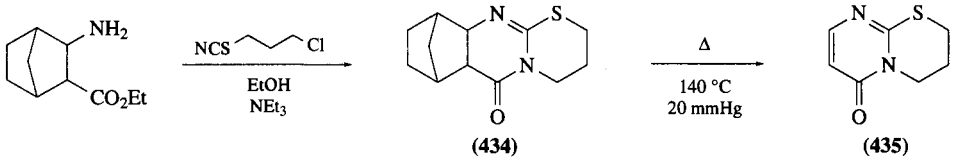


(**431**) X = CH_2, R = H
(**432**) X = CO, R = H
(**430**)
(**433**)

Scheme 32

(ii) Synthesis by ring fission

Retrodiene decomposition of (**434**) resulted in the pyrimidothiazinone (**435**) (Scheme 33) ⟨91T7673⟩.



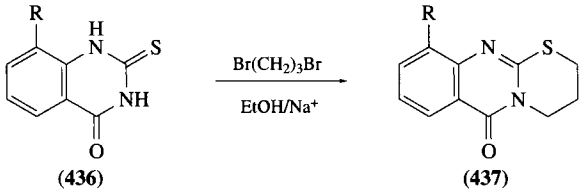
(**434**) (**435**)

Scheme 33

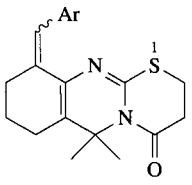
8.25.4.6.5 [1,3]Thiazino[2,3-b]quinazolines

(i) By bond formation adjacent to heteroatom

Several routes are analogous to those described in the previous section. Thus, quinazoline-2-thiones (**436**) reacted with 1,3-dibromopropane to afford (**437**) in low yields (Equation (103)) ⟨84JIC1050, 85AP(318)502⟩. There are further syntheses of this type ⟨73JMC633, 81ACH197⟩. The 4-oxo derivatives (**438**) were formed in good yields from the reactions of the corresponding quinazoline-2-thiones with 3-bromopropanoic acid ⟨78JCED351, 81ACH197⟩. With 3-chlorocrotonic acid, the 2,3-unsaturated-3-methyl analogue of (**438**) was formed ⟨83AP(316)379⟩. In these syntheses, the first step is *S*-alkylation; in one case the *S*-alkylated intermediate was isolated ⟨81ACH197⟩.

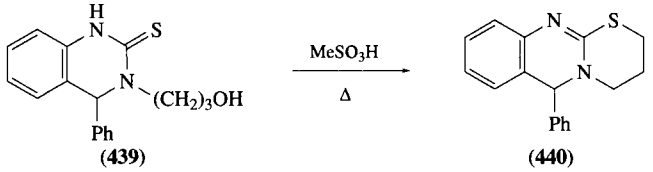


(436) (437) (103)

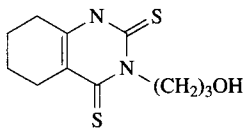


(438)

In another approach, *N*-3-substituted-quinazoline-2-thiones with a terminal hydroxy, halo, carboxy, or acyl group were synthesized, and cyclization to the thioxo group was effected in acidic media. Thus, (**439**) afforded (**440**) in excellent yield (Equation (104)) ⟨79CPB880⟩. Further syntheses of this type have been described ⟨73JMC633⟩. The dithioxoquinazoline (**441**) formed both the linear tricycle (**367**) and the angular isomer, the [1,3]thiazino[3,2-*c*]quinazoline (**368**), in approximately equimolar amounts (Equation (105)) ⟨77ZC444, 78PHA185⟩. The analogous fully unsaturated derivative unexpectedly furnished only the linear product, in high yield ⟨80PHA124⟩. The *N*(3)-γ-hydroxypropylquinazoline (**442**) and the acyl derivative (**443**) (Scheme 34), both prepared from isatoic anhydride, cyclized in acidic media to give the expected tricycles in high yields ⟨71IJC647⟩.

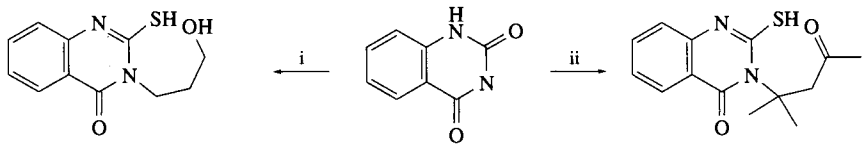


(439) (440) (104)



(441) (367) + (368) (105)

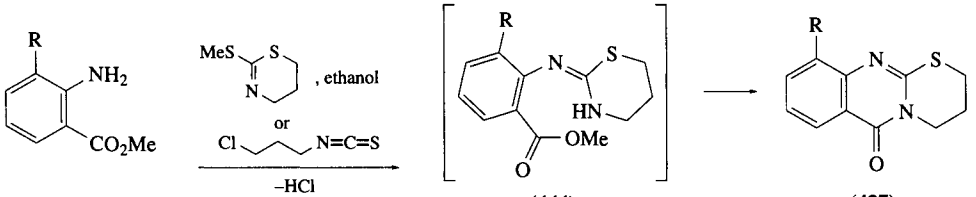
A quinazoline intermediate was postulated to form in the reactions of stereoisomeric alicyclic 2-aminocarboxylates with 3-halopropylisothiocyanate, leading to (**357**) and (**358**), respectively ⟨92T4949⟩. A few syntheses have been described which involve 1,3-thiazine intermediates. The reaction between anthranilic acid and 2-methylthio-4,5-dihydro-6*H*[1,3]thiazine resulted in (**437**) in 65% yield (Scheme 35) ⟨79IJC(B)107⟩. A further synthesis of this type has been described ⟨69MI 825-01⟩. Methyl anthranilates and 3-chloropropylisothiocyanate also yielded (**437**), through (**444**) ⟨79JHC391⟩. The biological oxidation of xylazine (**445**) resulted in (**437**; R = Me) ⟨92MI 825-02⟩.



(442) (443)

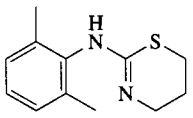
i, $H_2N(CH_2)_3CO_2H$, CS_2/NaOH; ii, $H_2NC(Me)_2CH_2COMe$, KSCN/HCl

Scheme 34



(444) (437)

Scheme 35

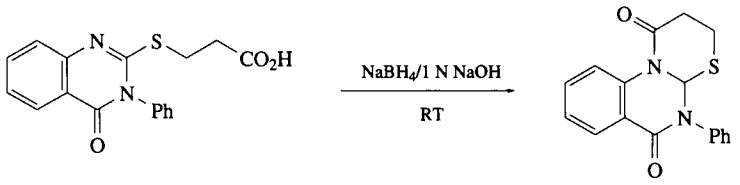


(445)

8.25.4.6.6 [1,3]Thiazino[3,2-a]quinazolines

(i) By bond formation adjacent to heteroatom [6 + 0(α)]

The quinazoline-2-mercaptopropanoic acid (**446**) with borohydride underwent reductive cyclization to (**447**) in good yield (Equation (106)) ⟨70JIC758⟩.



(446) (447) (106)

In another approach, the *N*(1)-γ-hydroxypropyl isomer of (**439**) was cyclized in methanesulfonic acid ⟨79CPB880⟩. Compounds (**360**)–(**362**) were formed (via the *N*-1-acylated intermediates) in high yields, as the only products in the reactions between the appropriate stereoisomeric quinazolinethiones and acetylenedicarboxylate ⟨89MRC959⟩.

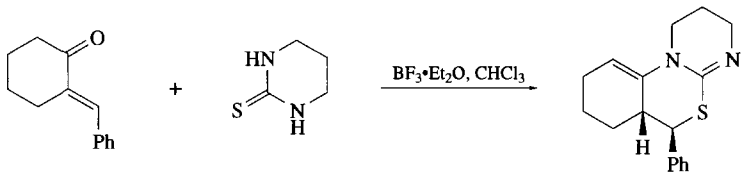
8.25.4.6.7 Pyrimido[1,2-a][3,1]benzothiazines

(i) By bond formation adjacent to heteroatom [6 + 0(α)]

The intermediate (**391**), synthesized from anthranilic acid, cyclized to (**390**) in excellent yield in diethyl ether. Starting from benzonitrile, the 6-imino analogue of (**390**) was obtained ⟨61JOC966, 63JOC740⟩.

(ii) From [3 + 3] atom fragments by bond formations adjacent to heteroatoms

The $BF_3 \cdot OEt_2$-catalyzed reaction of (**448**) with (**449**) yielded (**363**) (Equation (107)), via nucleophilic attack by the sulfur atom on the β-carbon of the unsaturated ketone ⟨87CB1449⟩.



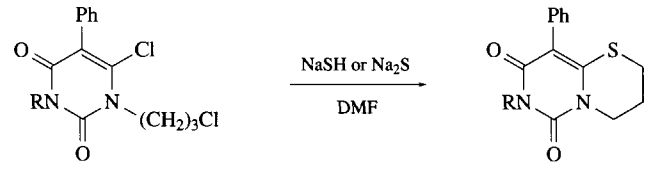
(448) (449) (363) (107)

8.25.4.6.8 Pyrimido[6,1-b][1,3]thiazines and their benzo-derivatives

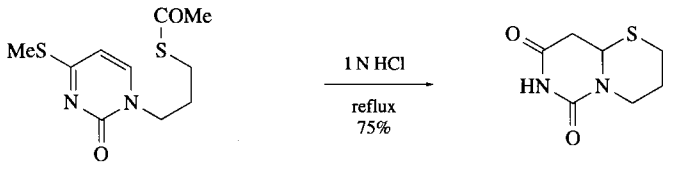
(i) By bond formation adjacent to heteroatom

5,6-Diamino-3,4-dihydro-2(1*H*)-pyrimidine-2-one-4-thione with 1,3-dibromopropane gave (**401**) ⟨92FES1315⟩.

The *N*-γ-chloropropyluracil derivative (**450**) cyclized to (**451**) with the elimination of HCl (Equation (108)) ⟨90EUP404525⟩, whereas the *N*-γ-acetylthiopropylpyrimidone (**452**) cyclized to (**394**) in 75% yield (Equation (109)), by addition of the thiol function onto the ring double bond ⟨72JCS(P1)2385⟩.

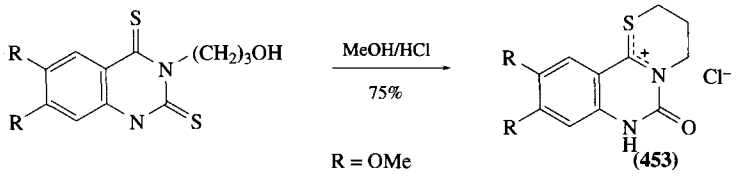


(450) (451) (108)



(452) (394) (109)

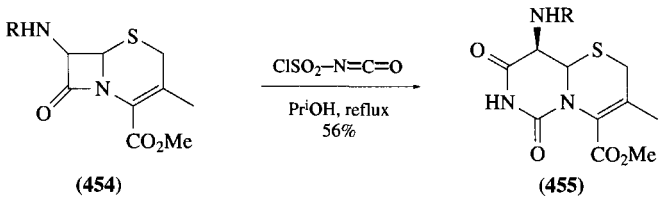
In a similar addition reaction, (**373b**) was formed from the open-chain (**373a**) to give a tautomeric equilibrium in protic solvents (see Section 8.25.4.4.5) ⟨88TL5445⟩. The [1,3]thiazino[3,2-*c*] quinazolines (**453**) were formed in good yields by cyclization of the appropriate *N*(3)-γ-hydroxypropylquinazolinedithiones (Equation (110)) ⟨91EGP293713, 91EGP293726⟩. Another derivative, (**368**), was formed by a similar route from (**441**), along with the linear tricycle (**367**) ⟨77ZC444, 78PHA185⟩.



(453) (110)

(ii) Synthesis by ring expansion

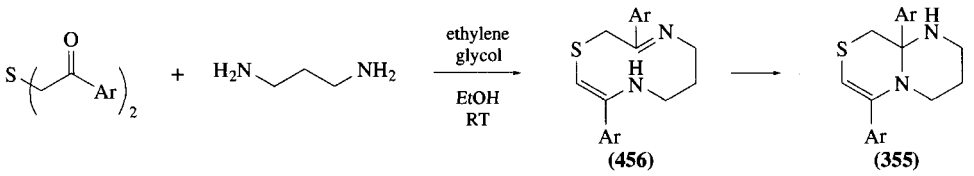
The cephem derivative (**454**) reacted with chlorosulfonyl isocyanate to undergo β-lactam ring expansion, resulting in (**455**) (Equation (111)) ⟨78JCS(P1)817⟩.



(111)

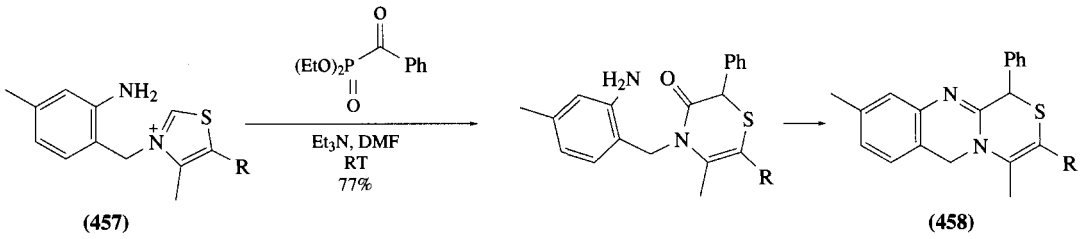
8.25.4.6.9 Pyrimido[2,1-c][1,4]thiazines and their benzo derivatives

Synthesis of the bicycle (**355**) via transannular ring closure of (**456**) has been reported (Scheme 36) ⟨79S623, 80IJC(B)1023⟩.



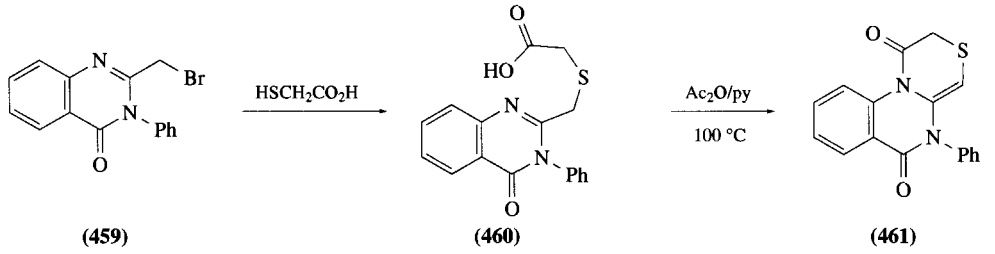
Scheme 36

The linear benzo derivatives, [1,4]thiazino[4,3-*b*]quinazolines (**364**) were formed on condensation of anthranilic acid with 1,4-thiazin-3-one in phosphoryl chloride ⟨87JPR321⟩ or with the corresponding lactim ether in ethanol ⟨79IJC(B)107⟩. Ring expansion of the thiazolium salt (**457**) by the action of diethyl benzoylphosphonate, followed by spontaneous ring closure gives (**458**) in good yield (Scheme 37) ⟨73CPB770⟩.



Scheme 37

Preparation of the [1,4]thiazino[4,3-*a*]quinazoline (**461**) was achieved by reacting the 2-bromomethylquinazolinone (**459**) with thioglycollic acid and cyclizing the intermediate (**460**) (Scheme 38) ⟨88IJC(B)578⟩. A similar sequence gave (**395**) ⟨73IJC1051⟩.



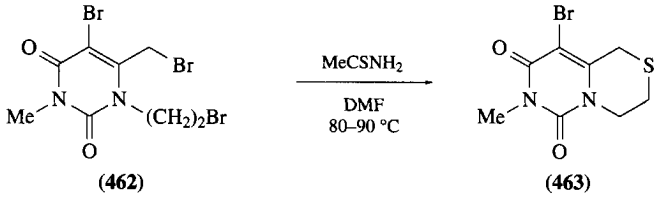
Scheme 38

A representative of the other angularly benzo-fused system, the pyrimido[2,1-*c*][1,4]benzothiazine (**311**; X = S), was prepared by the reaction of 3-aminobenzothiazine and EMME in a similar way to that described for (**311**; X = O) (see Section 8.25.3.6.8) ⟨81USP4254118⟩.

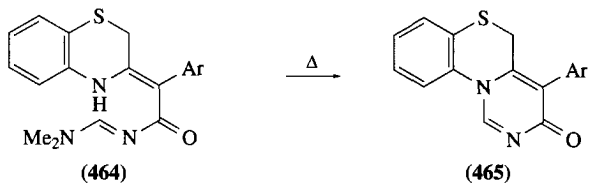
8.25.4.6.10 Pyrimido[6,1-c][1,4]thiazines and their benzo derivatives

Compound (**463**) was formed in good yield from [5 + 1] atom fragments in the reaction between the 1-bromomethyl-6-bromoethyluracil (**462**) and thioacetamide (Equation (112)) ⟨92JHC741⟩. The

pyrimido[6,1-*c*][1,4]benzothiazine (**465**) formed in good yield on thermal cyclization of the benzothiazine (**464**) (Equation (113)) ⟨87JOC1366⟩.



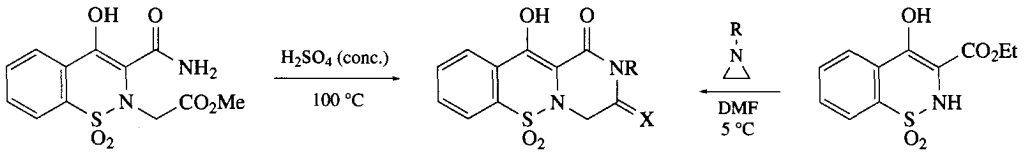
(112)



(113)

8.25.4.6.11 Pyrazino[1,2-b][1,2]benzothiazines (benzo derivatives of the unknown pyrazino[1,2-b][1,2]thiazines)

Cyclization of the benzothiazine-3-carboxamide (**466**) resulted in (**467**) (Scheme 39) ⟨74JOC1554⟩, while reaction of the 3-carboxylate (**468**) with aziridines led to (**469**) ⟨74JOC1560⟩.



(**467**) X = O; R = H
(**469**) X = H_2; R = H, alkyl, aralkyl

Scheme 39

8.25.4.6.12 Pyrazino[1,2-c][1,3]thiazines

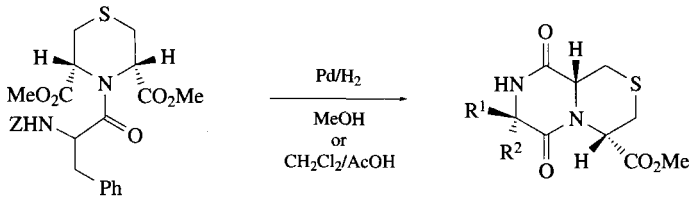
No information has been found on the preparation of these compounds. The reactions of formylrifamicin with various pyrazino derivatives with a broad general formula have been described ⟨85USP4551450⟩ but no specific example is given for a pyrazino[1,2-*c*][1,3]thiazine.

8.25.4.6.13 Pyrazino[2,1-b][1,3]thiazines

The pyrazino[2,1-*b*][1,3]thiazin-5-ium trifluoroacetate salt (**319**; X = S) was obtained from the protonated pyrazino derivative (**318**; X = S) by intramolecular cycloamination, which proceeded instead of the expected Diels–Alder reaction (see Section 8.25.2.6.9) ⟨89T6519⟩.

8.25.4.6.14 Pyrazino[2,1-c][1,4]thiazines and their benzo derivatives

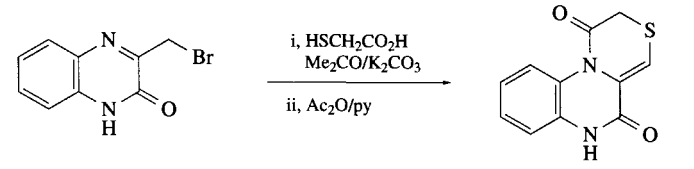
The stereoisomeric cyclic dipeptides (**471**) and (**472**) were formed upon *N*-deprotection of the dipeptide (**470**) (Equation (114)). The ratio of the isomers was influenced by the nature of the solvent through stabilization of a rotamer of (**470**) ⟨90JHC1661⟩. Compound (**356**) was obtained similarly by deprotection of the appropriate dipeptide with HBr/AcOH ⟨79BSB683⟩. The [1,4]-thiazino[4,3-*a*]quinoxaline (**474**) was prepared in good yield from 2-bromomethylquinoxaline (**473**) and thioglycollic acid (Equation (115)) ⟨90MI 825-01⟩.



(470) Z = Protective group

(471) R^1 = Me, R^2 = Bn
(472) R^1 = Bn, R^2 = Me

(114)



(473) (474)

(115)

8.25.4.7 Synthesis of Particular Classes of Compounds and Critical Comparison of the Routes Available

There is just one group of compounds in this chapter where a number of derivatives have been synthesized, that is, pyrimido[2,1-*b*][1,3]thiazines and their benzo derivatives. Pyrimido[2,1-*b*][1,3]thiazines, apart from a few genuine and special syntheses (as of (**435**)), were almost exclusively prepared by the [3 + 3] route, reacting either a pyrimidine-2-thione (2-thiol) or a 2-amino-[1,3]thiazine with bifunctional electrophiles with three carbon atoms. The benzo-fused derivatives were synthesized by analogous routes.

8.25.4.8 Important Compounds and Applications

Characteristic biological effects of these classes of compounds are as antibacterials and antivirals.

8.25.4.8.1 Pyrimido[1,2-b][1,3]thiazine derivatives

Compounds (**417**; R^1 = CN; R^2 = 4-halophenyl) have been demonstrated to exert high activity against herpes virus ⟨87LA797⟩ and have leishmanicidal activity ⟨90AP(323)895⟩. For other derivatives of (**417**) antifungal and Gram-negative antibacterial activities have been described ⟨84JHC1307⟩ (**414**; $R^1 = R^2 = NH_2$) has analgesic and antiinflammatory effects ⟨88KFZ557⟩. Pyrimido[1,2-*a*]-[1,3]benzothiazines of type (**390**) exert antibacterial activity ⟨61JOC966⟩, other derivatives have been patented for their strong hypotensive effect ⟨78JAP(K)78044593⟩.

8.25.4.8.2 Pyrimido[4,3-b][1,3]thiazine derivatives

9-nitro derivatives have been patented as insecticides ⟨76USP3985735, 77USP4031087⟩. Compounds of type (**400**) have antibacterial activity ⟨92FES1315⟩ while (**412**) exerts antipyretic and antiinflammatory effects ⟨79GEP(O)2811131, 79GEP(O)2811163⟩. The [1,3-]thiazino[3,2-*c*]quinazolines (**453**) have been demonstrated to exert plant virucidal ⟨91EGP293713⟩ and immunostimulant ⟨91EGP293726⟩ activities.

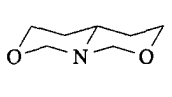
8.25.5 BICYCLIC 6-6 N-BRIDGEHEAD SYSTEMS WITH TWO EXTRA O ATOMS OR TWO EXTRA S ATOMS, OR ONE EXTRA O AND ONE EXTRA S ATOM 1 : 1, AND THEIR BENZO-FUSED DERIVATIVES

8.25.5.1 Introduction

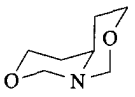
This group of compounds covers N-bridgehead oxazino-oxazines, thiazino-oxazines, and thiazino-thiazines, and also their benzo-fused derivatives. Of the theoretically possible 10 oxazino-oxazines, three have ring file numbers, but no reference has been found for [1,4]oxazino[4,3-*c*][1,3]oxazines. The number of known benzo-fused systems is four. Of the theoretically possible 16 thiazino-oxazines, three are known and one benzo-fused system. Finally, of the 10 theoretically possible thiazino-thiazines two are known and one benzo-fused system (see Table 7). None of the groups of compounds was considered in CHEC-I, nor in previous reviews, therefore the whole of the literature has been surveyed.

8.25.5.2 Theoretical Methods

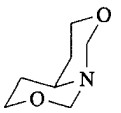
Conformational analysis using molecular mechanics was carried out on the perhydro [1,3]oxazino[3,4-*c*][1,3]oxazines (**494**). Energies, dipole moments, main geometrical features, and planarities at the nitrogen atoms were determined for the conformers. Stability was discussed in terms of anomeric interaction and steric repulsion. The compounds were shown to exist as equilibrium mixtures of three conformers, (**494a**, **b**, and **c**). Results were in good agreement with the NMR experimental data ⟨91JST(263)157⟩.



(494a)



(494b)



(494c)

8.25.5.3 Experimental Structural Methods

8.25.5.3.1 X-ray diffractometry

No work has been published in this field.

8.25.5.3.2 NMR spectroscopy

Proton and ^{13}C NMR spectroscopy have been widely used to elucidate structures of the compounds discussed in this chapter. Nitrogen-15 NMR investigations have not been reported. Several more specialized studies are mentioned below.

(i) [1,3]Oxazino[3,4-c][1,3]oxazines

The preferred conformation of (**494**) was studied, it exists predominantly in the *trans*-fused (**494a**) conformation ⟨73JCS(P2)1379⟩.

Table 7 Bicyclic 6-6 nitrogen bridgehead systems with two extra *O* atoms 1 : 1; one extra *O* and one extra *S* atom 1 : 1; two extra *S* atoms 1 : 1; and their known benzo-fused derivatives. (Systems which are unreported are named in italics.)

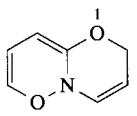
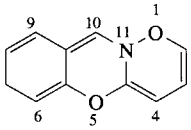
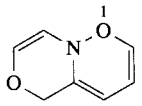
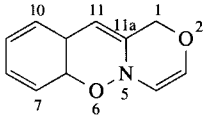
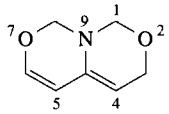
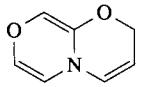
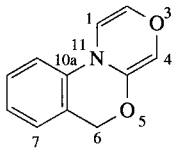
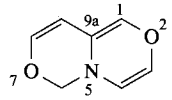
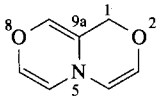
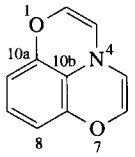
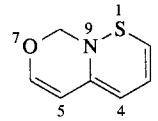
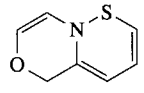
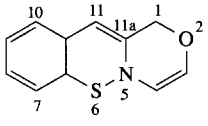
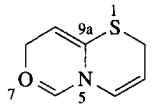
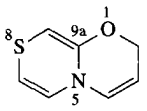
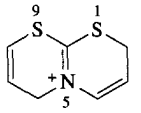
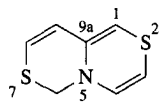
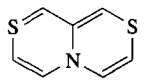
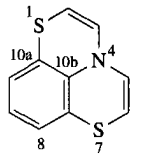
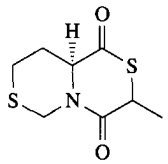
Compound	*Ring system*	*Name and ring file number*
(475)		*2H-[1,2]Oxazino[3,2-*b*][1,3]oxazine*
(476)		7*H*-[1,2]Oxazino[3,2-*b*][1,3]benzoxazine, RF 34903
(477)		5H-[*1,2*]*Oxazino*[*3,2*-c][*1,4*]*oxazine*
(478)		1*H*-[1,4]Oxazino[4,3-*b*][1,2]benzoxazine, RF 34901
(479)		1*H*,3*H*,8*H*-[1,3]Oxazino[3,4-*c*][1,3]oxazine, RF 13576
(480)		*2H-[1,3]Oxazino[2,3-*c*][1,4]oxazine*
(481)		6*H*-[1,4]Oxazino[4,3-*a*][3,1]benzoxazine, RF 34902
(482)		6*H*-[1,4]Oxazino[4,3-*c*][1,3]oxazine, RF 13578
(483)		1*H*-[1,4]Oxazino[4,3-*c*][1,4]oxazine, RF 13575
(484)		[1,4]Oxazino[4,3,2-*de*][1,4]benzoxazine, RF 34900
(485)		8*H*-[1,2]Thiazino[2,3-*c*][1,3]oxazine, RF 13584
(486)		5H-[*1,2*]*Thiazino*[*3,2*-c][*1,4*]*oxazine*
(487)		1*H*-[1,4]Oxazino[4,3-*b*][1,2]benzothiazine, RF 34907

Table 7 (continued).

Compound	*Ring system*	*Name and ring file number*
(**488**)		2*H*,6*H*,8*H*-[1,3]Thiazino[3,2-*c*][1,3]oxazine, RF 13583
(**489**)		2*H*-[1,4]Thiazino[3,4-*b*][1,3]oxazine, RF 13582
(**490**)		2*H*,6*H*-[1,3]Thiazino[2,3-*b*][1,3]thiazin-5-ium, RF 13726
(**491**)		6*H*-[1,4]Thiazino[4,3-*c*][1,3]thiazine, RF 13725
(**492**)		[*1,4*]*Thiazino*[*3,4*-c][*1,4*]*thiazine*
(**493**)		[1,4]Thiazino[**4**,3,2-*de*]-1,**4**-benzothiazine, RF 35147

*(ii) [1,4]Thiazino[3,4-*c*][1,3]thiazines*

The configuration of the separated diastereoisomers of (**495**) was determined ⟨85H(23)889⟩.



(**495**)

8.25.5.3.3 IR and UV spectroscopy

The IR spectrum of the *trans*(3*H*,9a*H*)-(**495**) exhibits the lactam carbonyl band at 1638 cm^{-1}, whereas the *cis*(3*H*,9a*H*)-(**495**) diastereomer at 1675 cm^{-1}. As shown by Dreiding models the carbonyl group of the latter is twisted out of the plane, which explains the difference in the absorption ⟨85H(23)889⟩. Characteristic cyclic ether, lactam, and lactone bands of the oxazino-oxazines (**497**) and (**498**) are given ⟨64AP(297)632⟩.

8.25.5.3.4 Mass spectrometry

Very few data are available. Compounds (**495**) give peaks from (M^+), (M^+—CO), M^+—CO-CHMe) and (M^+—$HSCH_2CH_2$) ⟨85H(23)889⟩.

8.25.5.4 Thermodynamic Aspects

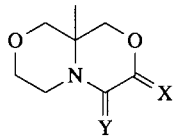
No work has been published.

8.25.5.5 Reactivity

8.25.5.5.1 Electrophilic attack at heteroatoms

(i) N-*Alkylation*

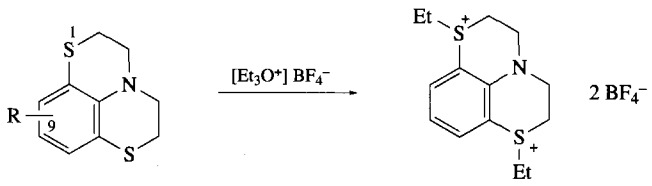
The [1,4]oxazino[4,3-*c*][1,4]oxazine (**496**) gives a quaternary salt with methyl iodide ⟨64AP(297)632⟩.



(496) X = Y = H_2
(497) X = O, Y = H_2
(498) X = H_2, Y = O

(ii) S-*Alkylation*

Alkylation of the [1,4]thiazino[4,3,2-*d*,*e*]-1,4-benzothiazine (**499**) with Meerwein's reagent proceeded at the S atoms to give (**500**) (Equation (116)) ⟨67JHC339⟩.



(499) **(500)**

(116)

(iii) S-*Oxidation*

(**499**) with H_2O_2/AcOH gave the 1,1,7,7-tetraoxide ⟨70USP3530125⟩.

8.25.5.5.2 Electrophilic attack at carbon atoms

(i) Electrophilic substitution

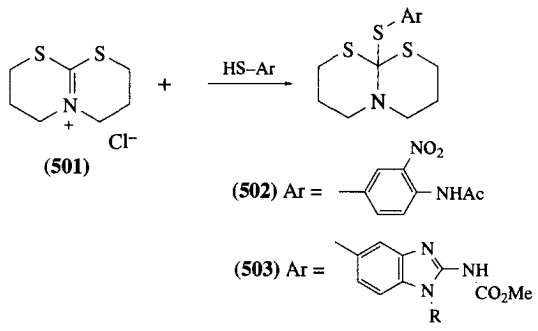
Compound (**499**) with phosphoryl chloride/DMF gave the 9-carboxaldehyde ⟨70USP3511831⟩.

(ii) Oxidative dimerization

Compound (**499**) on the action of nitrous acid underwent oxidative dimerization through the C-9 atoms ⟨70JHC245⟩.

8.25.5.5.3 Nucleophilic attack at carbon atoms

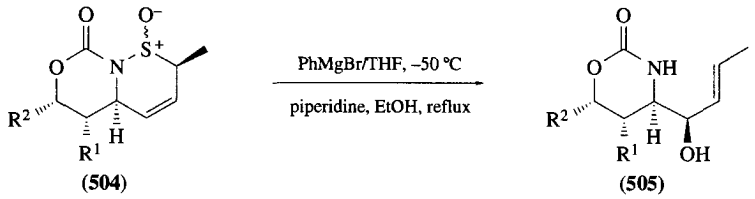
The [1,3]thiazino[2,3-*b*][1,3]thiazinium salt (**501**) reacted with aromatic thiols at C-9a, to form the addition products (**502**) (Equation (117)). The latter were further transformed to (**503**) ⟨77USP4031228⟩.



(117)

8.25.5.5.4 Other reactions

The N—S bond of the [1,2]thiazino[2,3-*c*][1,3]oxazine (**504**) was cleaved with PhMgBr to give an allylic sulfoxide which after further transformation furnished the secondary alcohol (**505**), as a single stereoisomer (Equation (118)) ⟨84JOC3243, 85T1173⟩.

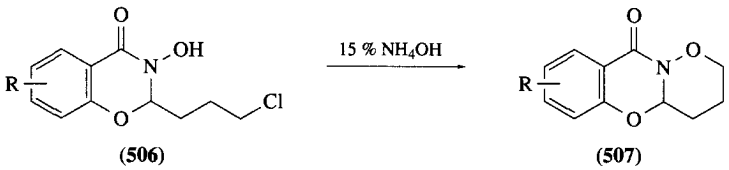


(118)

8.25.5.6 Synthesis

8.25.5.6.1 [1,2]Oxazino[3,2-b][1,3]benzoxazines (benzo derivatives of the unknown [1,2]oxazino[3,2-b][1,3]oxazines)

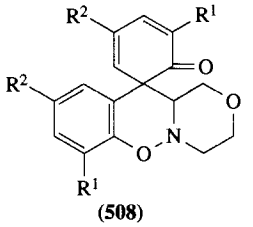
The benzoxazine (**506**) (prepared from salicylohydroxamic acid and 4-chlorobutyraldehyde) was cyclized to (**507**) (Equation (119)). Enantiomers of (**506**), separated through the quinine salts, gave the pure optical isomers of (**507**) ⟨77AF760⟩.



(119)

8.25.5.6.2 [1,4]Oxazino[4,3-b][1,2]benzoxazines (benzo derivatives of the unknown [1,2]oxazino[3,2-c][1,4]oxazines)

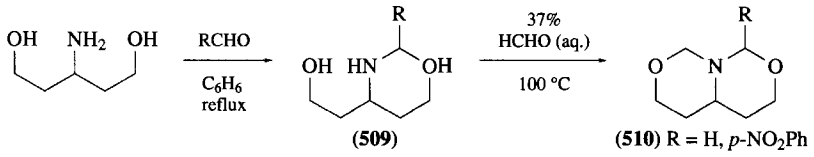
Only one derivative, (**508**), has been described which was prepared by the oxidative coupling of *o*-R^1-*p*-R^2-substituted phenols and morpholine, in the presence of CuCl complexes, in an O_2 atmosphere ⟨68ZOR1594⟩.



(508)

8.25.5.6.3 [1,3]Oxazino[4,3-c][1,3]oxazines

The perhydro derivatives (**510**) were synthesized from [5 + 1] atom fragments by reacting (**509**) with formaldehyde (Scheme 40) ⟨73JCS(P2)1379⟩.

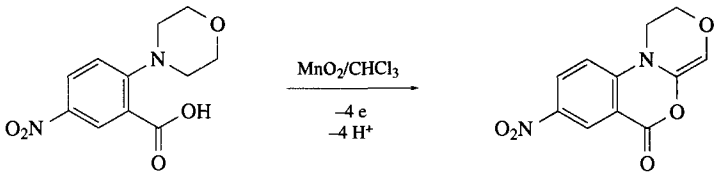


(**509**) (**510**) R = H, *p*-NO_2Ph

Scheme 40

8.25.5.6.4 [1,4]Oxazino[4,3-a][3,1]benzoxazines (benzo derivatives of the unknown [1,3]oxazino[2,3-c][1,4]oxazines)

Oxidative cyclization of *o*-(*N*-morpholino)benzoic acid (**511**), followed by further oxidation gave (**512**) in 25% yield (Equation (120)) ⟨68JCS(C)1722⟩.



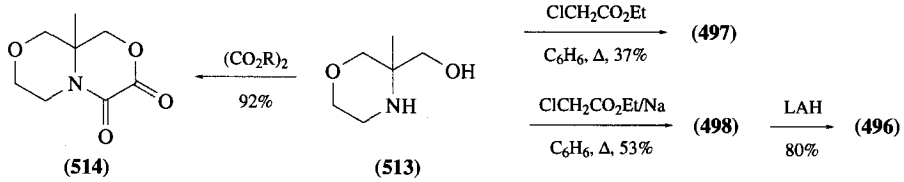
(**511**) (**512**) (120)

8.25.5.6.5 [1,4]Oxazino[4,3-c][1,3]oxazines

No reference has been found for this ring system; see Section 8.25.5.1.

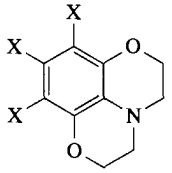
8.25.5.6.6 [1,4]Oxazino[4,3-c][1,4]oxazines and their benzo derivatives

Perhydro derivatives (**497**), (**498**), and (**514**) were synthesized from [4 + 2] atom fragments by reacting the morpholine derivative (**513**) with bifunctional electrophiles (Scheme 41), for example, ethyl chloroacetate and diethyl oxalate ⟨64AP(297)632⟩. The [1,4]oxazino[4,3,2-de]-1,4-benzoxazine derivative (**515**) was prepared in the reaction between chloropentafluorobenzene and diethanolamine ⟨88MI 825-03⟩.



(**514**) (**513**) (**497**) (**498**) (**496**)

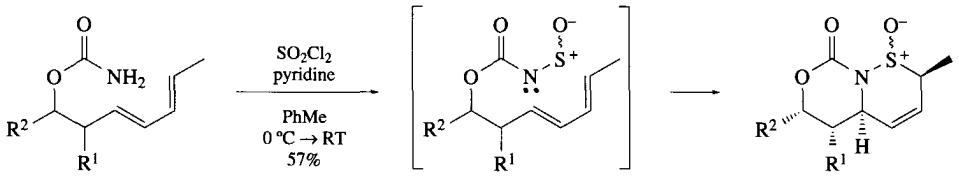
Scheme 41



(515) X = Cl, F

8.25.5.6.7 [1,2]Thiazino[2,3-c][1,3]oxazines

Compounds of type (**504**) were synthesized by the intramolecular cycloaddition of the *N*-sulfinyl derivative (**516**) (Scheme 42). Stereospecificity was attributed to a preferred conformation in the transition state ⟨84JOC3243, 85T1173⟩.



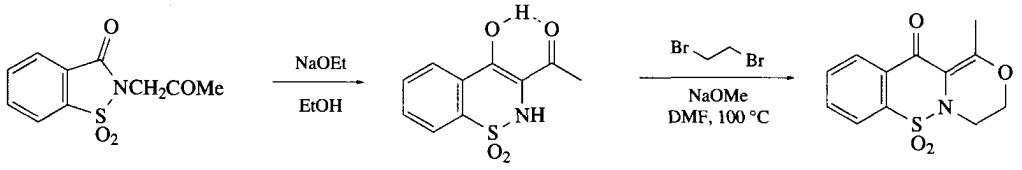
R^1 = OBn, R^2 = H
R^1 = H, R^2 = Me

(516) (504)

Scheme 42

8.25.5.6.8 [1,4]Oxazino[4,3-b][1,2]benzothiazines (benzo derivatives of the unknown [1,2]thiazino[3,2-c][1,4]oxazines)

The only known derivative, (**518**), was synthesized from [4 + 2] atom fragments, by reacting the 3-acyl-1,2-benzothiazine (**517**) with 1,2-dibromoethane (Scheme 43) ⟨74JOC1554, 74USP3821212⟩.

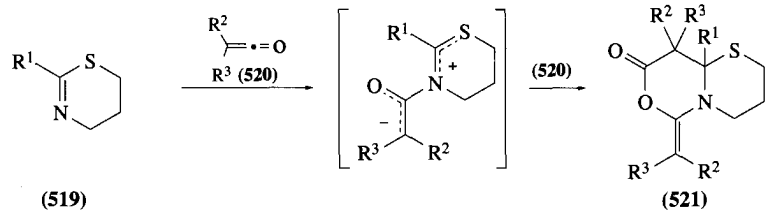


(517) (518)

Scheme 43

8.25.5.6.9 [1,3]Thiazino[3,2-c][1,3]oxazines

Cycloaddition of the ketene (**520**; $R^1 = R^2 = Cl$) to the thiazine (**519**) resulted in the 2 : 1 cycloadduct (**521**), in moderate yield, beside 1 : 1 and 1 : 2 adducts ⟨75AP(308)481⟩. Similarly was prepared (**521**; R^1 = H, R^2 = CN, R^3 = Bu^t) ⟨79LA334⟩.

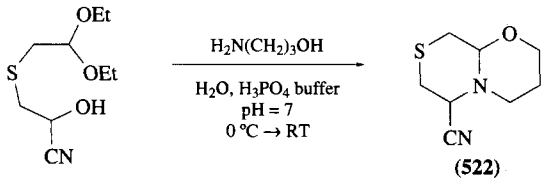


(519) (521)

Scheme 44

8.25.5.6.10 [1,4]Thiazino[3,4-b][1,3]oxazines

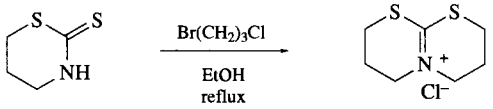
Condensation of the acetal of thiodiacetaldehyde cyanohydrin with 3-aminopropanol furnished the perhydro derivative (**522**) in 45% yield (Equation (121)) ⟨71JOC226⟩.



(522) (121)

8.25.5.6.11 [1,3]Thiazino[2,3-b][1,3]thiazines

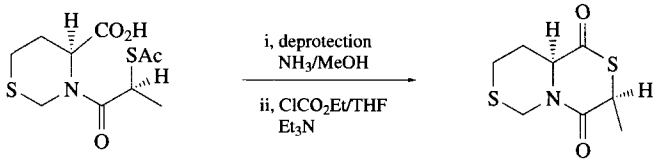
The thiazinium salt (**523**) was synthesized from [3 + 3] fragments by reacting 1,3-thiazolidine-2-thione with 1,3-dihalopropane (Equation (122)) ⟨77USP4031228⟩.



(523) (122)

8.25.5.6.12 [1,4]Thiazino[3,4-c][1,3]thiazines

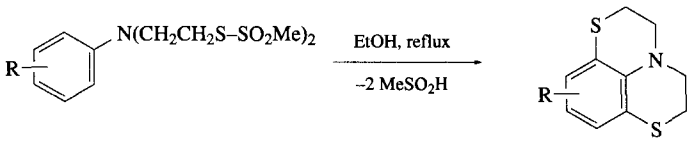
The only known derivative, (**495**), was prepared by the ring closure of the *N*-acylated 1,3-thiazine-4-carboxylic acid (**524**) (Equation (123)). Diastereoisomers of (**495**) were separated ⟨85H(23)889⟩.



(524) (495) (123)

8.25.5.6.13 [1,4]Thiazino[4,3,2-de]-1,4-benzothiazines (benzo derivatives of the unknown [1,4]thiazino[3,4-c][1,4]thiazines)

The bis[(methylsulfonylthio)alkyl]anilines (**525**) cyclized to (**526**) via electrophilic attack by the partially positive sulfur atoms to the aromatic carbons (Equation (124)). The yields reflected the substituent effect in aromatic electrophilic substitutions: R = H: 57%; R = *p*-OMe, *p*-Me: 90–98%; R = *m*-NO_2: 0% ⟨67JHC339⟩.



(525) (526) (124)

8.25.5.7 Important Compounds and Applications

The oxazino-benzoxazines (**507**) exhibit antiinflammatory, antipyretic and analgesic activity ⟨77AF766⟩. The oxazino-benzothiazine (**518**) has been described as a stabilizer for plastics against

UV light ⟨74USP3821212⟩. The thiazino-thiazines (**503**) display anthelmintic and fungicidal activity ⟨76USP3962437⟩, their substituted derivatives exhibit protozoal growth-inhibiting activity ⟨77USP4031228⟩. The thiazino-benzothiazines (**500**) have been demonstrated to exert fungicidal activity ⟨70USP3509139⟩, and other derivatives of (**499**) have pesticidal activity ⟨70USP3511831, 70USP3510481, 70USP3530125⟩.

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8.26
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 3 : 0

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and

MOHINDER PAL MAHAJAN
Guru Nanak Dev University, Amritsar, India

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8.26.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT 710

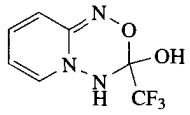
8.26.10 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS 710

8.26.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE 711

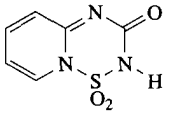
8.26.12 IMPORTANT COMPOUNDS AND APPLICATIONS 711

8.26.1 INTRODUCTION

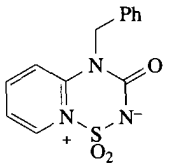
Reports concerning bridgehead nitrogen bicyclic systems containing three extra hetero atoms in one of the rings are very rare (**1**)–(**5**) ⟨79H815, 86H2255, 77JCR(S)238⟩.



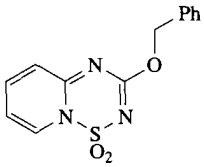
(**1**)



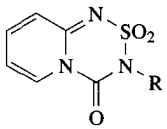
(**2**)



(**3**)



(**4**)



(**5**)

8.26.2 THEORETICAL METHODS

The theoretical aspects of these compounds have not yet been explored.

8.26.3 EXPERIMENTAL STRUCTURAL METHODS

8.26.3.1 X-ray Crystallography

No x-ray crystallographic data for these heterocycles is available.

8.26.3.2 NMR Spectra

The ^{1}H NMR spectral data is only available for compound (**3**), where —CH_2— and aromatic protons have been shown to appear at δ 5.45 and 7.00–8.90, respectively ⟨86H(8)2255⟩. The —CH_2— carbon for (**3**) and (**4**) in ^{13}C NMR spectra appeared at δ 71.7 and 49.7, respectively ⟨79H(6)815⟩.

8.26.3.3 Mass Spectra

The mass spectra of these compounds showed, in addition to the molecular ion peaks, peaks due to C_5H_4N and $C_5H_4N_2O$ fragments for (**4**) ⟨79H(6)815⟩.

8.26.3.4 IR Spectra

The infrared spectrum of pyrido[1,2-*b*][1,2,4,6] thiatriazine-5(6*H*)-one-1,1-dioxide (**2**) exhibited absorptions at 1680 cm^{-1} and 1620 cm^{-1}, whereas its mesoionic compounds (**3**) and (**4**) showed a shift towards lower wave numbers.

8.26.3.5 UV Spectra

The UV spectrum for compound (**2**) showed absorption at 302 nm and 235 nm in methanol.

8.26.4 THERMODYNAMIC ASPECTS

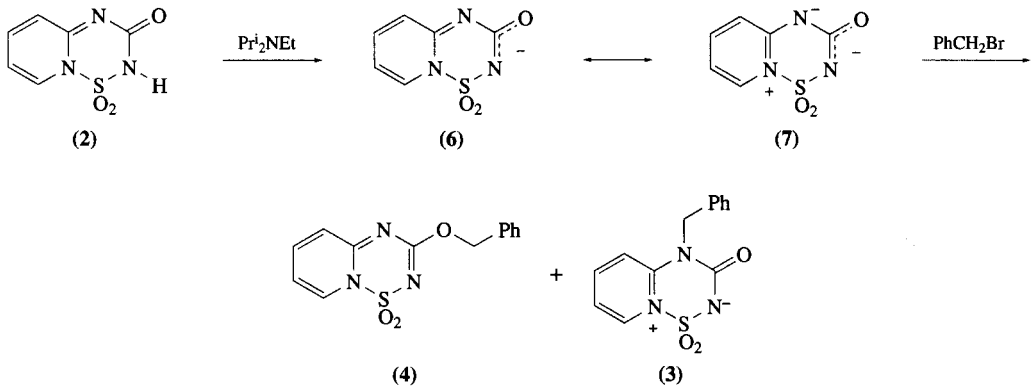
The thermodynamic aspects and the conformational studies of these compounds have not been investigated.

8.26.5 REACTIVITY OF FULLY CONJUGATED RINGS

The compounds under consideration in this chapter are not fully conjugated and hence are devoid of aromaticity.

8.26.6 REACTIVITY OF NONCONJUGATED RINGS

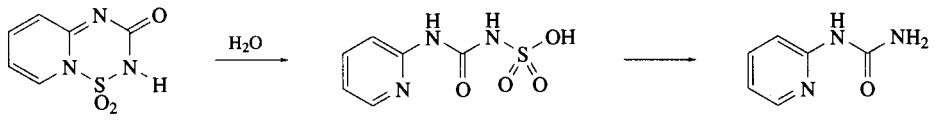
Pyrido[1,2,4,6]thiatriazine-5(6*H*)-one-1,1-dioxide (**2**), on benzylation in acetonitrile in the presence of diisopropylethylamine, gave equal amounts of compounds (**3**) and (**4**), probably formed via the intermediates (**6**) and (**7**) (Scheme 1) ⟨79H(6)815⟩.



(2) (6) (7) (4) (3)

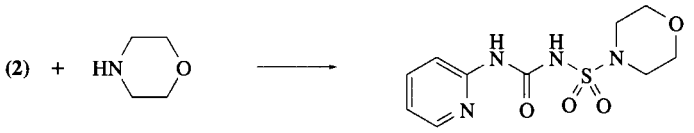
Scheme 1

Compound (**2**) is acidic and exhibited both electrophilic and nucleophilic properties ⟨79H(6)815⟩. The pyridothiatriazinone (**2**) is readily soluble in dilute aqueous sodium bicarbonate forming its sodium salt, which undergoes slow hydrolysis to urea (**9**) via (**8**) (Scheme 2). The electrophilic nature of the sulfonyl group in (**2**) was demonstrated by its reaction with morpholine to give (**10**) (Equation (1)).



(2) (8) (9)

Scheme 2



(10) (1)

8.26.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

No information under this heading is available.

8.26.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

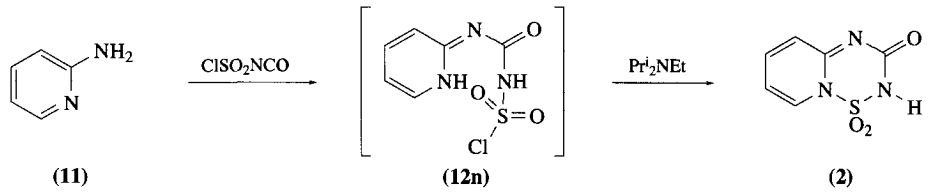
Reactivity of substituents attached to heteroatoms in these compounds has not been explored.

8.26.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Syntheses of the known compounds to be discussed in this chapter can not be classified in this category.

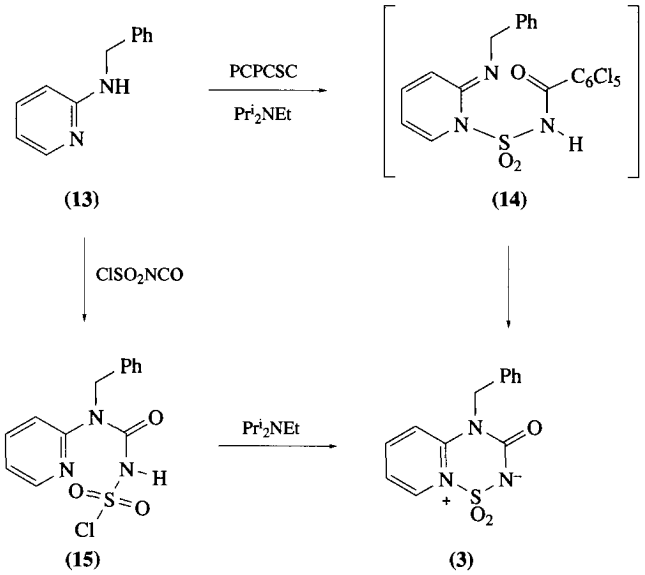
8.26.10 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS

2-Aminopyridine is reported to react vigorously with chlorosulfonyl isocyanate at 0 °C producing an urea intermediate (**12**) which in the presence of diisopropylethylamine was shown to yield pyrido[1,2-*b*][1,2,4,6]thiatriazine-5(6*H*)-one-1,1-dioxide (**2**) (Scheme 3) ⟨79H(6)815⟩. Its *N*-benzyl derivative (**3**) was selectively prepared by the reaction of 2-benzylaminopyridine (**13**) with either chlorosulfonyl isocyanate via intermediate (**15**) or pentachlorophenyl chlorosulfonyl carbamate (PCPCSC) in the presence of diisopropylethylamine via intermediate (**14**) (Scheme 4) ⟨86H(8)2255⟩. The reaction of 2-alkyl-2-chlorosulfonyl carbamoyl chlorides with 2-aminopyridine resulted in 2-alkylpyrido [1,2-*d*][1,2,4,6]thiatriazine-3(2*H*)-one-1,1-dioxides (**5**) (Equation (2)) ⟨77CR(S)238⟩.



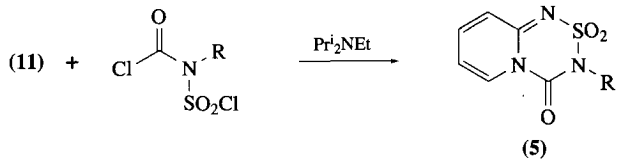
(11) (12n) (2)

Scheme 3



(13) (14) (15) (3)

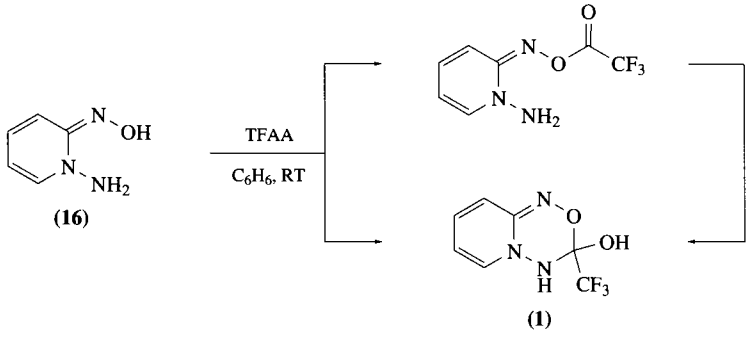
Scheme 4



(5) (2)

Treatment of 1-amino-2-hydroxyimino-1,2-dihydropyridine (**16**) with trifluoroacetic anhydride at room temperature in benzene for 15 mins resulted in the formation of 3-hydroxy-3-trifluoro-

methyl-3,4-dihydropyrido[2,1-*c*][1,2,4,5]oxatriazine (**1**) Scheme 5. The compound was characterised on the basis of IR data (absence of a carbonyl peak) since the NMR spectra of both the compounds were found to be identical ⟨81T1787⟩.



Scheme 5

8.26.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

One synthesis for each of these compounds does not permit a critical study to be carried out.

8.26.12 IMPORTANT COMPOUNDS AND APPLICATIONS

There are no reports concerning the application of such compounds.

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8.27
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Three Extra Heteroatoms 2 : 1

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8.27.1 INTRODUCTION

Of the various possible bicyclic 6-6 systems with one ring junction nitrogen atom dealt with in this chapter, the rings containing only nitrogen as the other heteroatoms have been most explored in the literature. The heterocyclic systems reported so far are shown; the parent systems are named, but the actual compounds, mainly oxo derivatives, are drawn below: 4*H*-pyrazino[2,1-*c*][1,2,4]triazine (**1**); 9*H*-pyrazino[1,2-*a*][1,3,5]triazine (**2**); 4*H*-pyrazino[1,2-*f*][1,2,4]triazine (**3**); 2*H*-pyridazino[6,1-*c*][1,2,4]triazine (**4**); 4*H*-pyridazino[2,3-*a*][1,3,5]triazine (**5**); 4*H*-pyridazino[6,1-*f*][1,2,4]triazine (**6**); 9a*H*-pyrimido[6,1-*c*][1,2,4]triazine (**7**); 2*H*,6*H*-pyrimido[1,2-*a*][1,3,5]triazine (**8**); 2*H*,4*H*,6*H*-pyrimido[1,6-*a*][1,3,5]triazine (**9**); 8*H*-pyrimido[1,2-*b*][1,2,4]triazine (**10**); 2*H*,4*H*,6*H*-pyrimido[1,6-*b*][1,2,4]triazine (**11**); 4*H*,6*H*-[1,3]thiazino[2,3-*c*][1,2,4]triazine (**12**); 3*H*,8*H*-[1,3]thiazino[3,2-*b*][1,2,4]triazine (**13**); 2*H*,6*H*-[1,3]thiazino[3,2-*a*][1,3,5]triazine (**14**); 2*H*,8*H*-pyrimido[2,1-*b*][1,2,4]thiadiazine (**15**); 2*H*,4*H*,8*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine (**16**); 4*H*-pyridazino[6,1-*c*][1,2,4]oxadiazine (**17**); 4*H*-pyrimido[2,1-*c*][1,2,4]oxadiazine (**18**); 4*H*,6*H*-pyrimido[6,1-*c*][1,2,4]oxadiazine (**19**); 2*H*,6*H*,8*H*-pyrimido[6,1-*b*][1,2,4]oxadiazine (**20**); 4*H*,6*H*-[1,3]oxazino[3,2-*a*][1,3,5]triazine (**21**); 8*H*-[1,3]oxazino[3,2-*d*][1,2,4]triazine (**22**); 2*H*,4*H*,8*H*-pyrimido[6,1-*d*][1,3,5]dioxazine (**23**); 4*H*,6*H*-pyrimido[2,1-*d*][1,3,5]oxathiazine (**24**); 1*H*, 3*H*, 6*H*-[1,3]thiazino[3,2-*c*][1,3,2]oxazaphosphorine (**25**).

8.27.2 THEORETICAL METHODS

There is almost no information available concerning the application of molecular mechanics or any other theoretical method for these heterocycles.

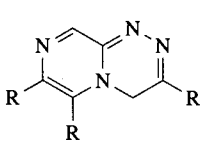
8.27.3 EXPERIMENTAL STRUCTURAL METHODS

Because of the diversity of these heterocyclic systems in general and the non-comparibility of the experimental conditions in particular, a detailed discussion of the experimental techniques is not attempted.

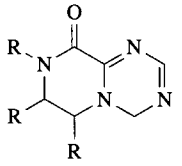
8.27.3.1 X-Ray Crystallography

The x-ray crystallography of only a few systems has been reported. Thus, for example, crystals of 2-amino-6,7-diphenyl-8-methyl-6,7,8,9-tetrahydropyridazino[1,2-*a*][1,3,5]triazine-4,9-dione (**26**) were found to be monoclinic having space group $P2_{1/C}$ ⟨75T541⟩, whereas crystals of 1-amino-2,6-dihydro-8-phenyl-2,6-dioxo-1*H*-pyrimido[1,2-*b*][1,2,4]triazine-3-acetic acid methyl ester (**27**) were shown to be triclinic in nature with space group P1 ⟨88JHC739⟩. The x-ray crystallographic study of pyrimido[2,1-*d*][1,3,5]oxathiazine (**28**) revealed that S and C-5 atoms are coplanar with the pyrimidine ring within 0.05 Å ⟨71JOC602⟩. The conformation of the oxathiazine ring is well described by the torsional angles around its bonds: C(1)-N(2), 0.3°; N(2)-S, −49.8°; C(5)-O(2), 81.8°; O(2)-C(6), −56.3°; C(6)-C(5), 5.1°; S-C(1), 20.9°. The x-ray crystallography data of compound (**29**) revealed that the crystals are monoclinic having space group $P2_{1/C}$ with a = 14.945(3), b = 9.465(1), c = 21.655(2) Å, $\beta = 112.70(2)°$. The important bond distances in Å are O(1)-C(2), 1.365, C(2)-C(21), 1.329, C(4)-C(41), 1.333, C(4)-N(5), 1.393, C(8)-C(81), 1.225, C(9)-C(10), 1.335. Unusual features are the lack of mesomeric interaction between amide carbonyl group C(8)-O(81) and the double bond between C(9) and C(10), as indicated by relatively long C(8)-C(9) distance (1.516 Å) as well as by a torsional angle O(81)-C(8), C(9)-C(10) of 159°, and the non-planarity of the ketene *O*,*N*-acetal unit around C(4), the angle between the planes O(3), C(4), N(5) and C(41), C(42), C(43) being 8.2° ⟨78CC820⟩.

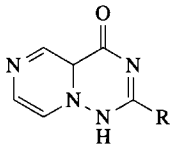
2-Phenylpyridazino[6,1-*f*][1,2,4]triazin-4-one (**6**) is monoclinic, having space group $P2_{1/n}$ with a = 19.057(7), b = 7.473(3), c = 7.826(3)Å, and $\beta = 94.76(3)°$ ⟨92AX(C)1152⟩. 2-Phenylpyrazino[3,2-*f*][1,2,4]triazin-4-one (**3**; R = Ph) is monoclinic having space group $P2_{1/n}$ with a = 14.452(2), b = 10.257(1), c = 7.048(3) Å, and $\beta = 98.11(2)°$ ⟨92AX(C)1152⟩. The geometries of both the compounds were similar. The bond distances between the carbonyl carbon and adjacent carbon atoms were rather long (1.463(6) Å for former and 1.476(6) Å for latter). The dihedral angle between the triazine and phenyl ring were close to 0° (2.77 and 3.22° respectively).



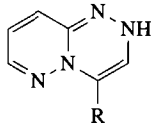
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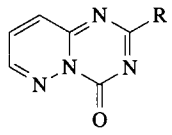
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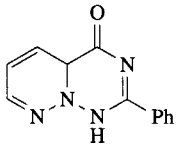
(3)



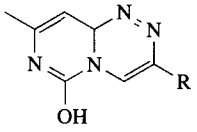
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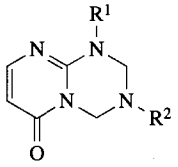
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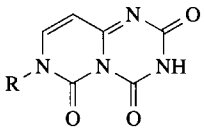
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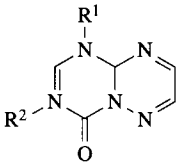
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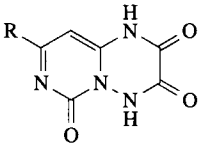
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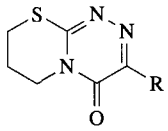
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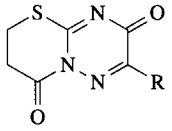
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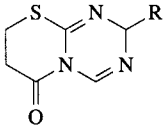
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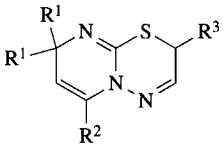
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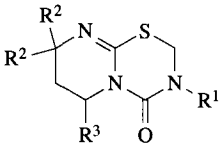
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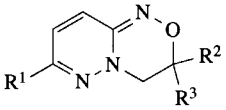
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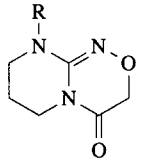
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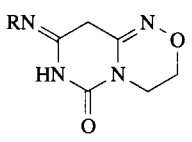
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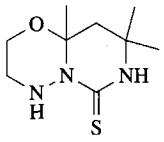
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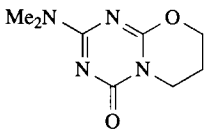
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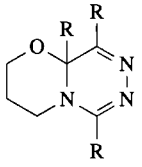
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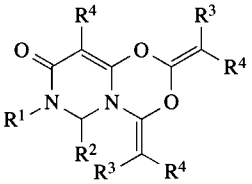
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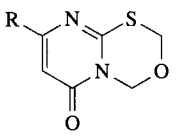
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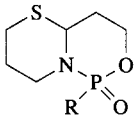
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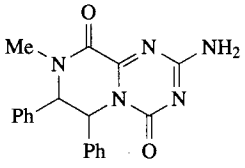
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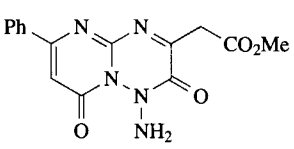
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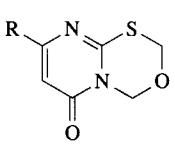
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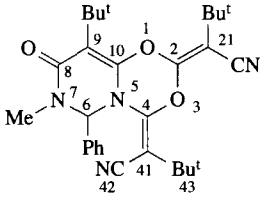
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(27)



(28)

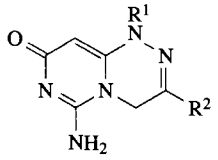


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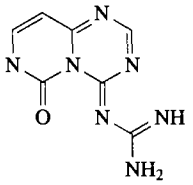
8.27.3.2 NMR Spectra

Almost all the reported compounds had been characterized with the help of ^{1}H NMR spectra. The high resolution proton magnetic resonance spectrum of the pyrimido[1,6-*a*][1,3,5]triazine (**9**; R = H) ⟨88JOC3959⟩ in addition to two doublets at δ 7.8 and 6.1 (J = 8.1 Hz) corresponding, respectively, to the 6- and 5-protons of the original pyrimidino ring, showed also the presence of a D_2O-exchangable proton at δ 11.2 for NH protons. In the case of (**30**), the C-5 proton appeared at high field at δ 5.60. The exocyclic NH_2 protons of (**30**) and (**31**) appeared as a broad singlets at δ 8.3 and 7.8, respectively ⟨80JOC3919, 81JOC1457⟩.

The ^{13}C spectra are only available for pyrimido[6,1-*c*][1,2,4]triazines ⟨81JOC1457, 85JOC2474, 86JOC3959⟩. The ^{13}C proton-decoupled spectrum of (**9**; R = H) showed a signal at δ 96.0 assigned to C-5 of the original pyrimidine ring, whereas in the coupled spectrum resonances at δ 166.6 and 144.2 were attributed to the CH carbon of the triazine and C-6 of the original pyrimidine rings ⟨88JOC3959⟩, respectively. In the case of (**31**), the signals at δ 102.0, 141.8, 145.0, and 160.0 were assigned to C-5, C-6, C-4, and carbonyl carbon of the original pyrimidine ring ⟨81JOC1457⟩.



(**30**)



(**31**)

8.27.3.3 Mass Spectra

The mass spectra of all these compounds showed the presence of molecular ion peaks. The pyrimidotriazines showed the loss of NH_2CN ⟨80JOC3919⟩, $CH_3N_2^+$ ⟨81JOC1457⟩ CO, CN, HCN, and HCNO fragments. The fast atom bombardment (FAB) mass spectra recorded for pyrimido[1,6-*a*][1,3,5]triazine (**31**) showed an MH^+ peak ⟨85JOC2474, 88JOC3959⟩.

8.27.3.4 IR Spectra

The infrared spectrum of all the compounds were mostly studied in solid state. In chloroform, the difference of the frequency ($\Delta\nu$) between the carbonyl (ν_1) and carbon nitrogen double bond (ν_2) of pyrimido[2,1-*c*][1,2,4]triazine (**32**) is greater than its imidazolotriazine counterpart ⟨75T433⟩. It has been established that in the solid state it exists as imino tautomers (**32**) and in the solution form, amino tautomer (**33**) predominates. However, in some cases the two forms exist in rapid equilibrium.



(**32**) (**33**)

8.27.3.5 UV Spectra

The UV spectra of only few of the heterocycles are available. The pyrimido[1,6-*a*][1,3,5]triazine (**9**) showed absorption in methanol at 307 and 240 nm ⟨88JOC3959⟩ and (**30**) in the region of 300 and 253.5 nm ⟨80JOC3919⟩. The pyrimido[2,1-*d*][1,3,5]oxathiazine exhibited the absorbance at 298 and 228 nm in methanol.

8.27.4 THERMODYNAMIC ASPECTS

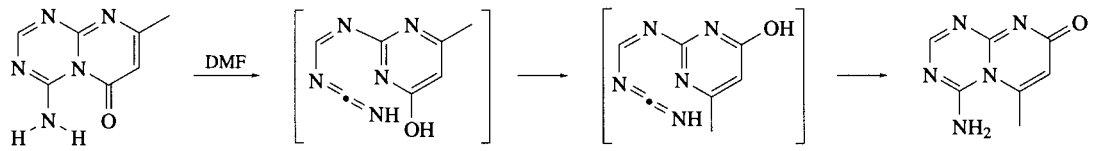
No information in this regard could be located in literature.

8.27.5 REACTIVITY OF FULLY CONJUGATED RINGS

The heterocyclic compounds containing a ring junction nitrogen atom are basically non-aromatic. No information is available, even on their corresponding aromatic quaternary salts.

8.27.6 REACTIVITY OF THE NONCONJUGATED RINGS

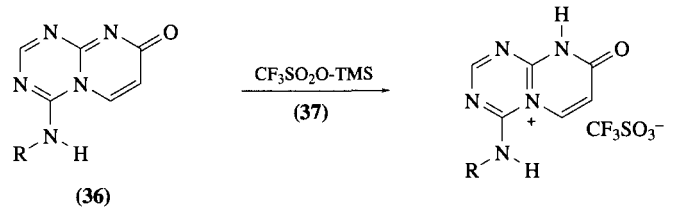
There are very few reports concerning the reactivities of the nonconjugated rings. 4-Amino-8-methyl-6-oxo-6*H*-pyrimido[1,2-*a*][1,3,5]triazine (**34**) was shown to undergo thermal rearrangement ⟨85JOC2474⟩ to 4-amino-6-methyl-8-oxo-8*H*-pyrimido[1,2-*a*][1,3,5]triazine (**35**) (Scheme 1). The rearrangement involved amine-assisted ring opening and its subsequent cyclization involving the other nitrogen atom of the pyrimidine unit.



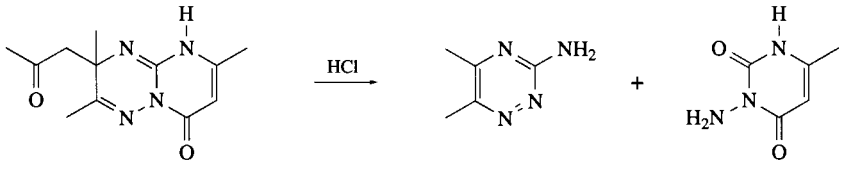
(**34**) (**35**)

Scheme 1

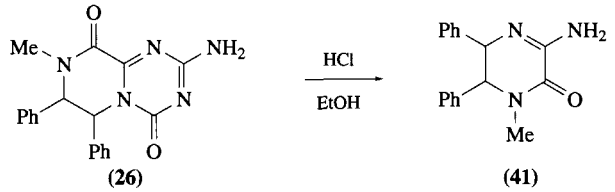
4-Aminopyrimido[1,6-*a*][1,3,5]triazine (**36**) was converted to the corresponding triflate salt by the action of trimethylsilyltrifluoromethane sulfonate (**37**) (Equation (1)) ⟨85JOC2474⟩. Treatment of pyrimido[1,2-*b*][1,2,4]triazine (**38**) with hydrochloric acid resulted in its degradation to (**39**) and (**40**), (Equation (2)) ⟨84H(22)1095⟩. Similarly pyrazino[1,2-*a*][1,3,5]triazine-4-one derivative (**26**) was degraded to 3-aminopyrazino-2-ones (**41**) (Equation (3)) ⟨75T533⟩.



(**36**) (1)

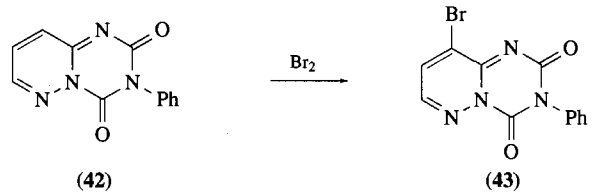


(**38**) (**39**) (**40**) (2)

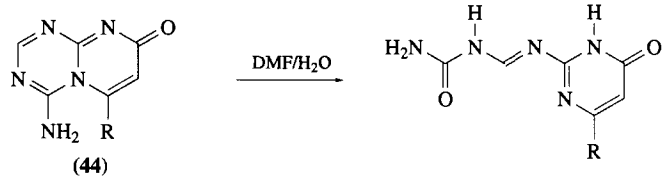


(**26**) (**41**) (3)

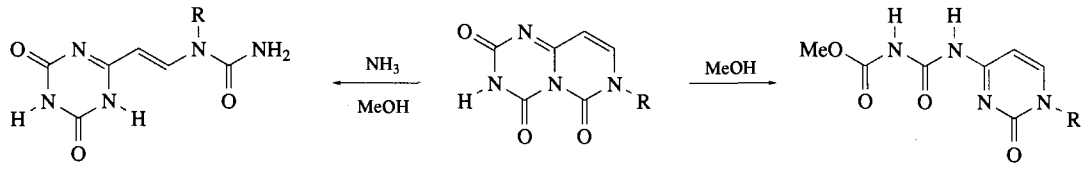
Bromination of 3-phenylpyridazino[2,3-*a*][1,3,5]triazine-2,4-dione (**42**) (Equation (4)) resulted in (**43**) ⟨72JOC2960⟩. The hydrolysis of (**44**) in DMF/H_2O resulted in the opening up of the triazine ring in preference to the pyrimidine ring (Equation (5)) ⟨85JOC2474⟩. Similar ring opening during the methanolysis of (**45**) (Scheme 2) gave (**46**) ⟨88JOC3959, 89T467⟩. Interestingly, the treatment of (**45**) with methanolic ammonia solution (Scheme 2) resulted in the opening up of pyrimidine ring leading to (**47**).



(42) (43) (4)



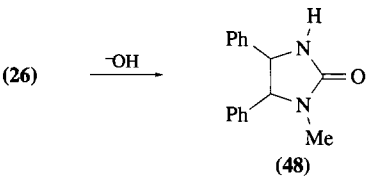
(44) (5)



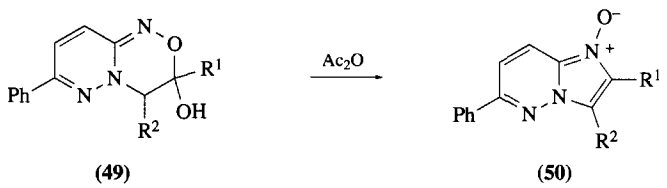
(47) (45) (46)

Scheme 2

The treatment of pyrazino[1,2-*a*][1,3,5]triazine-4,9-dione (**26**) with alkali (2N NaOH) (Equation (6)) resulted in its degradation to imidazoline (**48**) ⟨75T533⟩. Pyridazino[6,1-*c*][1,2,4]oxadiazine (**49**), when heated in acetic anhydride, resulted in ring contracted (**50**) (Equation (7)) ⟨83CPB3811⟩.



(26) (48) (6)



(49) (50) (7)

8.27.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

No information is available regarding the reactivities of substituents attached to ring carbon atoms.

8.27.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

There are reactions of substituents attached to ring heteroatoms.

8.27.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Synthesis of these compounds are not discussed under this section, but below.

8.27.10 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS

The known reports concerning the synthesis of bicyclic ring function nitrogen heterocycles containing three additional heteroatoms are divided into three categories. In category 1, the parent molecule is a heterocyclic ring containing two heteroatoms. In category 2, the parent heterocyclic ring has three heteroatoms, and other synthetic methods fall in category 3.

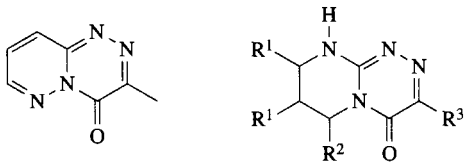
8.27.10.1 Synthesis from Heterocycles Containing Two Heteroatoms

8.27.10.1.1 Synthesis from hydrazino intermediates

The use of a hydrazino group attached to different heterocycles having two heteroatoms was successfully explored for the synthesis of various bicyclic systems having bridgehead nitrogen atoms ⟨72AC(R)647, 78H(9)1571, 80JOC3919, 83GEP3146299, 84GEP3302413, 84LA1302, 85JAP59206363, 85MIP125777, 92PS(72)145⟩. 4*H*-Pyrazino[2,1-*c*][1,2,4]triazines (**52**) were synthesized by treatment of 2-hydrazinopyrazine (**51**) with bromoketones (Equation (8)). Similarly, pyridazino[6,1-*c*][1,2,4]triazine (**53**), pyrimido[2,1-*c*][1,2,4]triazine (**54**), [1,3]thiazino[2,3-*c*][1,2,4]triazine (**12**), and 9*a*4*H*-pyrimido[6,1-*c*][1,2,4]triazine (**7**) were obtained from their corresponding hydrazino derivatives.



(51) (52) (8)

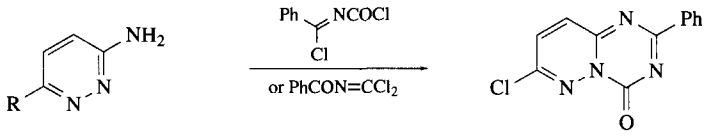


(53) (54)

8.27.10.1.2 Synthesis from amino intermediates

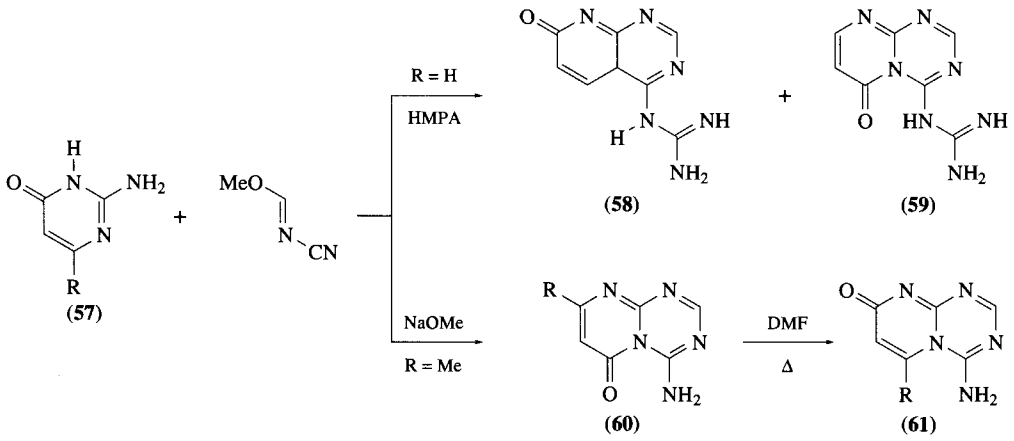
The reaction of 3-amino-6-chloropyridazine (**55**) with either *N*-(phenylchloromethylene)carbamic acid chloride or benzoyl isocyanide dichloride formed 2-phenylpyridazino[2,3-*a*][1,3,5]triazine-4-one (**56**) in moderate yield (Equation (9)) ⟨72JOC2960⟩. Substituted aminopyridazines on reaction

with PhO_2CNCO gave mesoionic pyridazino[2,1-*b*][1,2,4]triazine-2,4-diones ⟨76JPS1505⟩. The [1,2-*a*] and [1,6-*a*]pyrimidotriazines (**58**), (**59**), (**60**), and (**61**) were prepared from 2-aminopyrimido-4-ones (**57**) and methyl *N*-cyanoformimidate in HMPA and sodium methoxide (Scheme 3) ⟨85JOC2474⟩. Cytosine, cytidine, and isocytosine were shown to undergo similar reactions with methyl *N*-cyanoformimidate yielding various pyrimido[1,6-*a*][1,3,5]triazines (Equation (10)) ⟨81JOC1457⟩. Various carbonyl isocyanates or isothiocyanates ⟨70LA(742)85, 74JOC1819, 88JOC3959⟩ were also used as building blocks for the synthesis of pyrimido[1,6-*a*][1,3,5]triazine-2,4,6-triones such as (**62**) and of [1,3]thiazino[3,2-*a*][1,3,5]triazine-8-one(thione)s (**64**) from thiazine (**63**) (Equations (10) and (11)) respectively.

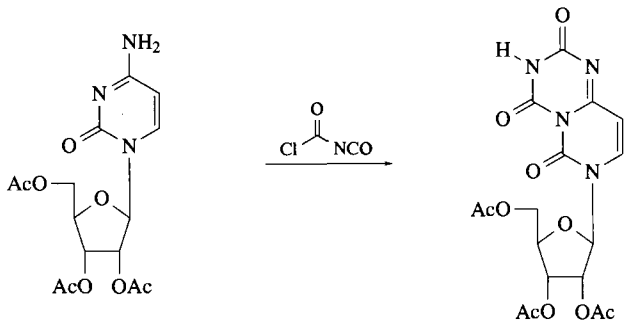


(9)

(55) (56)

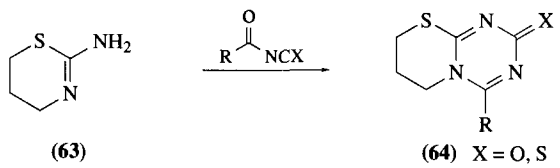


Scheme 3



(10)

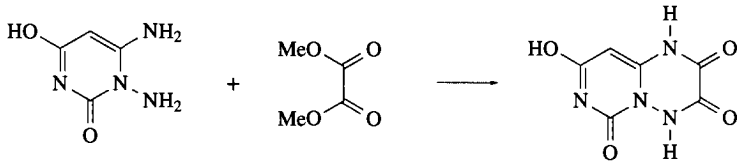
(62)



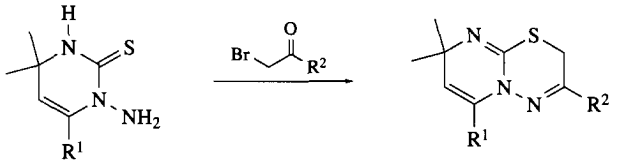
(11)

(63) (64) X = O, S

1,6-Diaminopyrimidines or 1-aminopyrimidine-2-thiones were found to be suitable molecular fragments for the synthesis of heterocycles. Thus, 1,6-diamino-2-oxo-4-hydroxypyrimidine (**65**) underwent cyclocondensation with dimethyl oxalate yielding 8-hydroxy-2*H*,3*H*,6*H*-pyrimido[1,6-*b*][1,2,4]triazine-2,3,6-trione (**66**) (Equation (12)) ⟨85JHC1317⟩. Similarly, the reactions of the 2-thione (**67**) with haloketones gave pyrimido[2,1-*b*][1,2,4]thiadiazines (**68**) (Equation (13)) ⟨71IJC404⟩.

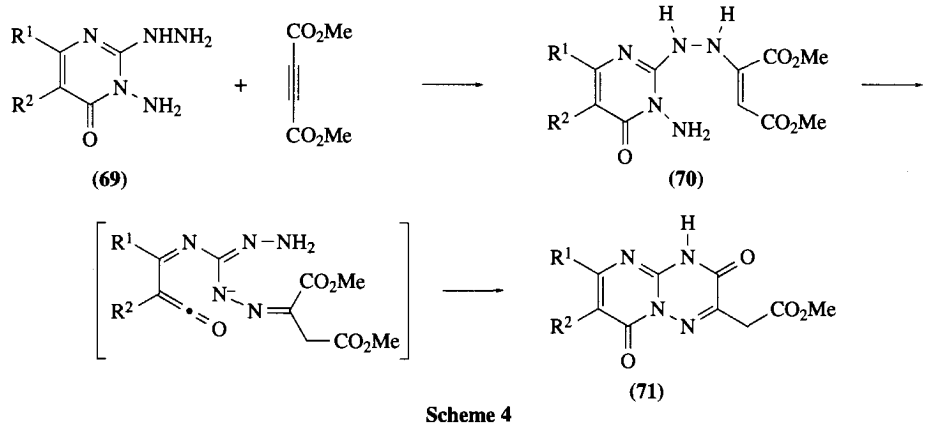


(65) (66) (12)



(67) (68) (13)

An unusual example of synthesis of pyrimido[1,2-*b*][1,2,4]triazine (**71**) involved the reaction of 1-amino-2-hydrazinopyrimidine-6-ones (**69**) with DMAD. The hydrazone intermediates (**70**) when heated under reflux in acetic acid underwent an interesting ring opening/reclosure resulting in the synthesis of pyrimido[1,2-*b*][1,2,4]triazine (**71**) (Scheme 4) ⟨88JHC739⟩.

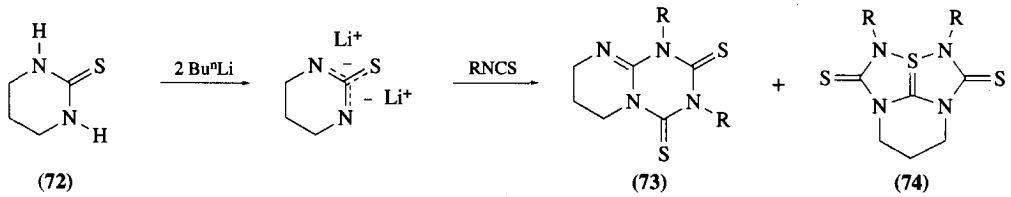


(69) (70) (71)

Scheme 4

8.27.10.1.3 Synthesis using other intermediates

The lithium dianion of cyclic thiourea (**72**) when reacted with alkyl isothiocyanates led to the formation of 7,8-dihydro-1,3-dimethyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-2,4(1*H*,3*H*)dithiones (**73**) and 3,4-dimethyl-1,6-propano-1*H*,6*H*-3a-thia(S^{iv})-1,3,4,6-tetraazapentalene-2,5(3*H*,4*H*)-dithione (**74**) (Scheme 5) ⟨86BCJ3693⟩.

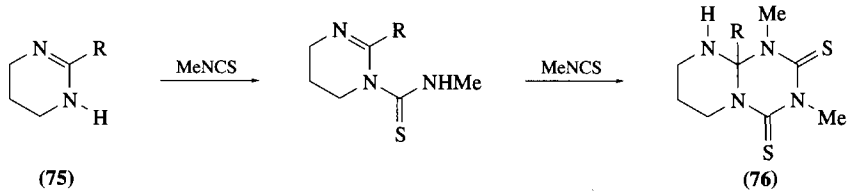


(72) (73) (74)

Scheme 5

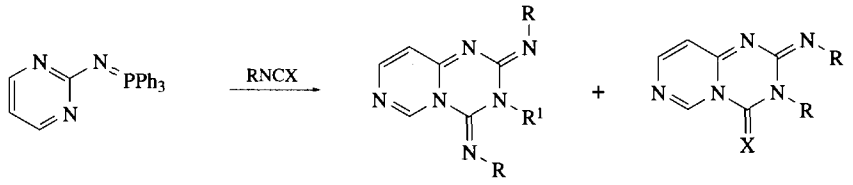
Pyrimidines (**75**) on cyclocondensation with two moles of isocyanates/isothiocyanates resulted in pyrimido[2,1-*b*][1,3,5]triazine derivatives (**76**) (Scheme 6) ⟨71G569, 84H(22)501⟩. Pyrimidinyl iminotriphenylphosphine (**77**) when treated with isocyanate or isothiocyanate led to carbodiimides

which could not be isolated as monomers and behaved chiefly as 1,3-diazabutadienes giving dimeric cycloadducts (**78**) and (**79**) (Equation (14)) ⟨83JPR463⟩.



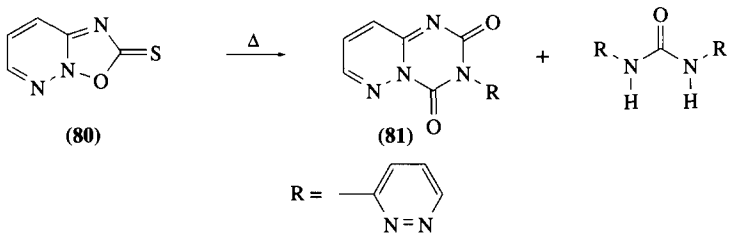
(**75**) (**76**)

Scheme 6



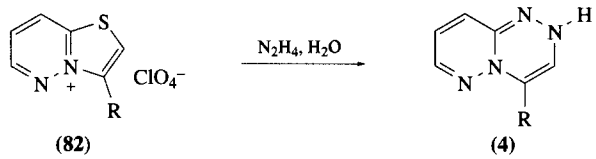
(**77**) (**78**) (**79**) (14)

Thermal decomposition of 2*H*-[1,2,4]oxadiazolo[3,2-*b*]pyridazine-2-thione (**80**) resulted in the formation of 3-(3-pyridazinyl)-2*H*-pyridazino[1,6-*a*][1,3,5]triazin-2,4(3*H*)-dione (**81**) and 1,3-di(3-pyridazinyl)urea (Equation (15)) ⟨79H(12)917, 80CPB3570⟩.

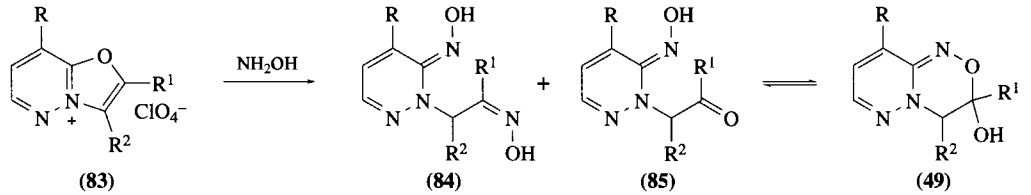


(**80**) (**81**) (15)

Treatment of thiazolo[3,2-*b*]pyridazinium perchlorate (**82**) with hydrazine hydrate gave various products along with pyridazino[6,1-*c*][1,2,4]triazine (**4**), as one of the products (Equation (16)) ⟨81CL1153, 83YZ399⟩. Similar reaction with oxazolo/thiazolo systems resulted in the corresponding pyrimido[2,1-*c*][1,2,4]triazine-5-ones ⟨74BRP1331059⟩. The oxazolo[3,2-*b*]-pyridazinium perchlorate (**83**) gave two products (**84**) and (**85**) with hydroxylamine (Scheme 7). The NMR spectra of the products showed the presence of (**84**) and (**85**) whereas IR spectra indicated that (**85**) exists in the cyclic form (**49**) (Scheme 7) ⟨83CPB3811⟩. Carbethoxyacetamidine hydrochloride (**86**) in presence of excess of pyridine reacted with *N*-methylimino dicarbonyl chloride to form 9-ethoxycarbonyl-3,7-dimethyl-2,4,6,8-tetraoxo-1,3,4,6,8-hexahydro-2*H*-pyrimido[1,6-*a*][1,3,5]triazine (**89**), ⟨75S647⟩, presumably via intermediates (**87**) or (**88**) (Equation (17)).

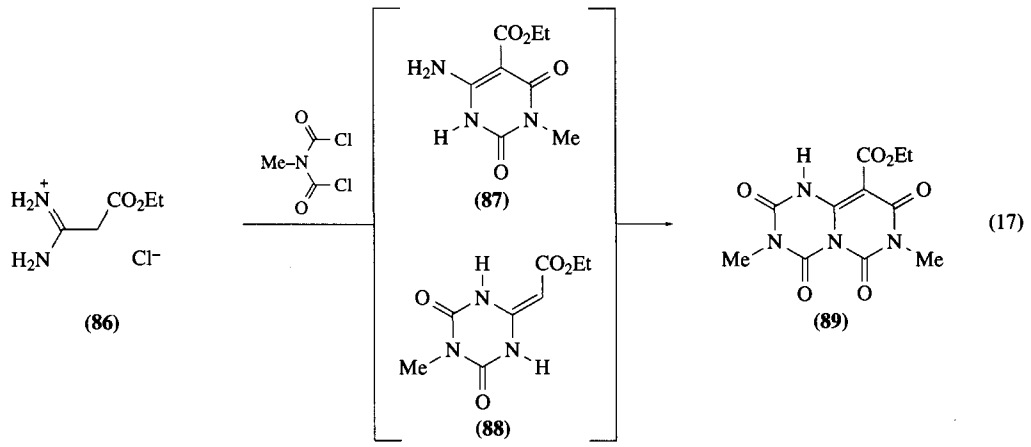


(**82**) (**4**) (16)



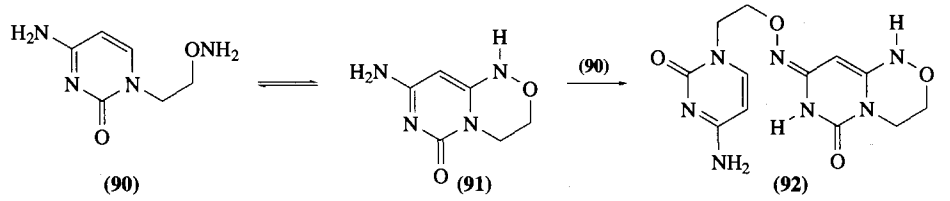
(**83**) (**84**) (**85**) (**49**)

Scheme 7

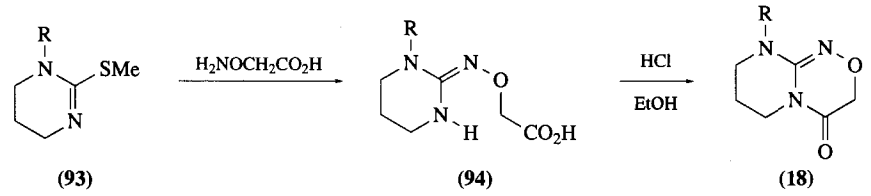


(17)

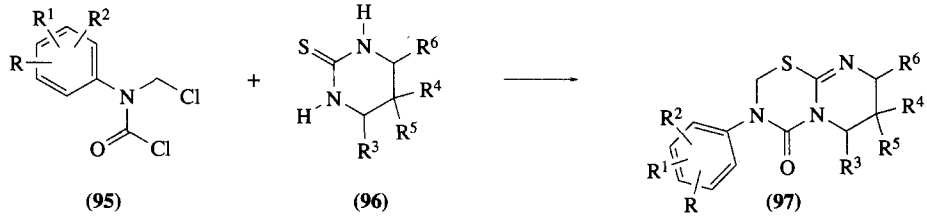
The intramolecular cyclocondensation of 1-(2-hydroxylaminoethyl) cytosine (**90**) gave pyrimido[2,1-*c*][1,2,4]oxadiazines (**91**) and (**92**) (Scheme 8) ⟨71JCS(C)867⟩. The attempted esterification of aminooxy acetic acid intermediate (**94**) led by ring closure to (**18**) (Scheme 9) ⟨70H(22)1879⟩. Some of the biologically active pyrimido[2,3-*b*][1,3,5]thiadiazines (**97**) were obtained from pyrimido-2-thiones (**96**) and *N*-aryl-*N*-chloromethylcarbamoylchlorides (**95**) (Equation (18)) ⟨83FRP2512450⟩.



Scheme 8



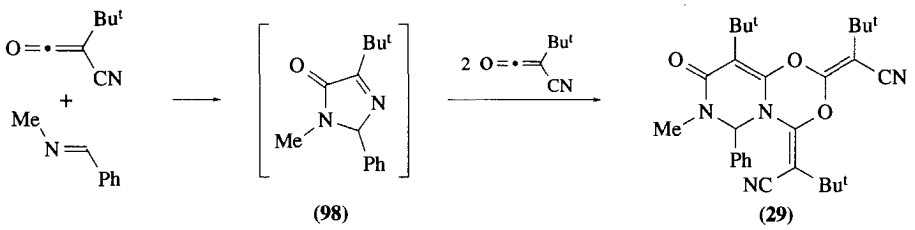
Scheme 9



(18)

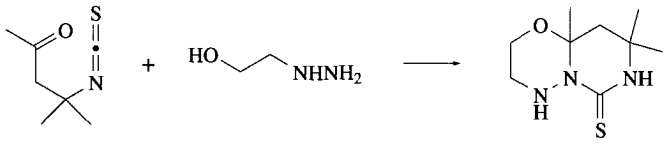
The unusual incorporation of the cyano group of *t*-butyl cyano ketene was observed in the reaction of an azomethine with excess of *t*-butyl cyanoketene resulting in pyrimido[6,1-*d*][1,3,5] dioxazine (**29**). It was said to proceed via an intermediate adduct (**98**), which further underwent [2 + 2 + 2] cycloaddition in the presence of two molecules of ketene (Scheme 10) ⟨78CC820⟩. 4-Isothiocyanato-4-methyl-2-pentanone and *N*-(2-hydroxyethyl)hydrazine in refluxing ethanol led to

formation of 7,8,9,10-tetrahydro-8,8,10-trimethyl -2*H*,6*H*-pyrimido[6,1-*b*][1,3,4]oxadiazin-6-thione (**20**) (Equation (19)) ⟨76M1241⟩.



(98) (29)

Scheme 10



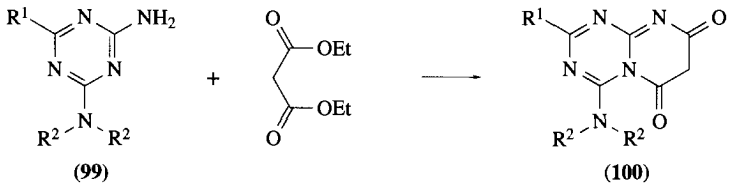
(20) (19)

8.27.10.2 Synthesis from Heterocycles Containing Three Heteroatoms

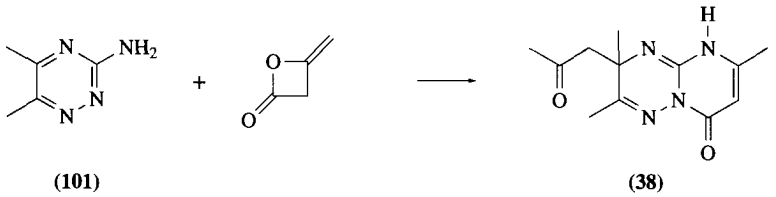
There are very few reports concerning the use of heterocycles containing three heteroatoms for the synthesis of target bicyclic systems.

8.27.10.2.1 Synthesis from aminotriazines

Pyrimido[1,2-*a*][1,3,5]triazine derivatives (**100**) were obtained by the condensation of the corresponding diaminotriazines (**99**) with diethyl malonate (Equation (20)) ⟨75GEP2450119⟩. The reactions of 3-amino-5,6-dimethyl-[1,2,4]triazine (**101**) with diketene gave substituted pyrimido[1,2-*b*][1,2,4]triazine (**38**) (Equation (21)) ⟨84H(22)1095⟩.

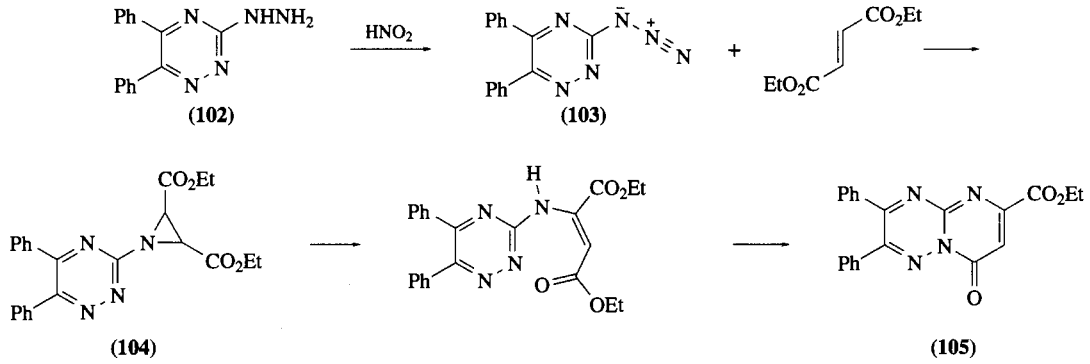


(99) (100) (20)



(101) (38) (21)

An interesting synthesis of pyrimido[1,2-*b*][1,2,4]triazine (**105**) involves 2-azidotriazine (**103**) (Scheme 11) ⟨83JIC475⟩, prepared by the nitrozation of 2-hydrazinotriazine (**102**). Heating a solution of (**103**) with diethyl fumarate in ethanol led to the formation of an aziridine intermediate (**104**), which on ring opening and further cyclisation yielded (**105**).

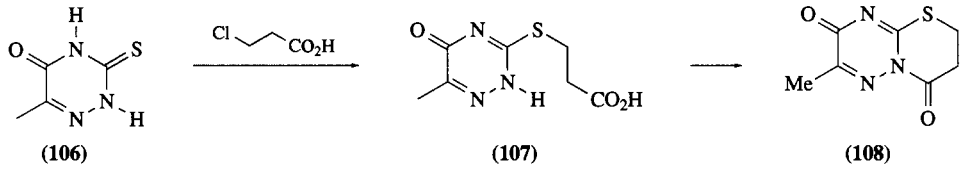


(102) (103) (104) (105)

Scheme 11

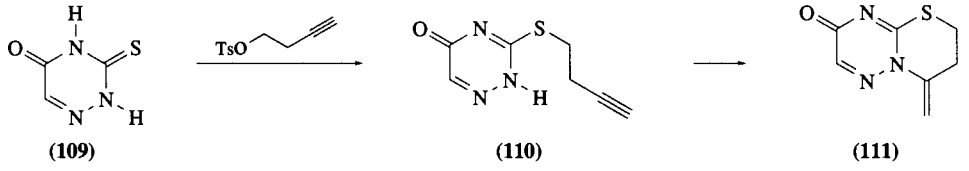
8.27.10.2.2 Synthesis from triazino-2-thiones

A number of 1,3-thiazinotriazinones (**108**) and (**111**) were prepared from triazino-2-thiones by cyclocondensation with suitable halo substrates (Scheme 12) ⟨68MI 827-01, 77IJC(B)46, 84MI 827-01⟩ or related system (Scheme 13) ⟨84H(22)1225⟩.



(106) (107) (108)

Scheme 12



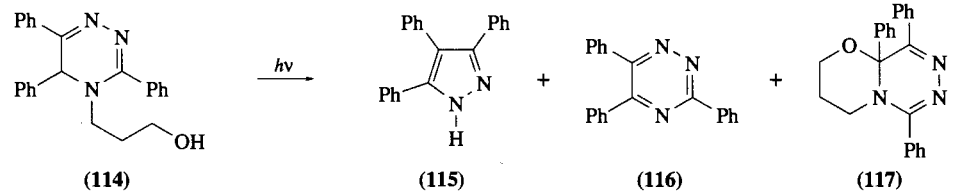
(109) (110) (111)

Scheme 13

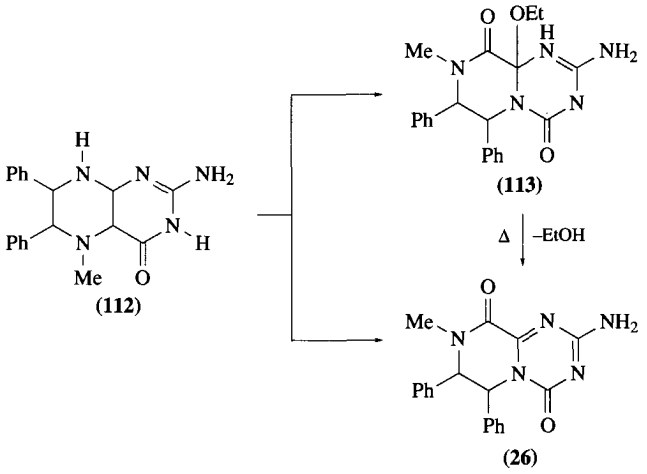
8.27.10.3 Other Synthetic Methods

Auto oxidation of 6,7-diphenyl-5-methyl-5,6,7,8-tetrahydropterin (**112**) in alcoholic phosphate buffer gave tetrahydro-4*H*,9*H*-pyrazino[1,2-*a*][1,3,5]triazine (**113**) and then (**26**) (Scheme 14). The auto-oxidation of (**113**) in water proceeded at an inconveniently slow rate, but was faster in alkali. Oxidation with $^{18}O_2$ in aqueous alkaline (H_2 ^{16}O) indicated the incorporation of heavy oxygen into the system ⟨75T541⟩.

The photolysis of 3-[3,5,6]-triphenyl-4,5-dihydro-1,2,4-triazin-4-yl]propan-1-ol (**114**) resulted in the formation of oxazino[3,2-*d*][1,2,4]triazine (**117**) along with some other products (**115**) and (**116**) (Equation (22)) ⟨88JCS(P1)3267⟩.

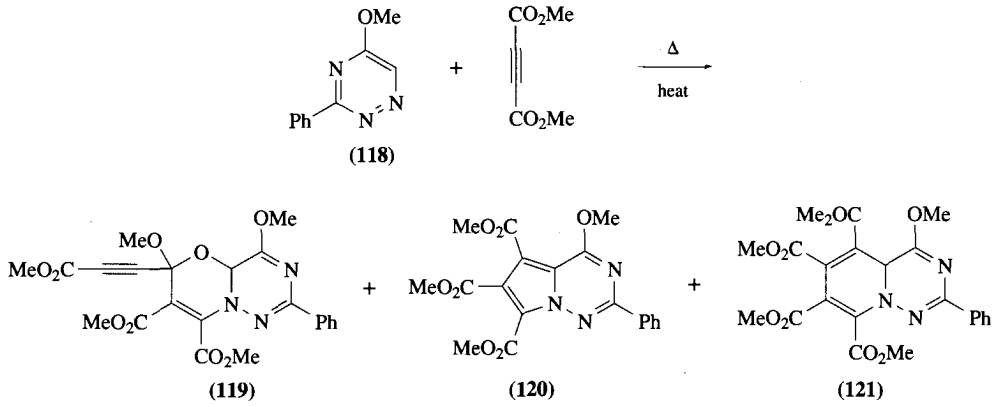


(114) (115) (116) (117) (22)



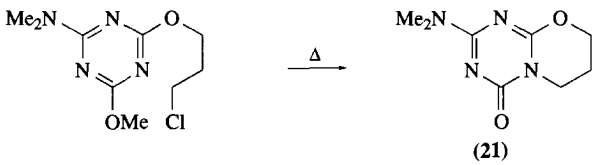
Scheme 14

Neat heating of 3-phenyl-5-methoxy-1,2,4-triazine (**118**) in the presence of dimethyl ethynedicarboxylate gave methyl 2,9-dimethoxy-3,4-bis(carbomethoxy)-7-phenyl[1,3]oxazino[2,3-*f*][1,2,4]-triazine-2-yl]propiolate (**119**) and other products (**120**) and (**121**) (Scheme 15) ⟨77LA1718⟩.



Scheme 15

Thermolysis of 2-methoxy-4-(3-chloro-1-propoxy)-6-dimethylamino-1,3,5-triazine resulted in the formation of [1,3]oxazino[3,2-*a*][1,3,5]triazine-4-one (**21**) (Equation (23)) ⟨80KGS411⟩.



(23)

8.27.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

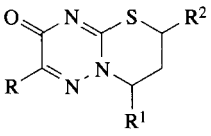
No examples were found suitable to carry out comparative study of these systems.

8.27.12 IMPORTANT COMPOUNDS AND APPLICATIONS

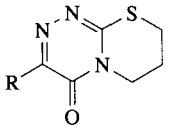
Many of these heterocyclic system are of biological importance but detailed information on their biological activities is still lacking.

The 1,3-thiazinotriazinones (**122**) and (**123**) have been found to be herbicidal in nature ⟨83GEP31463000, 84LA1302⟩. Some of the pyridazinotriazines (**124**) and (**125**) showed antimicrobial ⟨76JPS1505⟩, antiviral ⟨85MIP125777⟩, and antihypertensive ⟨85JAP59206363⟩ properties. Pyrimido[1,2-*a*][1,3,5]triazines (**100**) and (**126**) exhibited insecticidal ⟨75GEP2450119⟩ and fungicidal ⟨75GEP245893⟩ tendencies.

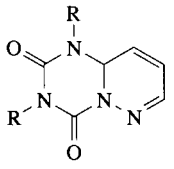
The 2-[bis(2-chloroethyl)amino]-2-oxo-3-oxa-7-thia-1-aza-2-phos-phabicyclo[4,4,0]decane (**127**) was found to be a potential antitumour agent with reduced toxicity.



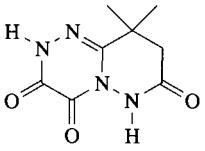
(**122**)



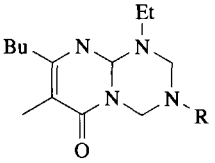
(**123**)



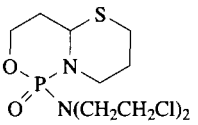
(**124**)



(**125**)



(**126**)



(**127**)

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8.28
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 3 : 1

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and

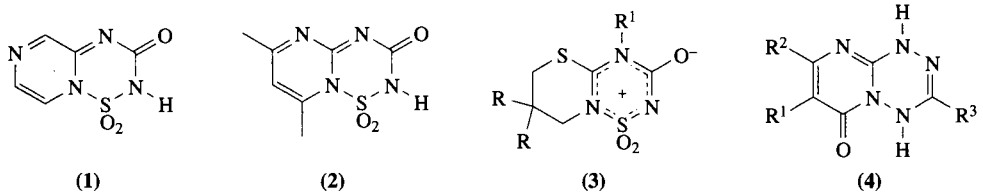
MOHINDER PAL MAHAJAN
Guru Nanak Dev University, Silchar, India

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8.28.1 INTRODUCTION

There are very few reports available concerning compounds with one-ring junction nitrogen atom and four extra heteroatoms (3 : 1). The systems known up to 1995 are pyrazino[1,2-*b*][1,2,4,6]-thiatriazine-3(2*H*)-one-1,1-dioxide (**1**), pyrimido[1,2-*b*][1,2,4,6]thiatriazine-3(2*H*)-one-1,1-dioxide

(**2**), mesoionic [1,2,4,6]thiatriazino[3,2-*b*][1,3]thiazine-4-one-1,1-dioxide (**3**) and 1,4-dihydro-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one (**4**).



(**1**) (**2**) (**3**) (**4**)

8.28.2 THEORETICAL METHODS

Theoretical methods have not been applied to such systems.

8.28.3 EXPERIMENTAL STRUCTURAL METHODS

X-ray crystallography studies on these compounds could not be found in the literature.

The ^{1}H NMR spectrum of (**4**) showed two NH protons at δ 9.3–9.8 ⟨87JOC2220⟩.

The compounds showed molecular ion peaks. The major fragmentation peaks observed for (**1**) were due to the loss of —NCO and —SO_2NH units ⟨79H815⟩.

Infrared spectral data of these compounds is not available. The UV spectrum of compound (**1**) showed absorption at 323 nm and 231 nm in methanol ⟨79H815⟩.

8.28.4 THERMODYNAMIC ASPECTS

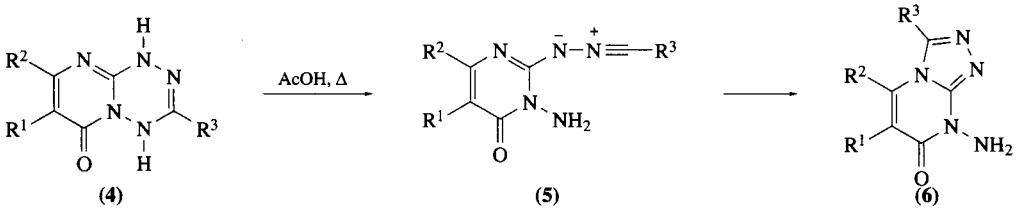
There is no information available concerning the molecular mechanical calculations and conformational aspects of these heterocycles.

8.28.5 REACTIVITY OF FULLY CONJUGATED RINGS

These heterocycles are not conjugated, and so no information could be provided here.

8.28.6 REACTIVITY OF NONCONJUGATED RINGS

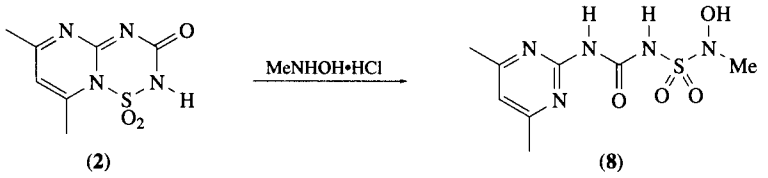
In contrast to the condensed thiatriazinedioxide (Chapter 8.26), the synthetic potential and reactivity of these thiatriazine derivatives has not been widely explored. Prolonged refluxing of (**4**) in acetic acid led to the cleavage of the tetrazine ring leading to nitrile imine intermediate (**5**). The intermediate (**5**) readily underwent intramolecular cyclization to 8-amino-1,2,4-triazolo[4,3-*a*]pyrimidin-7(8*H*)-ones (**6**) (Scheme 1) ⟨87JOC2220⟩.



(**4**) (**5**) (**6**)

Scheme 1

Pyrimido[1,2-*b*][1,2,4,6]thiatriazino-3(2*H*)-one-1,1-dioxide (**2**) was shown to undergo nucleophilic reaction with methyl hydroxyamine resulting in (**8**) (Equation (1)) ⟨85GEP3324802⟩.



(2) (8) (1)

8.28.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

No information about the reactivity of the substituents attached to ring carbon atoms is available.

8.28.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

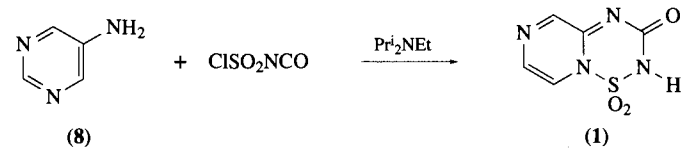
The synthetic utility of the substituents attached to ring heteroatoms has not been explored.

8.28.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

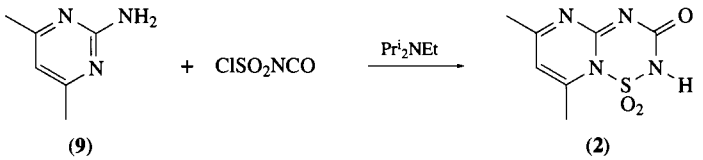
Ring Syntheses of these heterocycles can not be dealt with under this heading.

8.28.10 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS

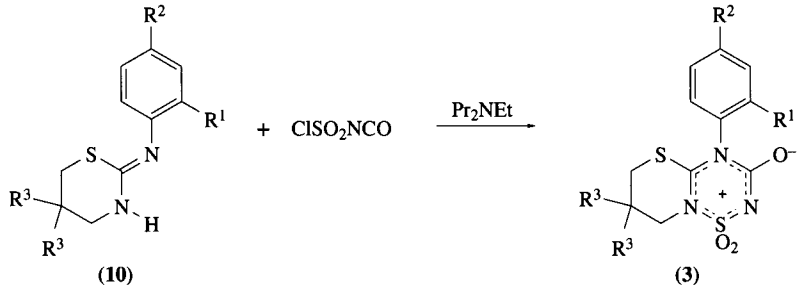
All the condensed thiatriazinedioxides (**1**)–(**3**) were prepared by cyclocondensation of 2-amino derivatives of appropriate heterocycles with chlorosulfonyl isocyanate in the presence of a base (Equations (2)–(4)) ⟨79H(6)815, 85GEP3324802, 88H(27)227⟩.



(8) (1) (2)

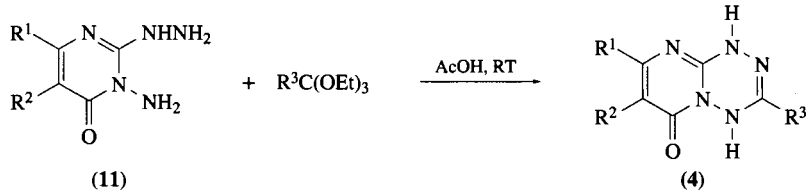


(9) (2) (3)



(10) (3) (4)

The pyrimido[1,2-*b*][1,2,4,5]tetrazines (**4**) were obtained from the cyclocondensation of 3-amino-2-hydrazine-4(3*H*)-pyrimidones (**11**) with an orthoester in the presence of acetic acid at room temperature (Equation (5)) ⟨87JOC2220⟩.



(11) (4) (5)

8.28.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

Examples of these compounds and information about their syntheses are too scarce to make a comparative study of them.

8.28.12 IMPORTANT COMPOUNDS AND APPLICATIONS

No relevant information concerning the applications of these heterocycles is available in the literature.

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8.29
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Four Extra Heteroatoms 2 : 2

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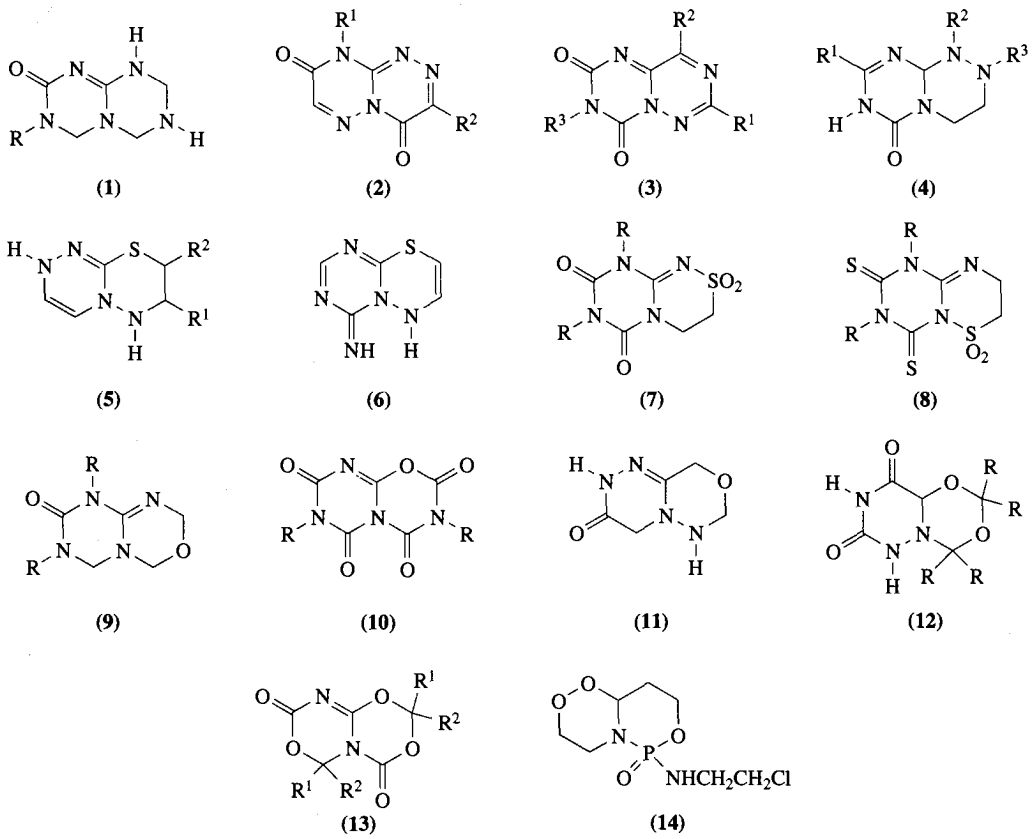
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8.29.1 INTRODUCTION

Bicyclic 6-6 systems with one nitrogen atom containing two additional heteroatoms in each ring are very scant in the literature. Among the various possible heterocycles, the available literature examples consist of the [1,3,5]triazino[1,2-*a*][1,3,5]triazine (**1**), [1,2,4]triazino[4,3-*b*][1,2,4]triazine (**2**), [1,3,5]triazino[2,1-*f*][1,2,4]triazine (**3**), [1,3,5]triazino[2,1-*c*][1,2,4]triazine (**4**), [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine (**5**), [1,3,5]triazino[2,1-*b*][1,3,4]thiadiazine (**6**), [1,3,5]triazino[2,1-*c*][1,2,4]thiadiazine-1,1-dioxide (**7**), [1,3,5]triazino[1,2-*b*][1,2,4]thiadiazine-1,1-dioxide (**8**), [1,3,5]triazino[1,2-*c*][1,3,5]oxadiazine (**9**), [1,3,5]triazino[2,1-*b*][1,3,5]oxadiazine (**10**), [1,2,4]triazino[4,3-*d*][1,3,4]oxadiazine (**11**), [1,2,4]triazino[6,1-*d*][1,3,5]dioxazine (**12**), [1,3,5]oxadiazino[3,4-*c*][1,3,5]dioxazines (**13**), and 6*H*, 8*H*-[1,2,4]dioxazino[4,3-c][1,3,2]oxazaphosphorine (**14**).



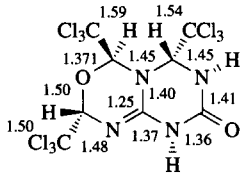
8.29.2 THEORETICAL METHODS

No reports are available concerning the application of theoretical methods to these molecules.

8.29.3 EXPERIMENTAL STRUCTURAL METHODS

8.29.3.1 X-ray Crystallography

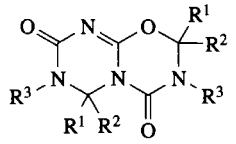
X-ray crystallographic studies have not been widely used to ascertain the structures of such systems. However, x-ray crystallographic data for (2S, 4S, 6R)-2,6,7,9-tetrahydro-2,4,6-tris(trichloromethyl)-8*H*-[1,3,5]triazin[1,2-*c*][1,3,5]oxadiazin-8-one (**15**) revealed that the dihedral angle between the planes of two rings is 10.4° ⟨82JOC3046⟩. The trichloromethyl groups exist in all axial alternating *trans* arrangement. The bond distance between the bridgehead carbon atom (C-6) and the nitrogen (N-3) of the oxadiazine ring is considerably shorter (1.29 Å) than that between C-6 and the nitrogen atom (N-2) of the S-triazine ring moiety (1.37Å) indicating a higher degree of double-bond character between C-6 and N-3 as compared with that between C-6 and N-2.



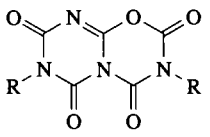
(15)

8.29.3.2 NMR Spectra

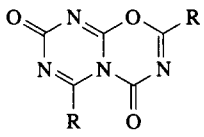
All the reported compounds were characterized by their ^1H NMR spectra. Due to the diversity of these heterocyclic systems, a comparison of their ^1H NMR spectra may not reveal any significant information. In a few cases, ^{13}C NMR spectra have also been used to ascertain the structures. The ^{13}C NMR spectra of different [1,3,5]-triazino[2,1-*b*][1,3,5] oxadiazines (**16**), (**17**), (**18**), and (**19**) are shown in the Table 1 ⟨86CB1133⟩.



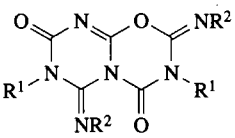
(16)



(17)



(18)



(19)

Table 1 Carbon-13 shifts (δ) for compounds (**16**) to (**19**).

Compounds	*R*	*R¹*	*R²*	*R³*	*C=O and ring carbons*	*Other carbons*
(16)		H	C_6H_5	CH_3	147.9/149.6, 153.2/153.9, 155.7/156.1, 69.1/69.3, 87.5/87.6	CH_3 31.3, 32.8, 33.2, 33.6
(16)		H	C_6H_5	$C(CH_3)_3$	148.1, 152.9, 156.2, 64.3, 84.5	CH_3 28.4, 29.0 C 57.5, 59.0
(16)		H	C_6H_5	$CH(CH_3)_2$	148.2, 152.9, 155.4, 64.3, 83.3	CH_3 19.8, 20.4, 20.7, 21.3 CH 47.7, 48.3
(16)		H	C_6H_5	c-C_6H_{11}	148.1, 152.7, 155.7, 63.7, 83.1	CH 54.8, 55.2
(16)		H	C_6H_5	C_6H_5	147.2, 153.1, 154.7, 70.1, 88.5	
(17)	$CH(CH_3)_2$				140.5, 141.5, 143.7, 150.8, 151.9	CH_3 18.7, 18.8, CH 49.0, 50.9
(17)	c-C_6H_{11}				140.7, 141.5, 143.9, 150.7, 151.9	CH_2 29.9, 25.2, 26.1, 26.2, 28.4, 28.6 CH 57.3, 59.0
(17)	$CH_2C(CH_3)_2$				143.3, 144.1, 145.9, 151.6, 153.3	CH_3 28.1, 28.4 CH_2 34.3, 34.5, C 53.4, 55.6
(17)	$CH_2CO_2C_2H_5$				142.4, 143.1, 145.0, 151.6, 152.1 (C=O), 166.6, 167.4	CH_3 14.3, 14.4 CH_2 44.2, 45.5, 62.3, 62.7
(17)	$CH_2C_6H_5$				142.9, 143.6, 145.3, 152.2 (2C)	CH_2 46.7, 48.5
(18)	$N(CH_3)_2$				145.2, 148.9, 153.5, 156.8	CH_3 36.9, 37.3, 37.4, 38.2
(19)		CH_3	$C(CH_3)_3$		123.0, 131.0, 145.1, 150.6, 154.3	CH_3 29.6 (3C), 30.2 (3C), 31.4, 32.4 C 54.8, 56.5
(19)		$CH(CH_3)_2$	$CH(CH_3)_2$		127.1, 131.9, 143.3, 150.6	CH_3 19.2, 23.4, 23.7 CH 47.6, 49.5, 50.6, 51.2
(19)	c-C_6H_{11}	c-C_6H_{11}			127.0, 131.9, 143.5, 150.6, 153.3.	CH 54.9, 57.9, 58.1, 59.1
(19)	$CH(C_6H_5)_2$	$CH(C_6H_5)_2$			129.5, 133.1, 143.0, 150.0, 153.2	

8.29.3.3 Mass Spectra

Mass spectra of these compounds, except for (**15**), displayed the corresponding molecular ion peaks ⟨82JOC3046⟩. The mass spectrum of (**18**) showed a weak molecular ion peak and peaks due to the fragmentation of different carbodiimide units. In some cases, loss of isocyanate units was also noticed ⟨86CB1133⟩. The electron impact mass spectrum of (**15**) ⟨82JOC3046⟩ showed the absence of molecular ion peak and an ion corresponding to 287 with a six-chlorine isotope pattern mass attributed to the loss of one CCl_3 group. Other significant losses observed were due to CCl_3CO, CCl_3CHO, CCl_3, and HCN. The chemical ionization mass spectrum showed a pseudomolecular ion at 505. Ions at m/z 469 (eight-chlorine isotope pattern) and 435 (seven-chlorine isotope pattern) were observed by field-desorption mass spectrometry.

8.29.3.4 IR Spectra

A change in the position of the oxygen atom in triazino-oxadiazines was found to greatly affect the carbonyl stretching frequency of the compound. For example, the carbonyl absorption for triazino[2,1-*b*][1,3,5]oxadiazine (**10**) was observed at 1780 cm^{-1} ⟨86CB1133⟩, whereas [1,3,5]triazino[1,2-*c*][1,3,5]oxadiazine (**9**) exhibited this absorption at 1690 cm^{-1} ⟨82JOC3046⟩. In the case of [1,3,5]triazino[2,1-*c*][1,2,4]thiadiazine-1,1-dioxide (**7**), carbonyl absorptions were observed at 1760 cm^{-1} and 1700 cm^{-1}. The C=N absorption for oxadiazines normally appeared around 1630 cm^{-1} ⟨82CB1133, 91JIC574⟩ and the appearance of an absorption peak at 1580 cm^{-1} for (**7**) was attributed to the SO_2 group.

8.29.3.5 UV Spectra

Ultraviolet spectral data for these compounds is not available.

8.29.4 THERMODYNAMIC ASPECTS

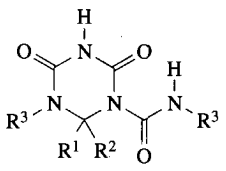
There are no references in the literature concerning conformational and thermodynamic aspects of these heterocycles.

8.29.5 REACTIVITY OF FULLY CONJUGATED RINGS

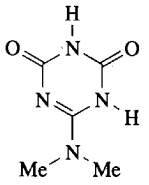
Compounds containing a bridgehead nitrogen atom along with other heteroatoms (e.g. O, S) at the ring site cannot be considered as fully conjugated. Hence no information is available under this heading.

8.29.6 REACTIVITY OF NONCONJUGATED RINGS

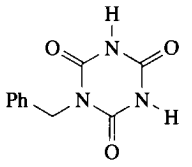
[1,3,5]Triazino[2,1-*b*] [1,3,5]oxadiazines were found to be highly sensitive to hydrolytic conditions ⟨86CB1133⟩. The compounds (**16**) and (**18**) underwent hydrolysis in aqueous solvent to the corresponding triazinediones (**20**) and (**21**). However, the hydrolysis of the N-benzyl derivative of (**18**) gave (**22**). The compounds (**7**), (**8**), and (**19**) in refluxing ethanol underwent ring opening leading to the ethoxy derivative of triazinones (**23**), (**24**), and (**25**).



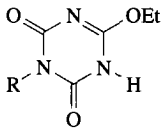
(20)



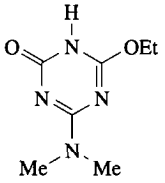
(21)



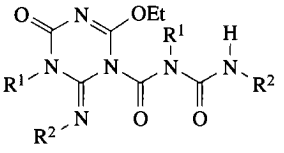
(22)



(23)



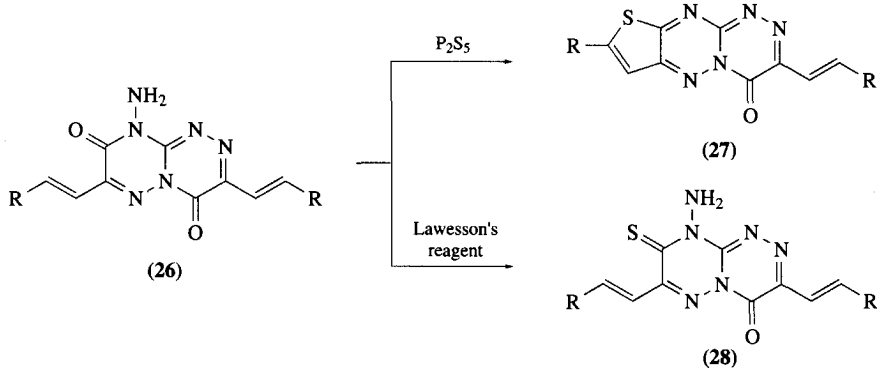
(24)



(25)

8.29.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

9-Amino-3,7-bis(styryl) [1,2,4]triazino[4,3-*b*][1,2,4]triazine-4,8-dione (**26**) on treatment with P_2S_5 underwent cyclocondensation leading to (**27**) (Scheme 1), but on the contrary the use of Lawesson's reagent gave the 8-thione (**28**) (Scheme 1) ⟨90SUL21⟩.



(26) (27) (28)

Scheme 1

8.29.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

No information regarding the substituents attached to any heteroatoms is available.

8.29.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

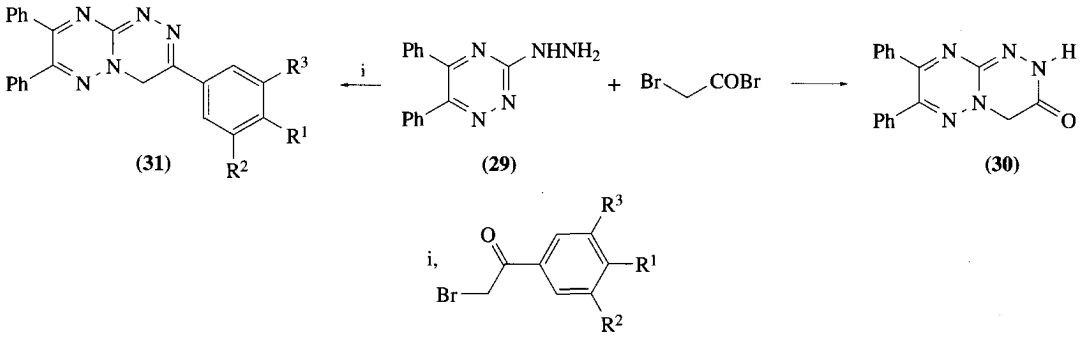
The bicyclic compounds discussed here are not classified in this category.

8.29.10 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS

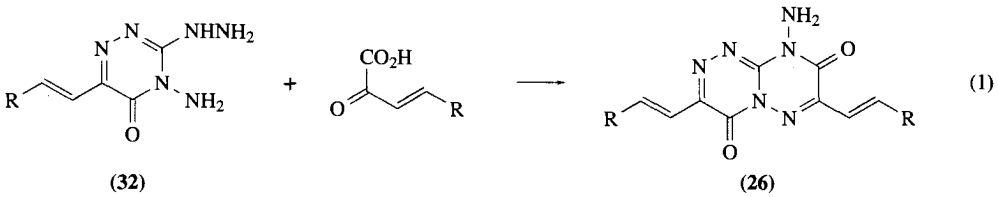
The triazine unit is the most frequently used building block for the syntheses of different condensed triazino heterocycles and the commonly used triazines for this purpose were either hydrazino- or aminotriazines.

8.29.10.1 From Hydrazinotriazines

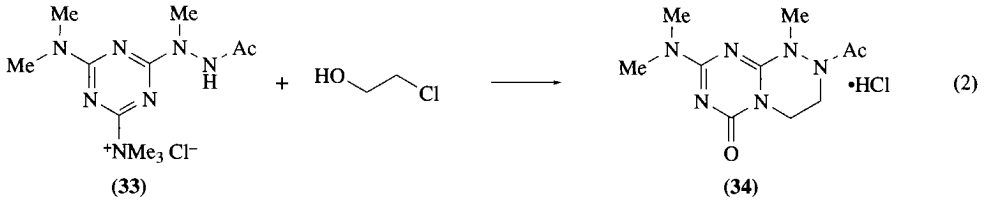
Most of the reported triazinotriazines have been prepared by this method. The reaction of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (**29**) with bromoacetyl bromide in ethanolic potassium hydroxide yielded 7,8-diphenyl-2*H*-[1,2,4]triazino[4,3-b][1,2,4]triazine-3(4H)-one (**30**) (Scheme 2) ⟨87IJC(B)1109⟩. Similar cyclocondensation of (**29**) with 3,4,5-trihydroxyphenacyl bromide led to the formation of 3-aryl-7,8-diphenyl-4*H*-[1,2,4]triazino[4,3-*b*][1,2,4]triazinones (**31**) ⟨87IJC(B)1109, 87JSC523, 89MI 829-01⟩. However, the reaction of 4-amino-3-hydrazino-1,2,4-triazine-5-ones (**32**) with arylidene pyruvic acids resulted in the formation of N-amino-[1,2,4]triazino[4,3-*b*][1,2,4]triazinones (**26**) (Equation (1)). Thermolysis of ammonium salt (**33**) (Equation (2)) with chlorohydrin led to the formation of [1,3,5]triazino[4,3-*c*][1,2,4]triazine (**34**) ⟨81KGS1125⟩.



Scheme 2



(1)

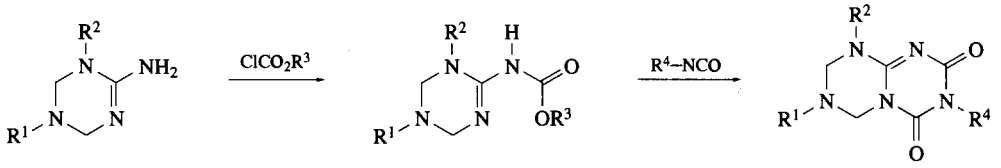


(2)

8.29.10.2 From Aminotriazines

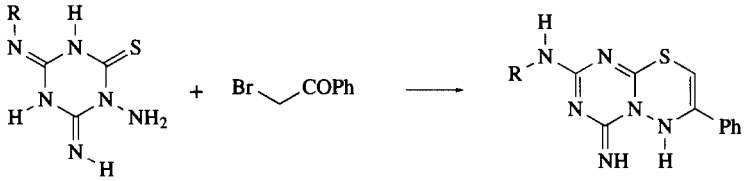
Aminotriazines, incorporating a guanidine or thiosemicarbazide unit, have proved to be important synthons in heterocyclic syntheses. [1,3,5]Triazino[1,2-*a*][1,3,5]triazines (**37**) were obtained by condensation of 2-amino-tetrahydrotriazines (**35**), a cyclic guanidine, with an alkyl chloroformate followed by cyclization with an isocyanate (Scheme 3) ⟨75GEP2451899⟩. 1-Amino-4-imino (or arylimino)-6-iminohexahydro-1,3,5-triazine-2-thione (**38**), prepared by the reaction of thiosemicarbazide and N-cyanoguanidine, on reaction with phenacyl bromide yielded 8-amino (or arylimino)-6-imino-3-phenyl-4*H*,6*H*-triazino[2,1-*b*][1,3,4]thiadiazine (**39**) (Equation (3)), ⟨76AJC1051⟩. Similar reaction of 4-amino-2,3,4,5-tetrahydro-3-thioxo-1,2,4-triazine-5-one (**40**) with α-halocarbonyl compounds gave the corresponding [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazines (**41**) (Equation (4)) ⟨68MI 829-01⟩. Isocyanate dimer (**43**), an interesting intermediate, has been utilized

for the synthesis of [1,3,5]triazino[2,1-*f*][1,2,4]triazine derivatives (**45**) from 6-amino-5-methylthio-1,2,4-triazines (**42**) via compound (**44**) (Scheme 4) ⟨85LA857⟩.

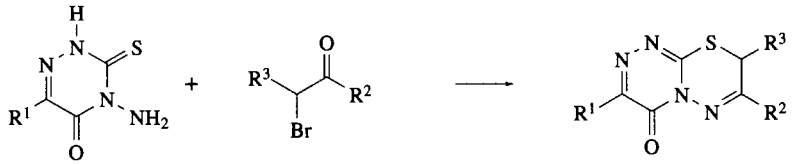


(35) (36) (37)

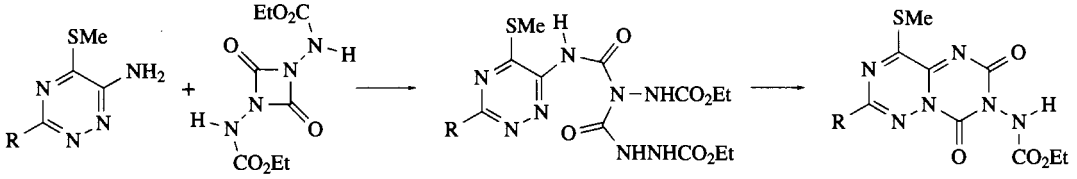
Scheme 3



(38) (39) (3)



(40) (41) (4)

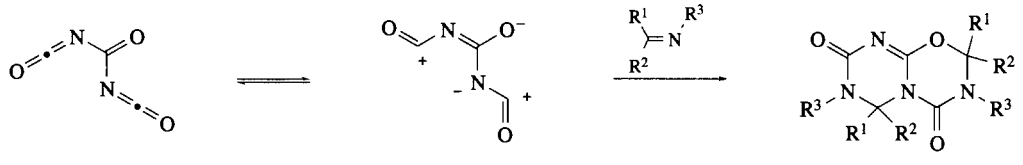


(42) (43) (44) (45)

Scheme 4

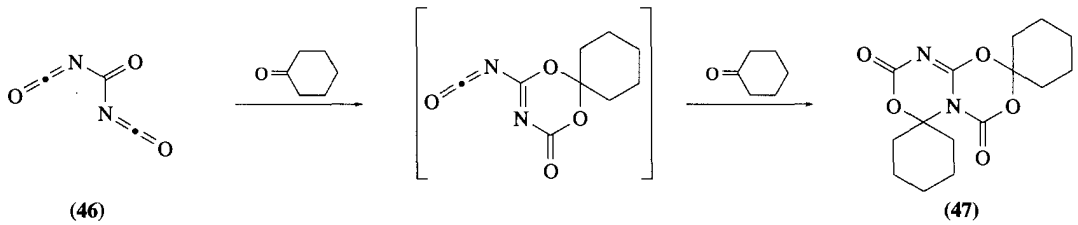
8.29.10.3 By Other Methods

Carbonyl diisocyanate (**46**) was shown to undergo a Diels–Alder type of cycloaddition with azomethines to give 2,3,6,7-tetrahydro-4*H*,8*H*-[1,3,5]triazino[2,1-*b*][1,3,5]oxadiazin-4,8-diones (**16**) (Scheme 5). A large variety of the triazino[2,1-*b*][1,3,5]oxadiazines were realized by the suitable selection of dienophiles. Thus, 1,3,5-triazino[2,1-*b*][1,3,5]oxadiazines (**17**), (**18**; R = NMe), and (**19**) and were synthesized by the reaction of carbonyl diisocyanate with alkyl or aryl isocyanates, dimethyl cyanamide, or aliphatic carbodiimides, respectively ⟨86CB1133⟩. Due to the high reactivity of the cumulated double bonds, carbonyl diisocyanate (**46**) was also found to undergo [4 + 2] cycloadditions with cyclohexanone to yield cyclohexan-1-spiro-9′-[1,3,5]-oxadiazino-[3,4-*e*][1,3,5]-dioxazin-5′ -spiro-1″-cyclohexane-2′,7′-dione (**47**) (Scheme 6) ⟨76LA1634⟩.



(46) (16)

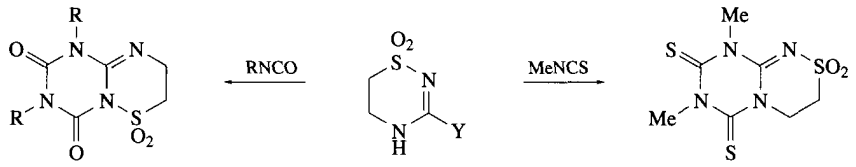
Scheme 5



(46) (47)

Scheme 6

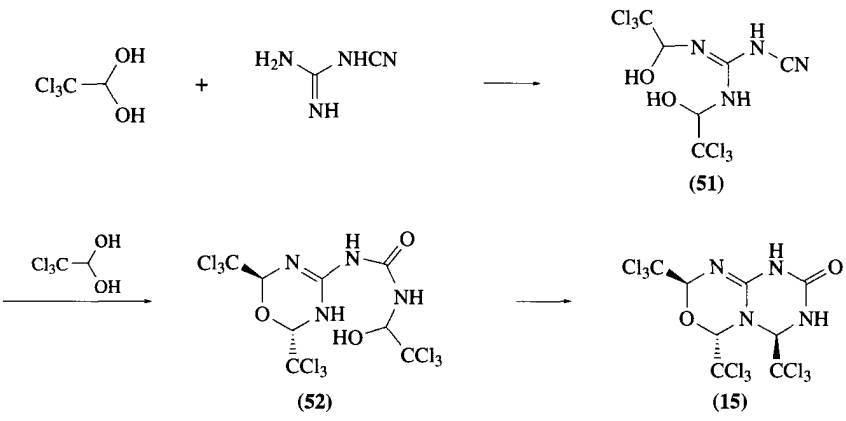
[1,2,4]Triazino [2,1-*c*][1,2,4]-thiadiazine-1,1-dioxide (**49**) was prepared by condensing thiadiazine-1,1-dioxide (**48**) with isocyanates, whereas [1,3,5]triazino[1,2-*b*][1,2,4]thiadiazine-1,1-dioxide (**50**) was obtained by the reaction of thiadiazine derivatives with methyl isothiocyanate (Scheme 7) ⟨74BSF1917⟩.



(49) (48) (50)

Scheme 7

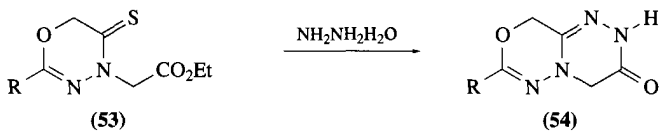
It was observed that 4-amino(substituted)-2,6-bis(trichloromethyl)-6*H*-[1,3,5]oxadiazine (**52**) or its hydrochloride underwent thionyl chloride assisted cyclization leading to good yields of (2S, 4S, 6R)-2,6,7,9-tetrahydro-2,4,6-tris(trichloromethyl)-8*H*-[1,3,5]triazino[1,2,-*c*][1,3,5]oxadiazine-8-one (**15**) (Scheme 8) ⟨82JOC3046⟩.



(51) (52) (15)

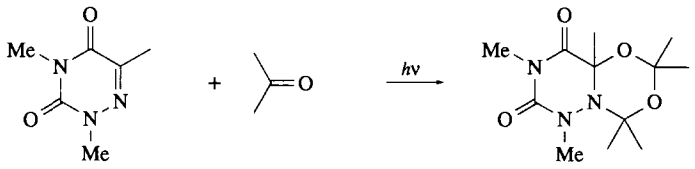
Scheme 8

Cyclocondensation of ethyl 5,6-dihydro-2-aryl-4*H*-[1,3,4]-oxadiazin-5-thione-4-acetates (**53**) with hydrazine hydrate gave [1,2,4]-triazino [4,3-*d*][1,3,4]oxadiazines (**54**) (Equation (5)) ⟨91JIC574⟩.



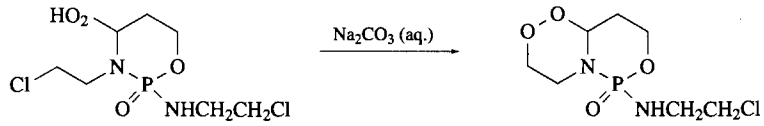
(53) (54) (5)

The photochemical reaction of azathymine derivative (**55**) with acetone afforded the [1,2,4]triazino[6,1-*d*][1,3,5]dioxazine (**56**) (Equation (6)) ⟨89MI 829-02⟩. This reaction involved the formation of a biradical via the reaction of the triplet state of acetone, which subsequently was trapped by another molecule of acetone.



(55) (56) (6)

Treatment of an oxazaphosphorine hydroperoxide with aqueous sodium carbonate led to the formation of 6*H*, 8*H*-[1,2,4]dioxazino[4,3-*c*][1,3,2]oxazaphosphorine (**14**) (Equation (7)) ⟨74JMC1237⟩.



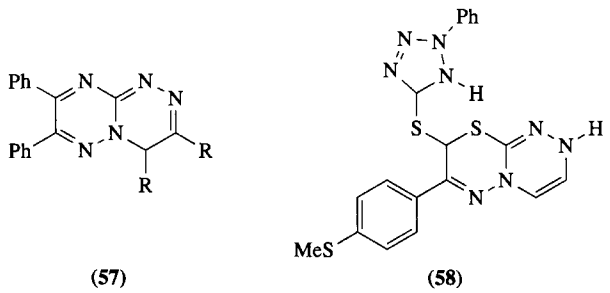
(14) (7)

8.29.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF VARIOUS ROUTES AVAILABLE

No worthwhile information could be obtained to report here.

8.29.12 IMPORTANT COMPOUNDS AND APPLICATIONS

The [1,3,5]triazino[1,2-*a*][1,3,5]triazine-2,4-diones (**37**) were found to be herbicidal ⟨75GEP2451899⟩ whereas many of the [1,2,4]triazino[4,3-*b*][1,2,4]triazines (**57**) showed antibacterial activities ⟨89MI 829-01⟩.



(57) (58)

The [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine (**58**) was found to be light sensitive in photographic recording and is used in producing photographic images ⟨82EUP45427⟩.

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8.30
Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Five Extra Heteroatoms 3 : 2

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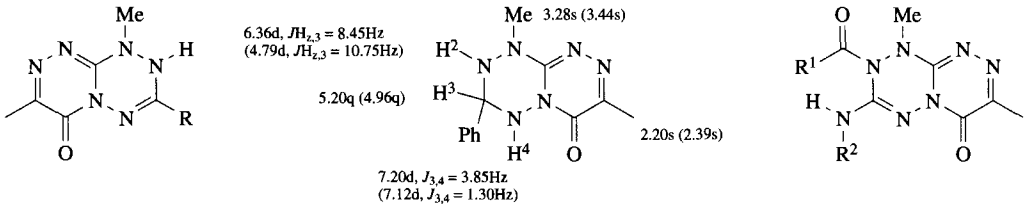
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8.30.1 INTRODUCTION

Only one such bicyclic 6-6 system, [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine, such as structure (**1**) has been reported in literature.



(1) (2) (3)

8.30.2 THEORETICAL METHODS

The theoretical studies on these molecules have not been reported.

8.30.3 EXPERIMENTAL STRUCTURAL METHODS

8.30.3.1 X-ray Crystallography

The structures of these molecules were not ascertained by x-ray crystallography.

8.30.3.2 NMR Spectra

The ^{1}H NMR spectra of (**1**; R = Ph) showed two singlets at δ 2.45 and 3.53 due to the carbon—methyl and nitrogen—methyl groups, respectively, whereas in the case of 3-substituted-1,2,3,4-tetrahydro-1,7-dimethyl-6-oxo-2*H*,4*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines (**2**), these signals appeared at δ 2.20 and 3.28, respectively ⟨88T2249⟩. The two NH and methine protons in the case of (**2**) appeared at δ 6.36 and 7.20, respectively and the 1- and 7-methyl protons for a similar system appeared at δ 3.38 and 2.34. The exocyclic NH proton of (**3**) varied with the substituent on nitrogen ⟨89JCS(P1)247⟩.

In order to ascertain the exact conformation of 3-phenyl-1,2,3,4-tetrahydro-1,7-dimethyl-6-oxo-2*H*, 4*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine (**2**), its ^{1}H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$. The enhancement of the signal at δ 6.36 ppm by irradiation of the nitrogen—methyl group, in the NOE experiments, revealed the presence of an AMX system comprising of protons H^2, H^3 and H^4 (δ_H (DMSO-d_6) values for these protons are indicated alongside structure (**2**) and the δ_H ($CDCl_3$) values are shown in parentheses). These spectra revealed that the —NH protons (H^2 and H^4) are well resolved and as narrow as the C—H proton (H^3), that the chemical shifts for protons H^2 are very sensitive to the nature of the solvent whereas chemical shifts for H^3 and H^4 do not show much variation on varying the solvent and that the vicinal coupling constants are sensitive to solvent variations.

8.30.3.3 Mass Spectra

The mass spectra of the compounds showed the molecular ion peaks. The other significant fragmentations observed were due to the loss of ArCHN, ArCN and Ar ⟨88T2249⟩.

8.30.3.4 IR Spectra

The infrared spectra of the compounds exhibited the amino N—H absorptions in the region of 2245–3177 cm^{-1} for (**2**) and 3296–3200 cm^{-1} for (**1**), and the carbonyl absorption for (**1**) and the exocyclic carbonyl group in case of (**3**) appeared at 1661 cm^{-1}.

8.30.3.5 UV Spectra

The UV spectral data for these compounds are not available.

8.30.4 THERMODYNAMIC ASPECTS

Based on the ^{1}H NMR and NOE experiments data, it was concluded that the tetrahydrotetrazine ring of 3-phenyl-1,2,3,4-tetrahydro-1,7-dimethyl-6-oxo-2*H*,4*H*-[1,2,4]triazino-[4,3-*b*][1,2,4,5] tetrazine (**2**) adopts a half-chair conformation (Figure 1). The ring is found to be more flattened in DMSO-d_6 than in $CDCl_3$ ⟨88T2249⟩.

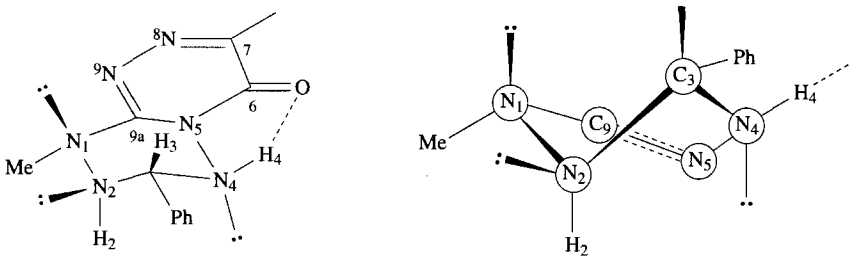


Figure 1 Conformation of compound (**2**).

8.30.5 REACTIVITY OF FULLY CONJUGATED AND NONCONJUGATED RINGS

Reactivities of these compounds have not been studied so far.

8.30.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Reactivities of substituents attached to ring carbon atoms have not been reported.

8.30.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

No information regarding this is available.

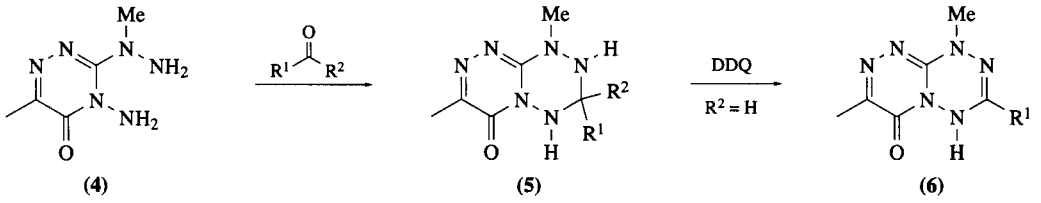
8.30.8 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

The synthesis of these heterocycles cannot be categorised in this way.

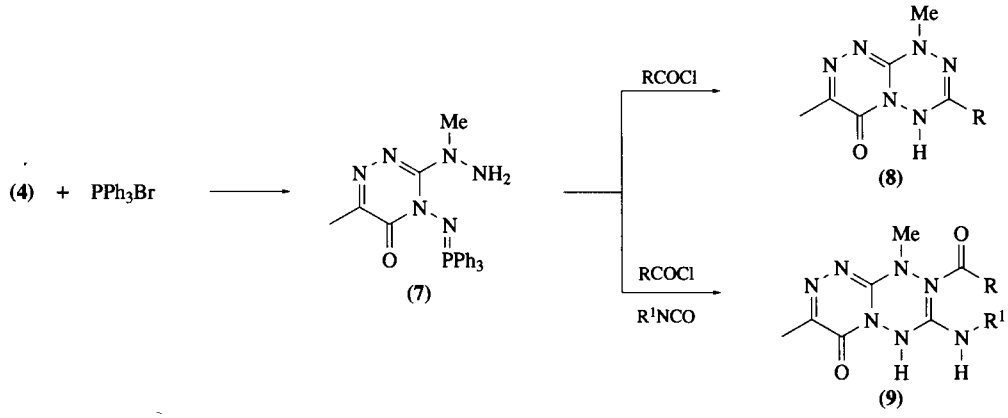
8.30.9 RING SYNTHESIS FROM DERIVATIVES OF ONE OF THE RINGS

The [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines reported ⟨88T2249, 89JCS(P1)247⟩ have been prepared from 4-amino-6-methyl-3(1-methylhydrazino)-5-oxo-4,5-dihydro[1,2,4]triazine (**4**). The cyclocondensation of triazine (**4**) with carbonyl compounds such as aldehydes, ketones and 1,2-dicarbonyl compounds in ethanol at reflux temperature gave the corresponding 1,2,3,4-tetrahydro [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines (**5**) (Scheme 1). The benzene solutions of these compounds on heating in presence of DDQ, gave the corresponding 1,4-dihydro[1,2,4]triazino[4,3-*b*][1,2,4,5]

tetrazines (**6**) ⟨88T2249⟩. The iminophosphorane (**7**) prepared from (**4**) and triphenylphosphine dibromide was found to undergo aza-Wittig reaction with aroylchorides ⟨88T2249⟩ and isocyanates ⟨89JCS(P1)247⟩, yielding (**8**) and (**9**) respectively (Scheme 2).



Scheme 1



Scheme 2

8.30.10 SYNTHESES OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

Because of the lack of extensive information a comparative study is not possible.

8.30.11 IMPORTANT COMPOUNDS AND APPLICATIONS

The applications of these compounds have not been reported.

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8.31
Bicyclic Systems with Two Ring Junction Nitrogen Atoms

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Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic

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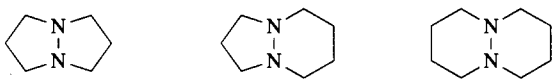
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8.31.1 INTRODUCTION

The first edition of *Comprehensive Heterocyclic Chemistry* published in 1984 has become an indispensable tool both for heterocyclic chemists and for others who require a truly comprehensive source of heterocyclic chemistry. The subject of this chapter is one of the rare parts of heterocyclic chemistry that were nearly completely neglected in the first edition. Some pieces of the subject are scattered throughout the respective volumes, but not enough to get thorough information about the area.

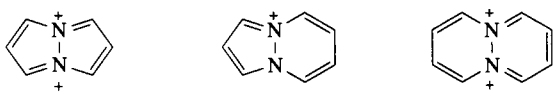
8.31.1.1 Survey of Possible Structures

This chapter deals with three main types of bicyclic heterocycles containing two ring junction nitrogen atoms, namely bicyclic 5-5, 5-6, and 6-6 ring fused systems which are depicted in their fully saturated forms as structures (**1**)–(**3**).



(**1**) (**2**) (**3**)

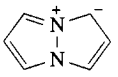
All of these basic heterocyclic types could be present in several degrees of saturation. The most unsaturated forms, that are fully conjugated, are their monocationic (6-5 bicyclic systems), or bicationic systems (5-5 and 6-6 bicyclic systems). It is evident that these species (**4**)–(**6**) have no neutral counterparts.



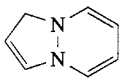
(**4**) (**5**) (**6**)

Mesomeric betaine structure (**7**) represents another degree of saturation. Use of the formula (**7**) is a simplification since no single structure can uniquely describe the bonding of mesomeric betaines and their true structure is a resonance hybrid of several dipolar structures ⟨77T3203⟩. Additional unsymmetrical substitution or aza substitution increases the number of possible distinct dipolar

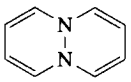
structures. There are other examples of mesomeric betaines with two ring junction nitrogen atoms not mentioned here that are treated accordingly in the respective subsections. The same degree of saturation as in mesomeric betaine (**7**) is present in structures (**8**) and (**9**) derived from structures (**5**) and (**6**), respectively. In contrast to mesomeric betaine structure (**7**), structures of compounds (**8**) and (**9**) can be described by uncharged covalent structures. A distinct group of these bicycles is represented by fully saturated compounds of general formulae (**1**)–(**3**). These groups of partially and fully saturated bicycles also include compounds having exomethylene, imino, and/or, most frequently, carbonyl groups on carbon atoms that have sp^3 hybridization in the parent bicycles.



(**7**)

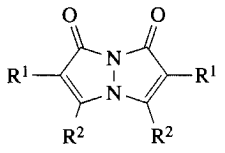


(**8**)

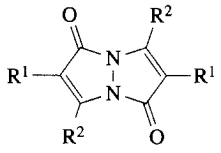


(**9**)

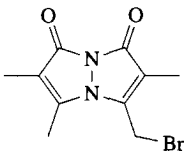
At this stage it is appropriate to include a brief note on nomenclature of the reviewed heterocyclic systems. Systematic heterocyclic nomenclature is routinely used for the most of the compounds in the current literature. For example, structures (**7**)–(**9**) are named pyrazolo[1,2-*a*]pyrazole, pyrazolo[1,2-*a*]pyridazine, and pyridazino[1,2-*a*]pyridazine, respectively. On the other hand, 5-5 bicyclic mesomeric betaines of this class are often treated as aza analogs of pentalene dianion and a numbering system based on the pentalene numbering is often adapted for these heteropentalenes. Similarly, fully saturated systems are usually treated as hetero analogs of the corresponding carbocyclic compounds and therefore for structures (**1**)–(**3**) the names 1,5-diazabicyclo[3.3.0]octane, 1,5-diazabicyclo[4.3.0]nonane, and 1,6-diazabicyclo[4.4.0]decane are used, respectively. Names such as perhydropyrazolo[1,2-*a*]pyrazole, perhydropyrazolo[1,2-*a*]pyridazine, and perhydropyridazino[1,2-*a*]pyridazine are sometimes alternatively used. Kosower has coined a special nomenclature ⟨78JA6516⟩ for 1,7-dioxo- and 1,5-dioxopyrazolo[1,2-*a*]pyrazoles which are termed *syn*- and *anti*-bimanes, respectively. Shorthand *syn*-(R^2,R^1)B and *anti*-(R^2,R^1)B is then used for structures (**10**) and (**11**), respectively. For compound (**12**), according to the bimane nomenclature called (BrCH_2,Me)(Me,Me)B, a trivial name bromobimane is used even in chemical catalogs.



(**10**)



(**11**)



(**12**)

Systematic heterocyclic nomenclature is used throughout the review except where the use of another type of nomenclature is more practical.

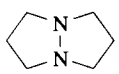
This introductory treatment has been done for structures containing only the two ring junction nitrogen atoms so far. It is evident that there is theoretically possible an enormous amount of corresponding hetero analogs containing additional heteroatoms in their structures. Due to the limited space, only structures containing nitrogen, oxygen and sulfur have been reviewed. It is not useful to try to mention all possible moieties and therefore only such bicyclic skeletons as are found in the literature with some of the possible degrees of saturation are mentioned in Figures 1–3. Benzo analogs of these bicyclic structures are also covered and in some cases only these analogs, and not the parent heterocycles, have been described. In all cases benzo analogs are mentioned in the subsections dealing with their parent bicyclic structures. Compounds in which the systems are embedded in more complex ring or cage structures have generally been excluded from consideration and are mentioned only where they have relevance to the reviewed subject.

8.31.2 THEORETICAL METHODS

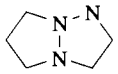
8.31.2.1 Semiempirical Methods

8.31.2.1.1 Heterocyclic cations

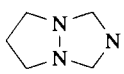
The electronic structure of monocation (**5**) and dication (**6**) has been investigated using semi-empirical CNDO/2 method ⟨69G1078⟩.



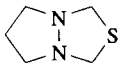
(1) pyrazolo[1,2-a]pyrazole



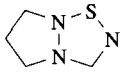
(13) pyrazolo[1,2-a][1,2,3]triazole



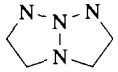
(14) pyrazolo[1,2-a][1,2,4]triazole



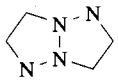
(15) pyrazolo[1,2-c][1,3,4]thiadiazole



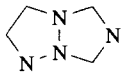
(16) pyrazolo[1,2-b][1,2,3,5]thiatriazole



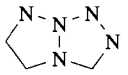
(17) 1,2,3-triazolo[1,2-a][1,2,3]triazole



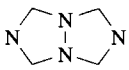
(18) 1,2,3-triazolo[2,1-a][1,2,3]triazole



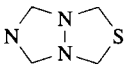
(19) 1,2,3-triazolo[1,2-a][1,2,4]triazole



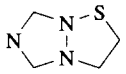
(20) 1,2,3-triazolo[1,2-a]tetrazole



(21) 1,2,4-triazolo[1,2-a][1,2,4]triazole



(22) 1,2,4-triazolo[1,2-c][1,3,4]thiadiazole



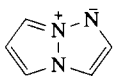
(23) 1,2,4-triazolo[1,2-b][1,2,3]thiadiazole

Figure 1 Nomenclature for bicyclic 5-5 systems with two ring junction nitrogens.

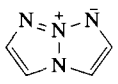
8.31.2.1.2 Conjugated mesomeric betaines

The prediction based on Hückel molecular orbital (HMO) calculations suggests that diazapentalenes of this type would be aromatic. For structure (7) an aromatic system with two electrons in a nonbonding orbital is suggested ⟨66JA1992⟩. Comparison of Hückel LCAO-MO calculations carried out with (7) with those of the pentalene dianion indicates that the increased coulombic attraction of the nitrogen atoms lowers the energy of certain of the molecular orbitals ⟨65JA528⟩. A similar study using the CNDO/2 method has also been reported ⟨69G1078⟩.

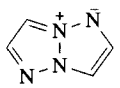
Compounds of the type **(51)**–**(53)** have a highlying HOMO and consequently a narrow gap between frontier molecular orbitals ⟨78TL1291⟩.



(51)



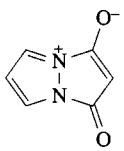
(52)



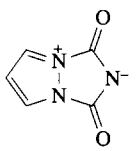
(53)

8.31.2.1.3 Cross-conjugated mesomeric betaines

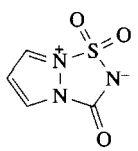
Several MO methods (MINDO/3 and Hückel procedures) have been used to evaluate theoretically this class of cross-conjugated mesomeric betaines, for example compounds **(54)**–**(57)** ⟨83H(20)23, 88JOC2898⟩.



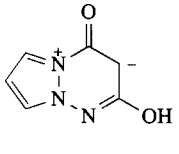
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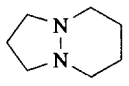
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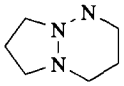
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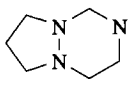
(57)



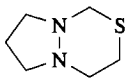
(2) pyrazolo[1,2-a]pyridazine



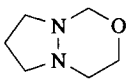
(24) pyrazolo[1,2-a][1,2,3]triazine



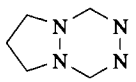
(25) pyrazolo[1,2-a][1,2,4]triazine



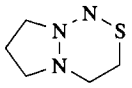
(26) pyrazolo[1,2-c][1,3,4]thiadiazine



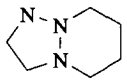
(27) pyrazolo[1,2-c][1,3,4]oxadiazine



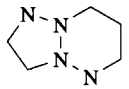
(28) pyrazolo[1,2-a][1,2,4,5]tetrazine



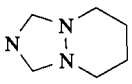
(29) pyrazolo[1,2-c][1,2,3,4]thiatriazine



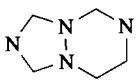
(30) 1,2,3-triazolo[1,2-a]pyridazine



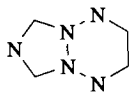
(31) 1,2,3-triazolo[2,1-a][1,2,3]triazine



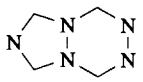
(32) 1,2,4-triazolo[1,2-a]pyridazine



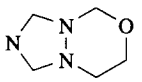
(33) 1,2,4-triazolo[1,2-a][1,2,4]triazine



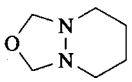
(34) 1,2,4-triazolo[1,2-b][1,2,3,4]tetrazine



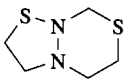
(35) 1,2,4-triazolo[1,2-a][1,2,4,5]tetrazine



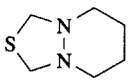
(36) 1,2,4-triazolo[1,2-c][1,3,4]oxadiazine



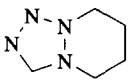
(37) 1,3,4-oxadiazolo[3,4-a]pyridazine



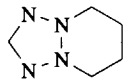
(38) 1,2,3-thiadiazolo[2,3-c][1,3,4]thiadiazine



(39) 1,3,4-thiadiazolo[3,4-a]pyridazine

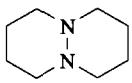


(40) tetrazolo[1,2-a]pyridazine

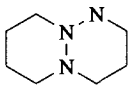


(41) tetrazolo[2,3-a]pyridazine

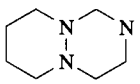
Figure 2 Nomenclature for bicyclic 5-6 systems with two ring junction nitrogens.



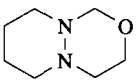
(3) pyridazino[1,2-a]pyridazine



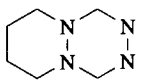
(42) pyridazino[1,2-a][1,2,3]triazine



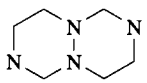
(43) pyridazino[1,2-a][1,2,4]triazine



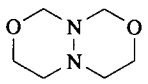
(44) pyridazino[1,2-c][1,3,4]oxadiazine



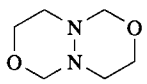
(45) pyridazino[1,2-a][1,2,4,5]tetrazine



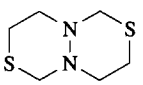
(46) 1,2,4-triazino[2,1-a][1,2,4]triazine



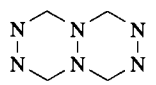
(47) 1,3,4-oxadiazino[3,4-c][1,3,4]oxadiazine



(48) 1,3,4-oxadiazino[4,3-c][1,3,4]oxadiazine



(49) 1,3,4-thiadiazino[4,3-c][1,3,4]thiadiazine

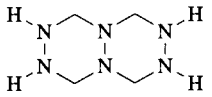


(50) 1,2,4,5-tetrazino[1,2-a][1,2,4,5]tetrazine

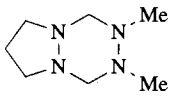
Figure 3 Nomenclature for bicyclic 6-6 systems with two ring junction nitrogens.

8.31.2.1.4 Fully saturated compounds

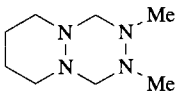
The conformations of (**1**)–(**3**) and (**58**)–(**60**) have been analyzed from their photoelectron spectra ⟨73AG410, 75CB1548, 75CB1557, 79CB853⟩. Quantum chemical calculations have been based on the MINDO/2 procedure ⟨75CB1557, 79CB853⟩. Semiempirical AM1 calculations of (**1**) and some of its derivatives have also been reported ⟨89JA5387⟩.



(**58**)



(**59**)



(**60**)

8.31.2.2 *Ab Initio* Calculations

8.31.2.2.1 Cross-conjugated mesomeric betaines

Ab initio calculations on (**54**) by STO-3G and 3-21G methods have been published ⟨88JOC2898⟩. Charge densities calculated by these methods have larger deviation than those calculated by semi-empirical methods.

8.31.3 EXPERIMENTAL STRUCTURAL METHODS

8.31.3.1 Infrared Spectroscopy

8.31.3.1.1 Conjugated mesomeric betaines

IR spectra of the parent diazapentalene (**7**) is simple with peaks at 3160(s), 1430, 1140, 1139(s), 1040, and 929(s) cm^{-1}, indicating a highly symmetrical structure ⟨66JA5588⟩. The carbonyl bands in the region of 1520–1585 cm^{-1} for the corresponding 1(3)-acyl-2-substituted derivatives of the parent compounds (**7**) and (**51**) indicate strong electron-donating character of the di- and triazapentalene rings ⟨65JA528, 78TL1291⟩.

8.31.3.1.2 Cross-conjugated mesomeric betaines

The cross-conjugated mesomeric betaines of this type show an intense carbonyl absorption in the range of 1670–1715 cm^{-1} and a shoulder on this absorption at 1725–1780 cm^{-1}. For example, the parent compound (**54**) has ν_{CO} 1745 cm^{-1} and 1695 cm^{-1} and the 5,6,7-trimethyl derivative of (**55**) has ν_{CO} at 1715 cm^{-1} and 1725 cm^{-1} ⟨88JOC2898⟩.

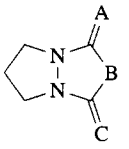
8.31.3.1.3 Partially saturated compounds

Bimanes represent the group of this class which has been studied most. Three bands are usually observed for the *syn*-isomers in the carbonyl region (1760–1790 cm^{-1}, 1735–1750 cm^{-1}, and 1660–1690 cm^{-1}) whereas *anti*-isomers show one strong band at 1680–1715 cm^{-1} often accompanied by a shoulder at 1735–1755 cm^{-1} ⟨80JA4983, 81JOC4578, 82JOC214⟩.

8.31.3.1.4 Fully saturated compounds

In the bicyclic systems under discussion, many IR spectra have been published but rarely complete assignments have been made. Selected published results of the 5-5 bicyclic systems are given as an example in Table 1.

Table 1 IR spectra of selected bicyclic 5-5 systems.



A	*B*	*C*	*ν (KBr)* (cm^{-1})	*Ref.*
S	S	S	3400, 1450, 1430, 1215, 1170, 1150 (C—N)	92PHA416
S	N-Me	S	3010, 1490, 1430, 1240, 1170, 1070 (C—N)	91PHA418
S	N-Ph	O	3400, 1730 (C=O), 1595, 1500, 1270 (C—N)	92PHA416
N-Ph	N-Ph	S	3260, 1590 (C=N), 1520, 1490, 1350 (C—N)	91PHA418
N-Ph	NH	NH	3280, 3120, 1670 (C=N), 1630, 1570 (NH), 1530, 1450, 1230 (C—N)	91PHA637

8.31.3.2 Ultraviolet Spectroscopy and Fluorescence

8.31.3.2.1 Conjugated mesomeric betaines

Because of the extreme ease with which the pyrazolo[1,2-*a*]pyrazole derivatives are oxidized in air, visible UV spectra of these simple compounds are difficult to obtain. It is necessary to use deoxygenated solvents to prevent oxidation by the dissolved oxygen. UV spectra of the parent compound (**7**) and its 2-bromo and 2-phenyl derivatives obtained thus have strong bands at 284 nm, 300 nm, and 244 nm, respectively ⟨66JA1992⟩. Bands in visible region reported earlier ⟨65JA5256⟩ are not present. Similarly, the 2-methyl derivative of (**51**) has a band at 285 nm (log $\varepsilon = 4.02$) ⟨78TL1291⟩. UV spectra of 1,3-diacetyl derivatives of (**7**) are much more complex with maxima at 219 (4.20), 223 (4.20), 322 (4.30) and 396 nm (log $\varepsilon = 4.50$) ⟨66JA5588⟩. Similarly, the 1-benzoyl-2-phenyl derivative of (**7**), having bands at 231 (4.44), 275 (4.14), 291 (4.02), and 400 (4.45), shows a broad absorption at 400 nm which correlates well with the prediction from LCAO-MO calculations ⟨65JA528⟩.

UV spectra of two possible isomeric dibenzo derivatives of (**52**) and (**53**) show many similarities and differences that have been noted ⟨51JCS3199⟩ between aromatic heterocycles and their carbocyclic analogs. Both compounds exhibit three main regions of absorption and in this respect they resemble benzophenanthrenes ⟨65JA528, 67JA2618⟩.

8.31.3.2.2 Cross-conjugated mesomeric betaines

The 2-phenyl-5,7-dimethyl derivative of (**54**) has a visible absorption maximum at 421 nm ⟨88JOC2898⟩. The UV spectra of derivatives of (**55**) are shifted significantly towards a shorter wavelength compared to the corresponding derivatives of (**54**). For example, the 5,6,7-trimethyl derivative of (**55**) has maxima at 233 nm (log $\varepsilon = 4.14$), 238.5 (4.14), and 288.5 (2.62) ⟨83H(20)23⟩.

8.31.3.2.3 Partially saturated compounds

1,7-Dioxopyrazolo[1,2-*a*]pyrazoles (*syn*-bimanes) have absorption spectra indicating three electronic transitions in the UV region, with either two bands and a shoulder or three bands. The largest wavelength absorption varies between 354 nm and 409 nm with log ε from 3.74 to 4.08 for dioxane solutions, for example for *syn*-(H,H)B λ_{max} 368 nm (log $\varepsilon = 3.79$). *anti*-Isomers without conjugating substituents show only one absorption band, the absorption maxima are more intense and invariably

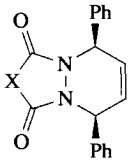
at considerably shorter wavelengths than those of the corresponding *syn*-compounds, with positions ranging from 317 nm to 354 nm and log ε between 4.04 and 4.27 ⟨80JA4983, 81JOC4578, 82JOC214, 83MI 831-01, 84CPB930, 86JA4527⟩. An ester group at the β-position and/or halogen at the α-position moves absorption maximum to longer wavelengths. The compound which shows the largest wavelength absorption maximum is *syn*-(CO_2Et,I)B, with maximum at 415 nm (log ε = 4.11) ⟨82JOC214⟩.

syn-Bimanes are strongly fluorescent with emission maxima 388–495 nm accompanied by shoulders at 20 nm longer wavelength, depending on substitution and solvent, and having quantum yields 0.6–0.9. In contrast, the fluorescence of the *anti*-isomers is very weak with quantum yields between 0.001 and 0.002 for maxima between 440 nm and 500 nm ⟨78JA6516, 80JA4983⟩. While the fluorobimane *syn*-(FCH_2,Me)(Me,Me)B is still strongly fluorescent, the chloro analog is only weakly fluorescent and the corresponding bromo derivative (**12**) is completely nonfluorescent ⟨81JOC1666⟩.

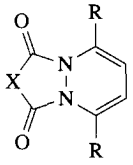
syn-Bimanes are often phosphorescent in matrices at 77K with maxima between 450 nm and 600 nm and quantum yields less than 0.009. *anti*-Isomers are strongly phosphorescent with maxima between 445 nm and 525 nm and quantum yields up to 0.45 ⟨80JA4983, 81JOC1666⟩.

The UV absorption maxima of selected partially saturated 5-6 and 6-6 bicyclic compounds are given in Tables 2 and 3, respectively.

Table 2 UV data of selected partially saturated bicyclic 5-6 systems.



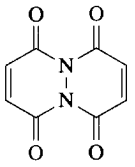
(**61**)



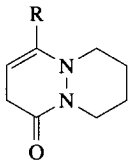
(**62**)

Structure	*X*	*R*	λ_{max} *(log ε)* (nm)	*Ref.*
(**61**)	CEt_2		346 (3.95), 423 (4.41)	87JOC101
(**62**)	N-Ph	H	369 (3.08)	85JOC5604
(**62**)	N-Ph	Ph	400 (3.24)	87JOC101

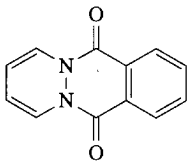
Table 3 UV data of selected partially saturated bicyclic 6-6 systems.



(**63**)



(**64**)



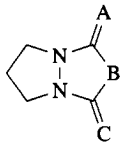
(**65**)

Structure	*R*	λ_{max} *(log ε)* (nm)	*Ref.*
(**63**)		228 (4.04), 340 (3.30)	66JOC1311
(**64**)	4-$MeOC_6H_4$	246 (4.26)	69JOC2720
(**65**)		400 (3.49)	85JOC5604

8.31.3.2.4 Fully saturated compounds

The UV absorption maxima of selected fully saturated 5-5 bicyclic compounds in methanol solutions are given in Table 4.

Table 4 UV data of selected fully saturated bicyclic 5-5 systems.

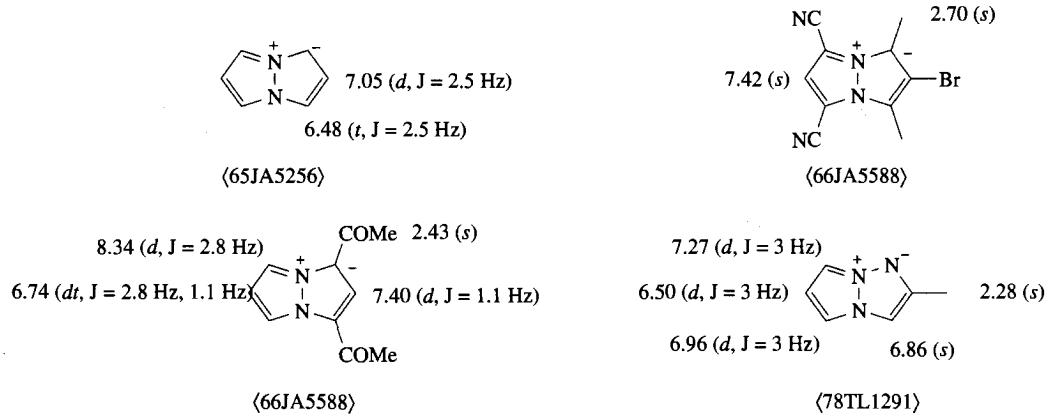


A	*B*	*C*	λ_{max} (*log* ε) (nm)	*Ref.*
S	S	S	265 (4.11), 336 (4.18)	92PHA416
S	N-Me	S	261 (4.51)	91PHA418
S	N-Ph	O	273 (4.09)	91PHA573
N-Ph	N-Ph	S	268 (4.36)	91PHA418
N-Ph	NH	NH	260 (4.31)	91PHA637

8.31.3.3 NMR Spectroscopy

8.31.3.3.1 Conjugated mesomeric betaines

The proton NMR spectrum of the simplest heteropentalene of this class (**7**) shows a characteristic A_2X system. The δ shifts are given, together with the data of several of its derivatives, in Scheme 1 ⟨65JA5256, 66JA5588, 78TL1291⟩. It should be noted that this diazapentalene compound absorbs at lower fields than the pentalene dianion, and the relative positions of the doublet and triplet are reversed ⟨64JA249⟩.



Scheme 1

8.31.3.3.2 Cross-conjugated mesomeric betaines

(i) Proton NMR spectroscopy

The simplest compound of this class (**54**) has a proton NMR spectrum which consists of a doublet at δ 4.22 (H-2), a doublet at δ 7.99 (H-5, H-7), and a sextet at δ 6.72 (H-6) with relative areas 1 : 2 : 1. The chemical shifts of H-2 in (**54**) and its simple derivatives are similar to the shifts of analogous protons in the enolate salts of diethyl malonate (δ 3.77), ethyl acetoacetate (δ 4.43), and acetylacetone (4.43) ⟨75TL1979⟩. This deshielding of the H-2 is indicative of the high charge densities at the C-2 position predicted also by theoretical calculations. Conversely, the chemical shifts of the H-5, H-7, and H-6 are analogous to the corresponding protons in the pyrazolium ion which occur for H-3 and H-5 at δ 8.57 and for H-4 at δ 6.87 ⟨80JA3971, 88JOC2889⟩. Proton NMR data of some other substituted derivatives of (**54**) have been published ⟨88JOC2889, 88JOC2898, 89S629⟩.

(ii) Carbon-13 NMR spectroscopy

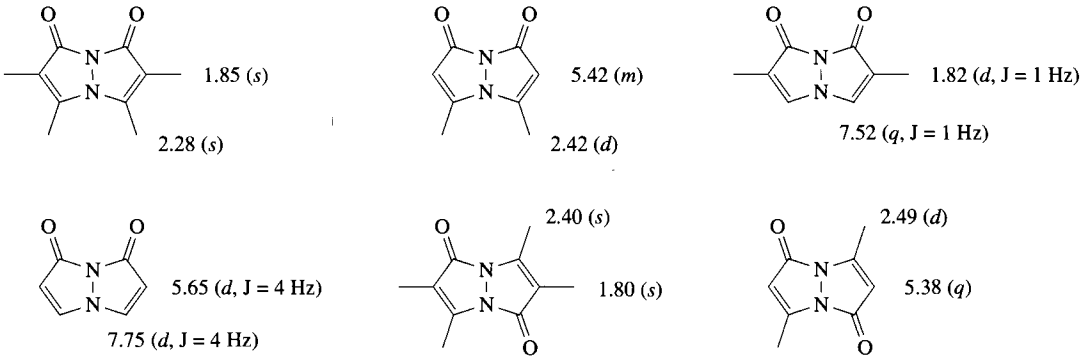
The ^{13}C NMR of (**54**) has also been reported having δ C-1, C-3 at 144.9, δ C-2 at 41.4, δ C-5, C-7 at 128.6 and δ C-6 at 110.8 ⟨88JOC2889⟩. Carbon-13 NMR data of some other substituted derivatives of (**54**) have been published ⟨88JOC2889, 88JOC2898, 89S629⟩.

The ^{13}C NMR spectrum of the 5,6,7-trimethyl derivative of (**55**) has signals at 7.47 (*q*), 9.81 (*q*), 121.86 (C-6), 141.55 (C-5, C-7), 150.19 (C-1, C-3). It is of interest to note that the ^{13}C signal of C-5(C-7) appears in the same region as the corresponding absorption in 3,4,5-trimethylpyrazole ⟨83H(20)23⟩.

8.31.3.3.3 Partially saturated compounds

(i) Proton NMR spectroscopy

Proton NMR spectra of the corresponding *syn*-(1,7-dioxo) and *anti*-(1,5-dioxo) isomers of pyrazolo[1,2-*a*]pyrazoles are quite similar and the positions are similar to those of related α,β-unsaturated carbonyl compounds (see Scheme 2) ⟨80JA4983, 82JOC207, 82JOC214, 84CPB930, 86JPR648⟩.

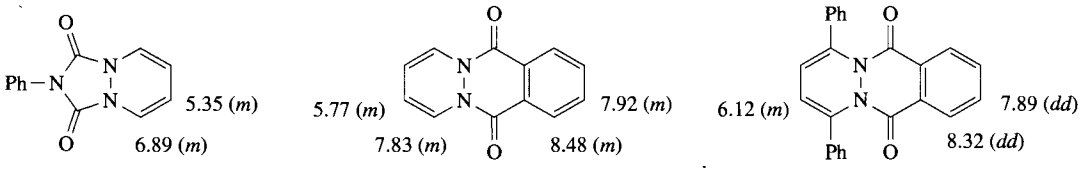


Scheme 2

(ii) Carbon-13 NMR spectroscopy

The ^{13}C NMR of *syn*- and *anti*-bimanes show very little difference between shifts of the carbons in the two isomers ⟨80JA4983⟩.

Both ^{1}H and ^{13}C NMR spectra of many other partially saturated compounds in question have been reported. The ^{1}H NMR data of selected compounds are shown in Scheme 3 as examples ⟨85JOC5604, 86JOC3123⟩.

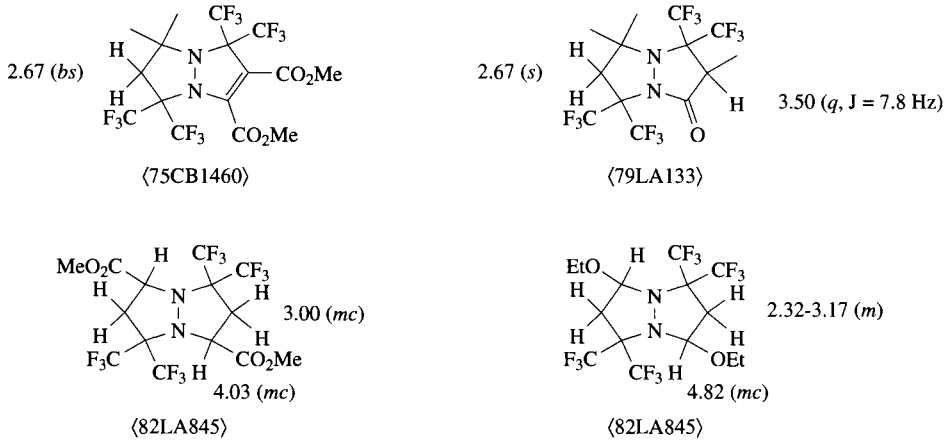


Scheme 3

8.31.3.3.4 Fully saturated compounds

(i) Proton NMR spectroscopy

Proton NMR spectra of many criss-cross adducts formed from hexafluoroacetoneazine have been reported ⟨75CB1460, 79LA133, 82LA845, 82LA853⟩. δ-Shifts of hydrogen atoms of some typical bicyclic compounds of this type, including one partially saturated one, are summarized in Scheme 4.



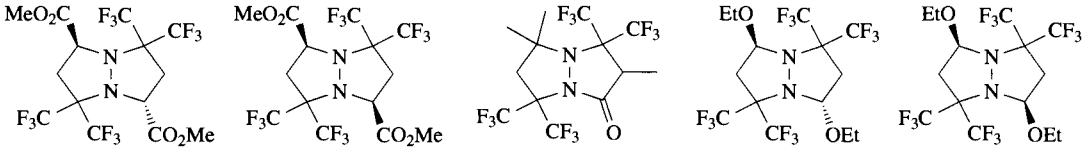
⟨75CB1460⟩ ⟨79LA133⟩ ⟨82LA845⟩ ⟨82LA845⟩

Scheme 4

(ii) Fluorine-19 NMR spectroscopy

Fluorine-19 NMR spectra of fluorine containing criss-cross adducts have been extensively studied ⟨79LA133, 82LA845, 82LA853⟩. Table 5 contains data of several interesting examples.

Table 5 ^{19}F NMR spectra of selected fluorine-containing bicyclic systems.



(66) **(67)** **(68)** **(69)** **(70)**

Compound	*δ* (ppm)		*Ref.*
(66)	−5.3 (*q*, *J* = 9.8 Hz, 6F)	−10.85 (*bq*, *J* = 9.8 Hz, 6F)	82LA845
(67)	−3.1 (*bq*, *J* = 10.0 Hz, 6F)	−11.3 (*bq*, *J* = 10.0 Hz, 6F)	82LA845
(68)	−7.7 (*q*, *J* = 9.0 Hz, 3F)	−9.2 (*q*, *J* = 10.5 Hz, 3F)	79LA133
	−8.9 (*q*, *J* = 9.0 Hz, 3F)	−12.6 (*q*, *J* = 10.5 Hz, 3F)	
(69)	−4.0 (*q*, *J* = 9.2 Hz, 6F)	−8.85 (*q*, *J* = 9.2 Hz, 6F)	82LA853
(70)	−4.2 (*q*, *J* = 10.5 Hz, 6F)	−9.25 (*bq*, *J* = 10.5 Hz, 6F)	82LA853

8.31.3.4 Mass Spectroscopy

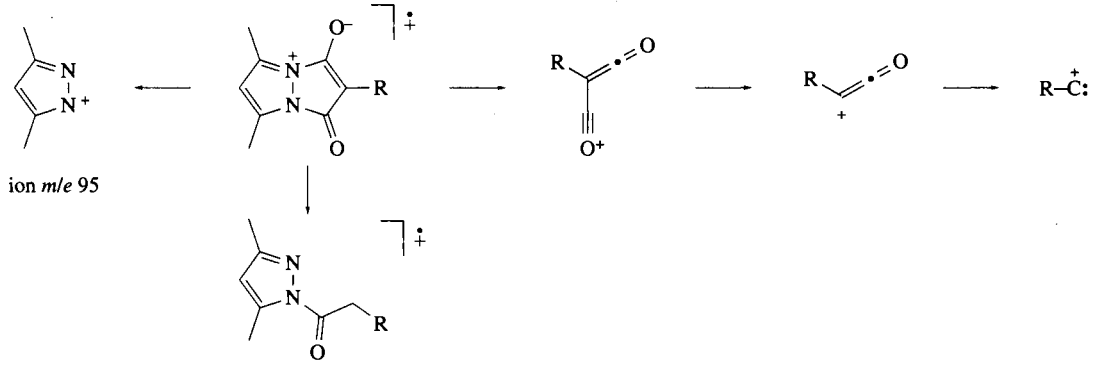
8.31.3.4.1 Conjugated mesomeric betaines

The mass spectra (MS) of (**7**) and its 2-bromo derivative has been recorded ⟨66JA5588⟩. The MS of the unsubstituted compound has the parent ion ($C_6H_6N_2$, *m/e* 106) as the most abundant peak, along with peaks of *m/e* 80 (parent less C_2H_2), 53, 52, and 39. The mass spectrum of the corresponding 2-bromo derivative has two sharp parent peaks of *m/e* 184 and 186, corresponding to $C_6H_5BrN_2$ with the ^{79}Br and ^{81}Br isotopes ⟨66JA5588⟩. The MS of the 2-methyl derivative of (**51**) has peaks of *m/e* 121, corresponding to the molecular ion ($C_6H_7N_3$), and 80 (parent less CH_3CN), 53, 52, and 39 ⟨78TL1291⟩.

8.31.3.4.2 Cross-conjugated mesomeric betaines

Most cross-conjugated mesomeric betaines show intense molecular ions in their electron-impact MS. Fragmentation of the molecular ion consistently follows two main pathways, the first being

cleavage of the C(1)—N(7) and C(3)—N(4) bonds to give rise to two fragments, the cationic heterocycle and the carbonyl ketene cation. Loss of CO from the molecular ion is the second fragmentation pathway generating a radical cation (Scheme 5) ⟨88JOC2898⟩.



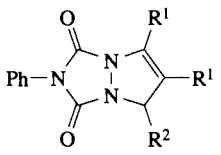
Scheme 5

The MS of the unsubstituted compound (**54**) has the highest ion (M + 1, *m/e* 137) as 15% of the intensity of the most abundant peak. The mass spectrum of its 5,7-dimethyl derivative shows a molecular ion of *m/e* 164 ⟨88JOC2889⟩.

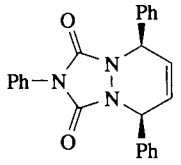
8.31.3.4.3 Partially saturated compounds

Mass spectra of some bimanes have been reported ⟨82JOC214⟩. Parent peaks, which correspond to the expected molecular weight for the compound in question, are obtained for most of the compounds.

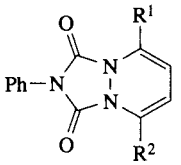
Many published results of MS of the compounds in question contain a molecular ion which is not the base peak. Compounds given in Scheme 6 are typical in this sense ⟨82ZOR1986, 84JOC587, 85JHC273, 85JOC5604, 86JOC3123, 87JOC101, 90JOC2478⟩.



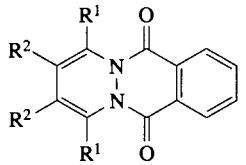
[R^1]	[R^2]	[*Ref.*]
CO_2Me	H	82ZOR1986
Ph	Me	90JOC2478



⟨87JOC101⟩



[R^1]	[R^2]	[*Ref.*]
H	H	85JOC5604
CO_2Me	H	85JOC587
Ph	Ph	87JOC101



[R^1]	[R^2]	[*Ref.*]
H	H	85JOC5604
Ph	H	86JOC3123
H	Me	85JHC273

Scheme 6

8.31.3.4.4 Fully saturated compounds

The mass spectra of several criss-cross adducts containing four trifluoromethyl groups have been reported. The spectra generally show the molecular ion and presence of other ions depending on the nature and position of substituents. Compounds containing ester groups on the bicyclic structure usually have $[M - CO_2R]^+$ as the principal ion. Ion $[M - CF_3]^+$ is also usually present ⟨82LA1730⟩.

8.31.3.5 X-ray Analysis

The Cambridge Structural Database contains many compounds treated in this chapter and only selected examples are mentioned here.

8.31.3.5.1 Conjugated mesomeric betaines

Studies of the crystal structure of 3,7-dibromo-2,6-dimethyl-[1,2,3]triazolo[1,2-*b*][1,2,3]triazole show that this dibromo derivative has a geometry consistent with its representation as a mesomeric betaine, having N(1)—C, 1.37 Å, C—C, 1.33 Å, N(4)—C, 1.40 Å, and N(4)—N(8), 1.36 Å ⟨63G1571⟩. Similar results have been obtained also for rubidium salts of 2,6-dimethyl-1,2,3-triazolo[1,2-*b*][1,2,3]triazole-3,7-dicarboxylic acid and 1,2,3-triazolo[1,2-*b*][1,2,3]triazole-2,6-dicarboxylic acid ⟨63G1556⟩. The dibenzo derivative of (**53**) has been shown by x-ray analysis to be planar ⟨76AX(B)2518, 76AX(B)2614⟩.

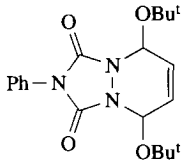
8.31.3.5.2 Cross-conjugated mesomeric betaines

A single crystal x-ray study of the 2-phenyl derivative of (**54**) shows that the molecule is pseudo-planar with a 2-fold axis of symmetry and that the 2-phenyl substituent is twisted 7.3° out of the plane. The published data is in agreement with negative charge delocalization over the β-diketone enolate and the phenyl ring and the positive charge being delocalized over the pyrazolium ring ⟨84AJC2577, 88JOC2898⟩. It is also of interest, that the x-ray data of the 5,6,7-trimethyl derivative of (**55**) shows remarkable consistency with the bond lengths of the 2-phenyl derivative of (**54**) ⟨83H(20)23⟩. Crystal structures of the 5,6,7-trimethyl derivative of (**56**) ⟨83H(20)845⟩ and the 2-phenyl derivative of (**57**) ⟨83H(20)1271⟩ have also been reported.

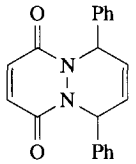
8.31.3.5.3 Partially saturated compounds

Single crystal x-ray analysis of several bimanes have been published. The N—N bond length varies from 1.370–1.407 Å, the shortest N—N distance of 1.370 Å is found in *anti*-(Me,H)B. The observed N—CO bond lengths vary from 1.390–1.435 Å, the *anti*-derivatives showing a shorter distance than the corresponding *syn*-derivatives ⟨79JA1620, 83JHC903, 86JPR648⟩. The data for crystals of both *syn*- and *anti*-(Me,Me)B have been published ⟨79JA1620⟩. The former is planar since it occupies a crystallographic inversion of the site of symmetry; the latter, occupying a general crystallographic position, is planar within experimental errors ⟨73ACS661, 79JA1620⟩.

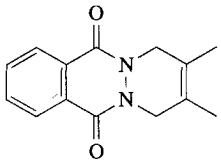
Beside bimanes, some other partially saturated systems, mainly 5-6 and 6-6 bicyclic compounds, have been studied by the x-ray diffraction method. For example, (**71**) ⟨87JA7104⟩, (**72**) ⟨81MI 831-01⟩, (**73**) ⟨77AX(B)3957⟩, and (**63**) ⟨77AX(B)2464⟩.



(71)



(72)



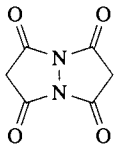
(73)

8.31.3.5.4 Fully saturated compounds

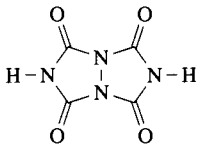
X-ray crystal structures of several bicyclic 5-6, 6-6, and 6-7 analogs of the ACE inhibitor captopril (see Section 8.31.15.2) have been published and compared with the structure of the model ⟨84JCS(P1)155, 86JCS(P1)1011⟩.

An x-ray structure of the fully saturated analog of *anti*-(H,H)B has been reported. The nitrogens are substantially nonplanar, the N—N distance is considerably longer than in *anti*-(H,H)B ⟨83JHC903,

87JA5724〉. X-ray spectra of (**66**) and (**67**) were used for their structural determination 〈82LA845〉. X-ray structures of several tetraoxo derivatives, for example compounds (**74**) 〈86AP(319)646〉 and (**75**) 〈88AG703〉, have been studied.



(74)



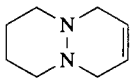
(75)

8.31.3.6 Miscellaneous

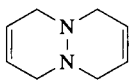
Methods used only for a specific subtype of compounds treated by this chapter are highlighted in this subsection.

8.31.3.6.1 Cyclic voltammetry

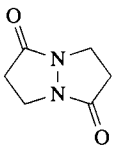
Compounds (**1**), (**3**), (**78**), and (**79**) have been studied by cyclic voltammetry and found to give chemically reversible one-electron oxidations with no evidence for radical decay 〈77JA1130, 78JA4012〉.



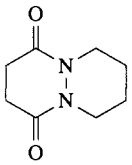
(76)



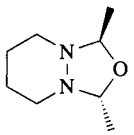
(77)



(78)



(79)



(80)

8.31.3.6.2 ESR spectroscopy

ESR spectroscopy of the radicals from (**1**)–(**3**), (**76**)–(**80**) and some of their derivatives have been reported 〈74JA2916, 87JA5724〉.

8.31.3.6.3 Dipole moment

Dipole moment measurements have been reported for some conjugated and cross-conjugated mesomeric betaines. For example, the 1,3-diacetyl derivative of (**7**) has a dipole moment of 2.12 D 〈66JA5588〉. The dibenzo derivative of (**52**) has a high dipole moment of 4.36 D which is in accord with the formulation of this compound as a mesoionic structure with unsymmetrically distributed charge 〈67JA2618〉. On the other hand, the dibenzo derivative of (**53**) has no detectable dipole moment. Experimental dipole moments of several derivatives of (**54**) have been found to range from 5.11–7.65 D. The presence of a 2-phenyl substituent results in an increase of the dipole moment of approximately 1.3 D 〈88JOC2898〉.

8.31.4 THERMODYNAMIC ASPECTS

8.31.4.1 Physical Properties and Stability

It is impossible to generalize these properties for such a wide spectrum of structures. Only some interesting and/or typical compounds are treated here.

8.31.4.1.1 Conjugated mesomeric betaines

The parent heteropentalenes of this class, (**7**), (**51**)–(**53**), have limited stability. For example, (**7**) is a rather unstable molecule and its sensitivity to air is especially pronounced. It is a colorless solid, soluble in, yet not affected by, water. In air it quickly turns green as does its 2-bromo derivative ⟨66JA5588⟩. The 2-phenyl derivative of (**7**) seems to be more stable than 2-unsubstituted or 2-bromo derivatives ⟨65JA528, 66JA1992⟩. Similar behavior has been reported also for (**51**) and its simple alkyl and aryl derivatives ⟨78TL1291⟩. Most of the mentioned compounds form picrates which give correct elemental analysis. Acylation of the parent structures changes the stability of these compounds. This can be demonstrated for the easily available 2-acyl or 2,4-diacyl derivatives, which are quite stable. For example, the 2,4-diacetyl derivative of (**7**) ⟨66JA5588⟩ or its 1-benzoyl-2-phenyl derivative ⟨65JA528⟩ have considerable thermal stability and the latter can be sublimed *in vacuo* at 160 °C. Similarly, the 2-methyl-3-acetyl derivative of (**51**) is quite stable ⟨78TL1291⟩. Many mono and dibenzo derivatives of the parent structures (**51**) ⟨71JHC707, 83JCS(P1)2491, 83JOC1080⟩, (**52**) ⟨67JA2618⟩, and (**53**) ⟨62JA2453, 67JA2618, 83JOC1080⟩ are also quite stable as can be demonstrated for dibenzo derivatives of the parent structures (**52**) and (**53**). The dibenzo derivative of (**52**) is a colorless solid (m.p. 255 °C) which does not exhibit visible fluorescence in solution. The dibenzo derivative of (**53**) is a yellow solid (m.p. 237–238 °C) which exhibits yellowish-green fluorescence under UV light ⟨67JA2618⟩. Dibenzo heteropentalenes of this class are generally weakly basic, being insoluble in dilute mineral acids, but soluble in concentrated ones, for example in sulfuric acid.

8.31.4.1.2 Cross-conjugated mesomeric betaines

Cross-conjugated mesomeric betaines of this class are relatively stable but they are very sensitive to traces of moisture. Derivatives of (**54**) are usually highly colored crystalline compounds, for example (**54**) itself is a yellow crystalline solid, m.p. 55–65 °C, and its 2-phenyl derivative is dark red, m.p. 247–248 °C ⟨80JA3971, 88JOC2889, 89S629⟩. On the other hand, the 5,6,7-trimethyl derivative of (**55**), which is also very moisture-sensitive, is a colorless solid, m.p. 161.5–162 °C ⟨83H(20)23⟩.

8.31.4.1.3 Partially saturated compounds

Both 1,5- and 1,7-dioxopyrazolo[1,2-*a*]pyrazoles (*anti*- and *syn*-bimanes, respectively) are crystalline, very stable solids which possess moderately high melting points. Some of these compounds sublime unchanged, for example *syn*-(Me,Me)B sublimes at 200 °C/760 mm, and the corresponding *anti*-derivative sublimes at 120 °C/0.1 mm ⟨78JA6516, 80JA4983⟩.

8.31.4.1.4 Fully saturated compounds

Most of the criss-cross benzaldazine adducts are high melting solids. On the other hand, adducts formed from hexafluoroacetoneazine have low melting points, usually below 100 °C.

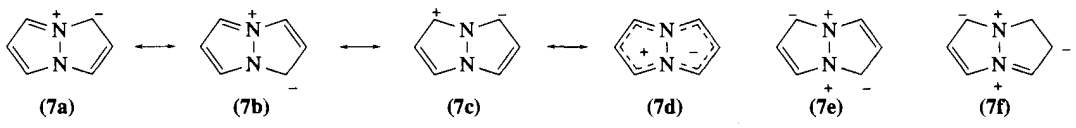
8.31.4.2 Possible Dipolar Structures and Tautomers

For most compounds, including mesomeric betaines which cannot be satisfactorily represented by a Lewis formula, all the molecules have the same structure. On the other hand, for many compounds there is a mixture of two or more structurally distinct tautomeric compounds that are in rapid equilibria. Since the subject of this chapter is so wide, it covers both compounds the structure of which is usually represented by several dipolar structures (mesomeric betaines) and compounds which are present as a mixture of tautomers. Both aspects are treated in this subsection.

8.31.4.2.1 Conjugated mesomeric betaines

No single structure can uniquely describe the bonding of mesomeric betaines and their true structure is a resonance hybrid of several dipolar structures. The possible dipolar structures for the

parent compound (**7**) are depicted in Scheme 7. Additional unsymmetrical substitution or aza substitution increases the number of possible distinct dipolar structures. Presumably, most of these resonance structures make significant contributions to the ground state, and monoexcited structures such as (**7e**) and (**7f**) will contribute to a lesser extent.

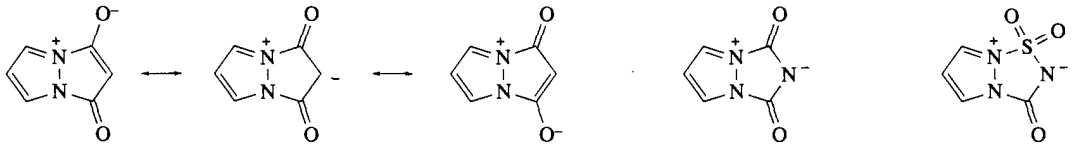


(**7a**) (**7b**) (**7c**) (**7d**) (**7e**) (**7f**)

Scheme 7

8.31.4.2.2 Cross-conjugated mesomeric betaines

The possible dipolar structures for the simplest case of the 5-5 ring system (**54**) are depicted in Scheme 8. A similar situation is also true for the corresponding aza analogs, for example (**55**), or thioazaanalog (**56**). It has been shown ⟨88JOC2898⟩ that the cross-conjugated mesomeric betaines contain distinct anionic and cationic segments. Many of the properties of these compounds are attributed to the specific cationic and anionic portions of these zwitterions and to the weak nature of the C(1)—N(7) and C(3)—N(4) bonds which join the cationic fragment with the anionic one.

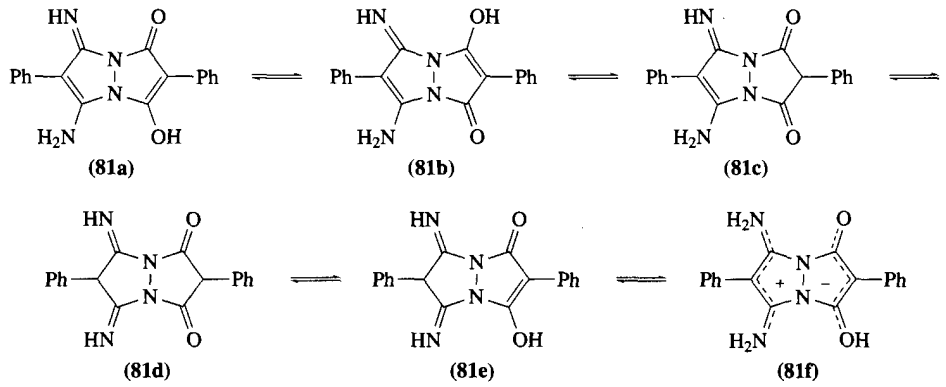


(**54a**) (**54b**) (**54c**) (**55**) (**56**)

Scheme 8

8.31.4.2.3 Partially saturated compounds

Compound (**81**) can exist in numerous covalent tautomeric forms, some of which are shown in Scheme 9, and in a zwitterionic form (**81f**) ⟨86S239, 88JHC1301⟩. The latter, which has an anion and a cation that are both stabilized separately by delocalization, was shown to predominate in the solid state by an x-ray study ⟨88JHC1301⟩.



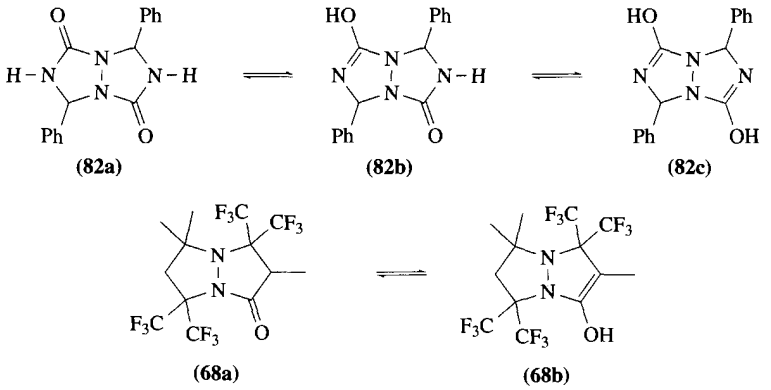
(**81a**) (**81b**) (**81c**)

(**81d**) (**81e**) (**81f**)

Scheme 9

8.31.4.2.4 Fully saturated compounds

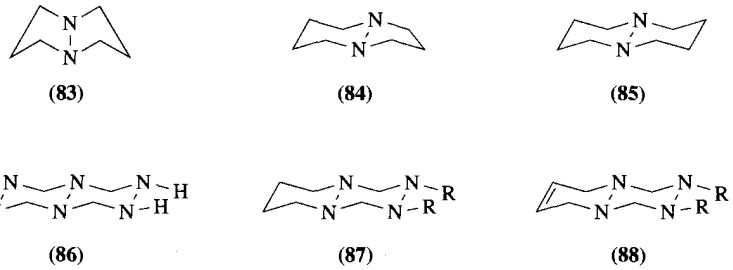
For compounds of the type (**82**) and (**68**), keto-enol tautomerism is possible. IR data of (**68**) suggests the presence of the keto form in solid state (Scheme 10) ⟨79LA133⟩.



Scheme 10

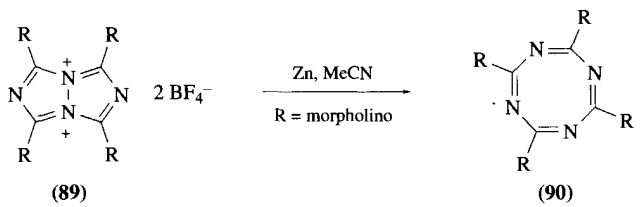
8.31.4.3 Conformational Analysis

Conformational analysis of some partially and fully saturated bicyclic structures has been extensively studied in the context of conformational analysis of hydrazines. Spectral studies of perhydropyrazolo[1,2-*a*]pyrazole, perhydropyrazolo[1,2-*a*]pyridazine, and perhydropyridazino[1,2-*a*]pyridazine show that only the presence of conformers (**83**), (**84**), and (**85**), respectively, are consistent with the data ⟨76JA5748, 76SA(A)157, 88JA7945, 89JA5387, 90JA5080⟩. Similarly, preferences of conformations (**86**), (**87**), and (**88**) are explained in terms of steric, electronic, and entropy effects ⟨67CC206, 74JCS(P2)948, 75CB1548, 76JA5748, 76SA(A)157⟩. Conformational analysis of similar perhydropyridazino[1,2-*c*][1,3,4]oxadiazine ⟨80JCS(P2)91⟩ and perhydro-1,2,4,5-tetrazino[1,2-*d*:4,5-*d*]-bis[1,2,4,5]dioxadiazine ⟨79JCS(P2)1133⟩ have also been reported.



8.31.5 REACTIVITY OF CONJUGATED HETEROCYCLIC CATIONS

The only reaction of derivatives of heterocyclic cations of general formulae (**4**)–(**6**) reported so far is the reaction of (**89**) leading to (**90**) (Equation (1)) ⟨91AG(E)334⟩.



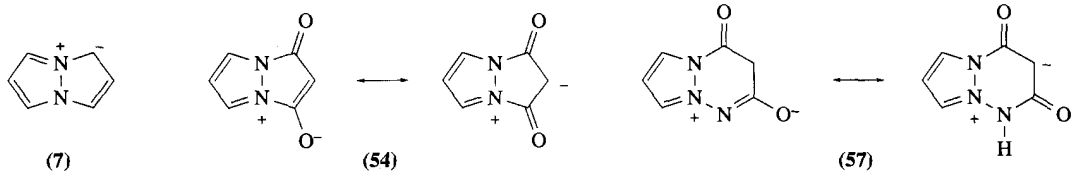
(1)

8.31.6 REACTIVITY OF MESOMERIC BETAINES

8.31.6.1 General Considerations

Conjugated, cross-conjugated, and pseudo cross-conjugated mesomeric betaines have been defined ⟨85T2239⟩. It is evident from the definition, that mesomeric heteropentalene (**7**) and its

analogs belong to the conjugated mesomeric betaines and are of the type B of the Ramsden classification. Mesomeric olates, such as (**54**) and (**57**), are representatives of cross-conjugated mesomeric betaines (Scheme 11).



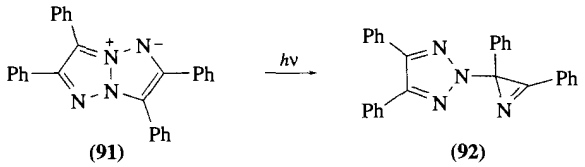
(7) (54) (57)

Scheme 11

Conjugated heteropentalene mesomeric betaines are electron rich with high energy HOMO and can be regarded as masked 1,3-dipolarophiles. Their main reactions are electrophilic substitution and cycloaddition reaction with electron-deficient 1,3-dipolarophiles.

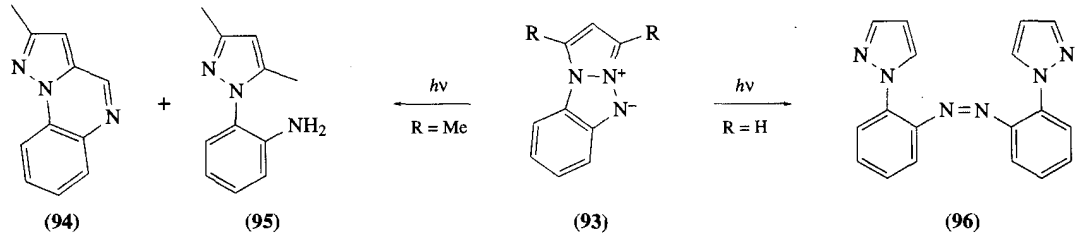
8.31.6.2 Intramolecular Photochemical Reactions

A limited amount of material on photochemical reactions of mesomeric betaines of this type is available in the literature. For example, photoisomerization of tetraphenyl derivative (**91**) leads to triazole derivative (**92**) which can be isolated in more than 80% yield (Equation (2)) ⟨84TL2613⟩.



(91) (92) (2)

The benzo derivative (**93**) having R = Me is rather photostable, but its prolonged irradiation yields a mixture of 1-methylpyrazolo[1,2-*a*]quinoxaline (**94**) and pyrazole (**95**) in roughly equal amounts. Unsubstituted derivative (**93**) (R = H) gave azo derivative (**96**) under the same conditions (Scheme 12) ⟨91JA6928⟩.



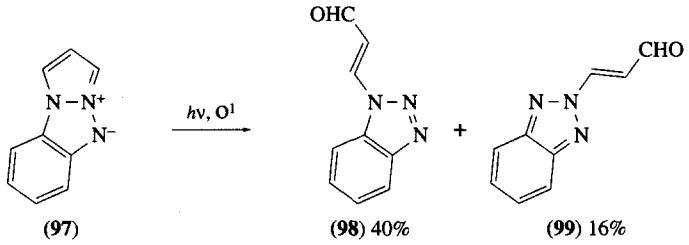
(94) (95) (93) (96)

Scheme 12

8.31.6.3 Photooxidation Reactions

Singlet oxygen oxidation of some heteropentalene mesomeric betaines having two ring function nitrogen atoms has been studied. Rose Bengal sensitized photooxidation of (**97**) in inert solvents provides a mixture of aldehydes (**98**) and (**99**) (Equation (3)) ⟨83JOC1080⟩. The corresponding dimethyl derivative (**122**) under the same conditions provides a more complex mixture containing

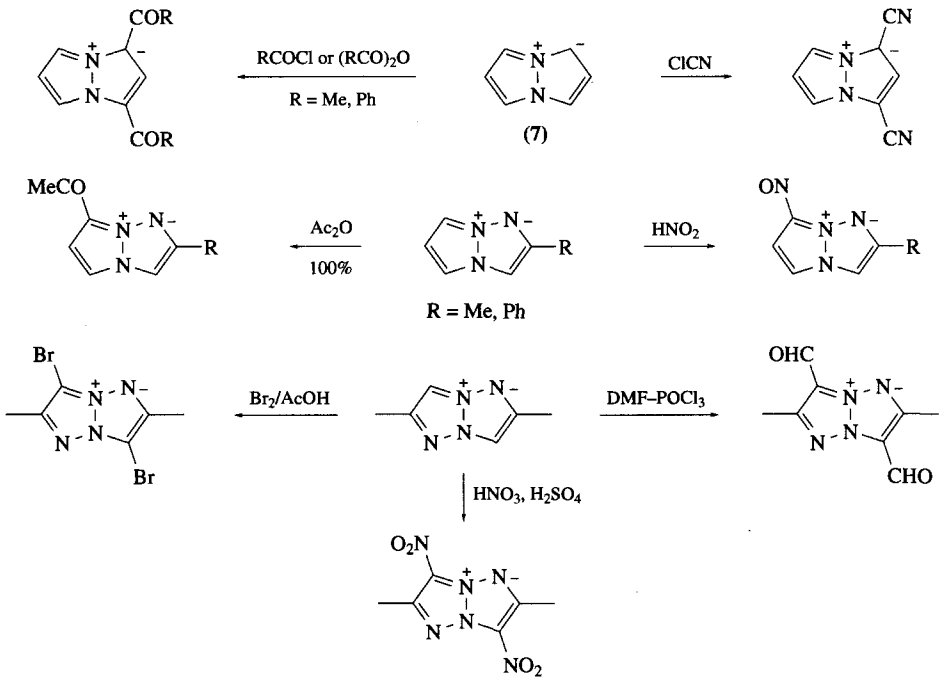
not only ketones corresponding to aldehydes (**98**) and (**99**), but also epoxy ketones formally derived by a double bond oxidation of the ketones ⟨81CC1089, 83JCS(P1)581⟩.



(97) (98) 40% (99) 16% (3)

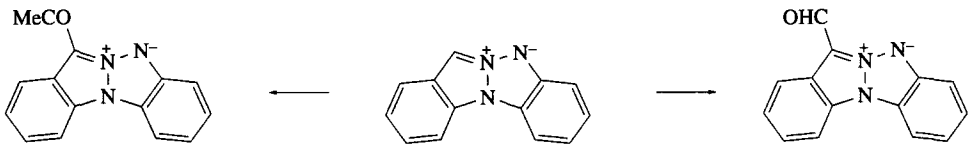
8.31.6.4 Electrophilic Attack at Carbon

Generally the electrophilic attack at carbon of conjugated mesomeric betaines of this type is very easy and requires mild conditions. Electrophilic substitution of extremely air-sensitive pyrazolo[1,2-*a*]pyrazole (**7**) provides stable 1,3-disubstituted derivatives, for example diacyl or dicyano derivatives ⟨65JA4393, 66JA5588⟩. Electrophilic substitution of some other conjugated mesomeric betaines has been reported (Scheme 13) ⟨63CB1827, 78TL1291⟩.



Scheme 13

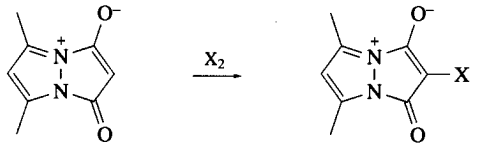
Dibenzo derivative (**100**), still having one hydrogen atom at the heteropentalene moiety, is also a suitable substrate for electrophilic substitution (Scheme 14). Acetyl and formyl derivatives are formed under Vilsmeier–Haack conditions, that is, using Me_2NCOR–$POCl_3$ at 0 °C ⟨73CL175⟩.



(**100**)

Scheme 14

Cross-conjugated mesomeric betaine (**101**) undergoes facile electrophilic substitution at position-2 with bromine and iodine to give the corresponding derivatives (Equation (4)) ⟨86CC144, 88JOC2898⟩.



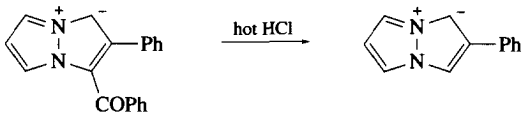
(4)

(**101**)

X	*Yield* (%)
Br	43
I	16

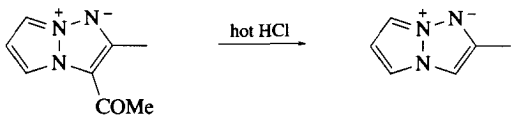
8.31.6.5 Reactions with Nucleophiles

Relatively stable acyl substituted compounds, for example (**102**) and (**103**), are easily deacylated to the corresponding unsubstituted derivatives by treatment with hot hydrochloric acid (Equations (5) and (6)) ⟨65JA528, 66JA1992, 78TL1291⟩.



(5)

(**102**)

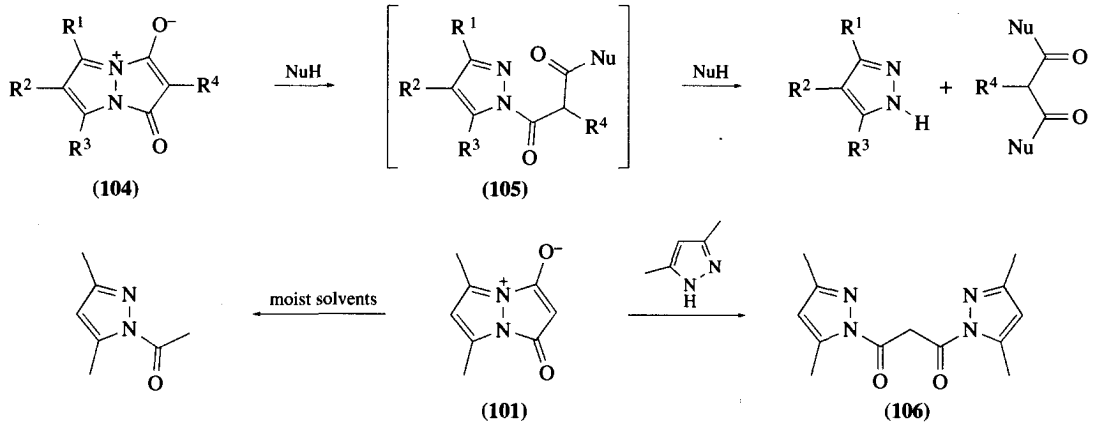


(6)

(**103**)

Cross-conjugated mesomeric betaines (**104**) react with nucleophiles such as water, alcohols, and amines. Initially, intermediates of a general formula (**105**) are formed and then nucleophilic attack of an additional equivalent of the nucleophile provides the corresponding pyrazole and malonic acid derivatives ⟨82JOC295, 86CC144, 88JOC2898⟩. The bis pyrazole derivative (**106**), which is an equivalent of the intermediate (**105**), can be isolated in 74% yield when mesomeric betaine (**101**) reacts with 3,5-dimethylpyrazole. In some cases different products of nucleophilic attack are isolated. For example, dimethyl derivative (**101**) in moist solvents provides quantitatively the corresponding *N*-acetyl pyrazole (Scheme 15) ⟨86CC144⟩.

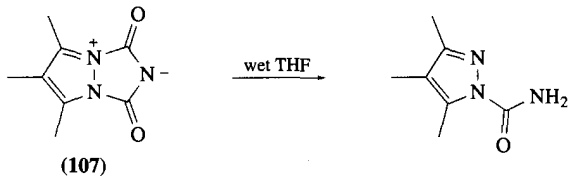
Similar reactivity has also been described for some other cross-conjugated mesomeric betaines. For example, mesomeric 1-oxo-1*H*-pyrazolo[1,2-*a*][1,2,4]triazol-4-ium-3-olate (**107**), though reasonably stable in air, is instantaneously hydrolyzed in moist THF to give the corresponding *N*-



(**104**) (**105**) (**101**) (**106**)

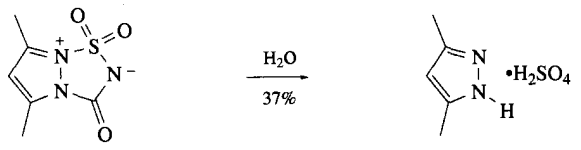
Scheme 15

aminocarbonyl derivative (Equation (7)) ⟨83H(20)23⟩. Similar solvolysis of (**108**) and (**109**) has also been reported (Equations (8) and (9)) ⟨83H(20)845⟩.



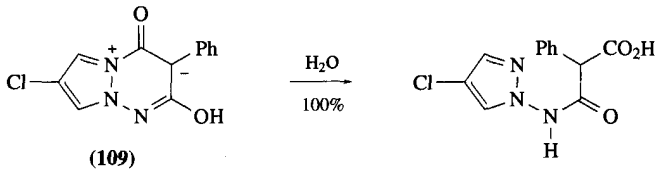
(7)

(**107**)



(8)

(**108**)



(9)

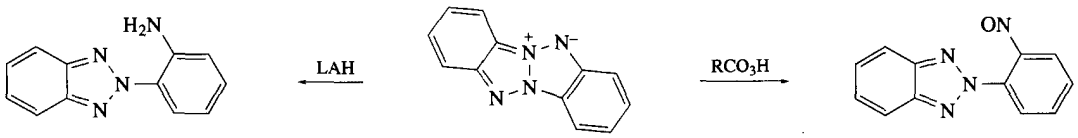
(**109**)

8.31.6.6 Reduction

LAH reduction of (**110**) provides the corresponding amino derivative (**111**) (Scheme 16) ⟨67JA2618⟩.

8.31.6.7 Oxidation

Oxidation of (**110**) with peracids provides nitroso derivative (**112**) (Scheme 16) ⟨67JA2626⟩.



(**111**) (**110**) (**112**)

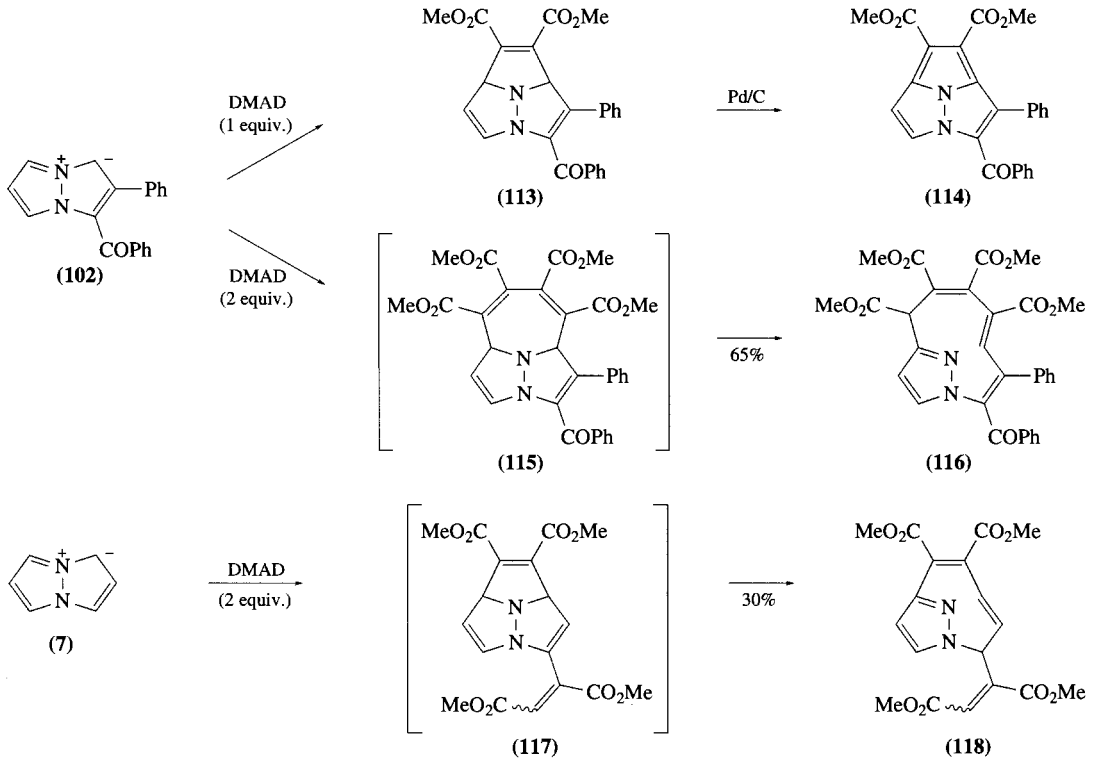
Scheme 16

8.31.6.8 Dipolar Cycloaddition Reactions

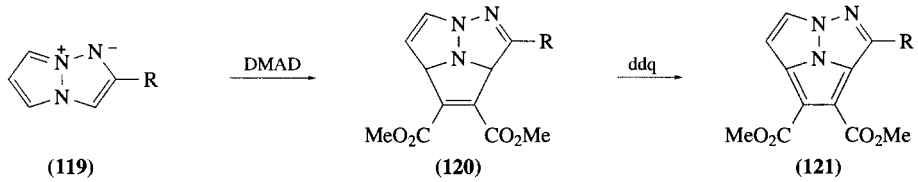
1,3-Dipolar cycloaddition reactions of conjugated heteropentalene mesomeric betaines possessing an azomethine ylide 1,3-dipole have been extensively studied. The reaction of 1-benzoyl-2-phenyl derivative (**102**) with one equivalent of DMAD gives the adduct (**113**) which without isolation can be dehydrogenated *in situ* to yield azacyclazine (**114**). The same compound, treated with two molar equivalents of DMAD without palladium, provides pyrazole derivative (**116**), presumably via intermediate adduct (**115**). Unsubstituted derivative (**7**) on the same treatment provides 30% of (**118**), presumably via intermediate tricyclic compound (**117**) (Scheme 17) ⟨66PNA(55)1385⟩.

Addition of an equimolar amount of DMAD to (**119**) provides good yields of cycloadducts (**120**), which can be oxidized with ddq to stable tricyclic derivatives (**121**) (Scheme 18) ⟨78TL1291⟩.

Similar treatment of dimethyl benzo derivative (**122**) leads to (**123**). When the reaction is performed in methanol, a stable enamine (**124**) is obtained. Acidic hydrolysis then provides pyrazole derivative (**95**) ⟨83JCS(P1)2491, 84JOC2670⟩. Unsubstituted benzo derivative (**97**) treated with DMAD in acetonitrile provides a mixture containing (**125**) and two other products (**126**) and (**127**) (Scheme 19) ⟨83JCS(P1)2491, 84JOC2670⟩.

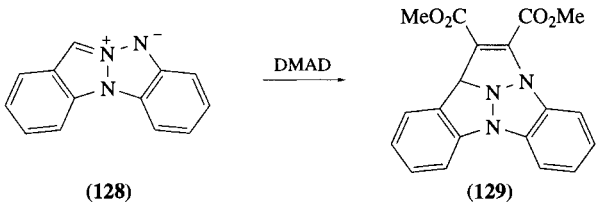


Scheme 17



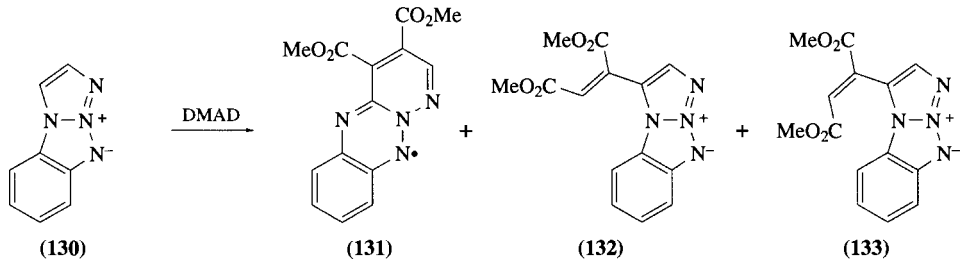
Scheme 18

Dibenzoderivative (**128**) provides with DMAD the expected 1,3-adduct (**129**) (Equation (10)) ⟨73TL597, 74H(2)27⟩.

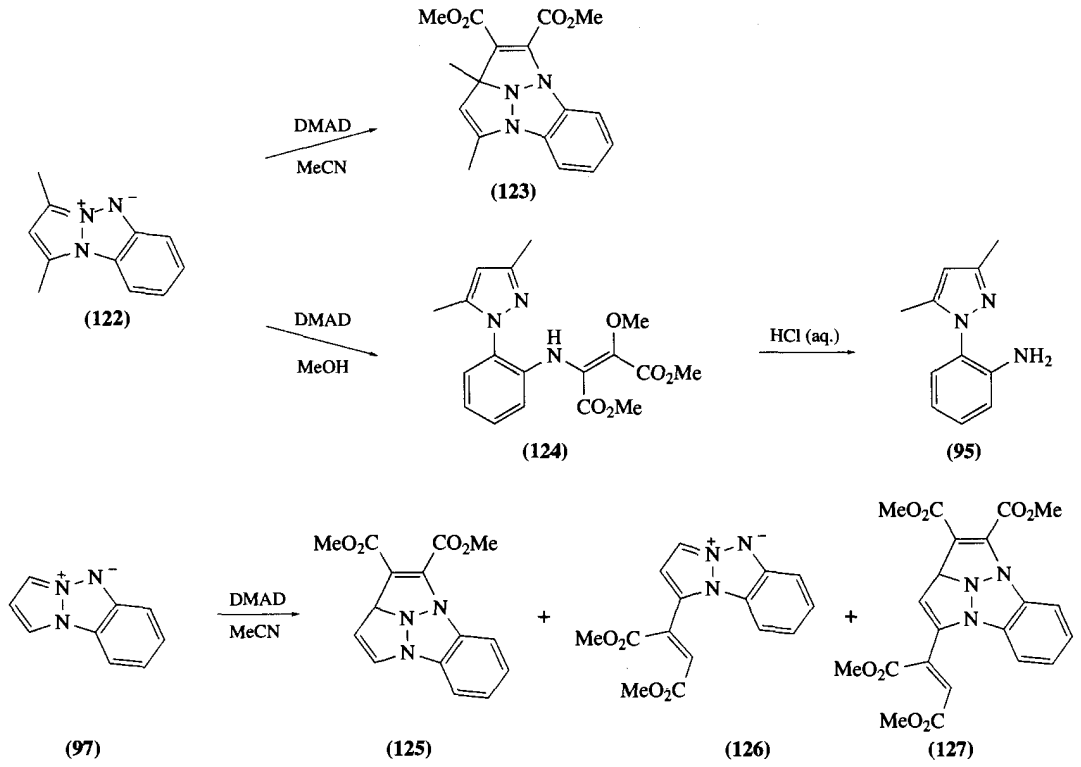


(10)

Reaction of benzo derivative (**130**) with DMAD provides a stable radical (**131**) and only minor amounts of (**132**) and (**133**) are detected (Equation (11)) ⟨84JOC2670⟩.



(11)



Scheme 19

8.31.7 REACTIVITY OF NONCONJUGATED RING SYSTEMS

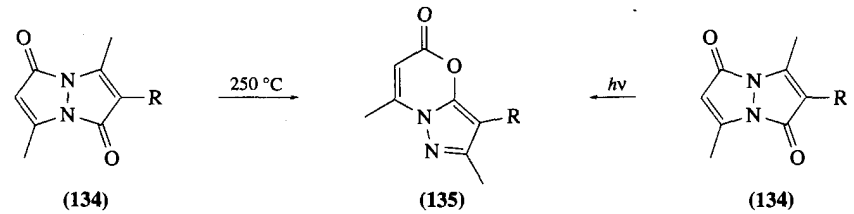
8.31.7.1 General Survey

This section covers all nonconjugated 5-5, 5-6, and 6-6 ring systems except mesomeric betaines and fully saturated systems.

8.31.7.2 Thermal and Photochemical Reactions

Thermolysis of (**134**) at 250 °C for several hours gives only small yields of (**135**) with good recovery of the starting material ⟨80JA4983, 84CPB930⟩. Photochemical treatment of this type of compound in acetonitrile provides much better yields of the same products (Scheme 20) ⟨84CPB930⟩.

Photolysis of (**136**) in methanol yields two mono adducts (**137**) and (**138**) in a ratio of 2 : 1 and a small amount of two dimers (**139**) and (**140**). The same reaction performed in dichloromethane or ether provides small amounts of the same dimers as formed in methanol and pyrrolotriazine (**143**)

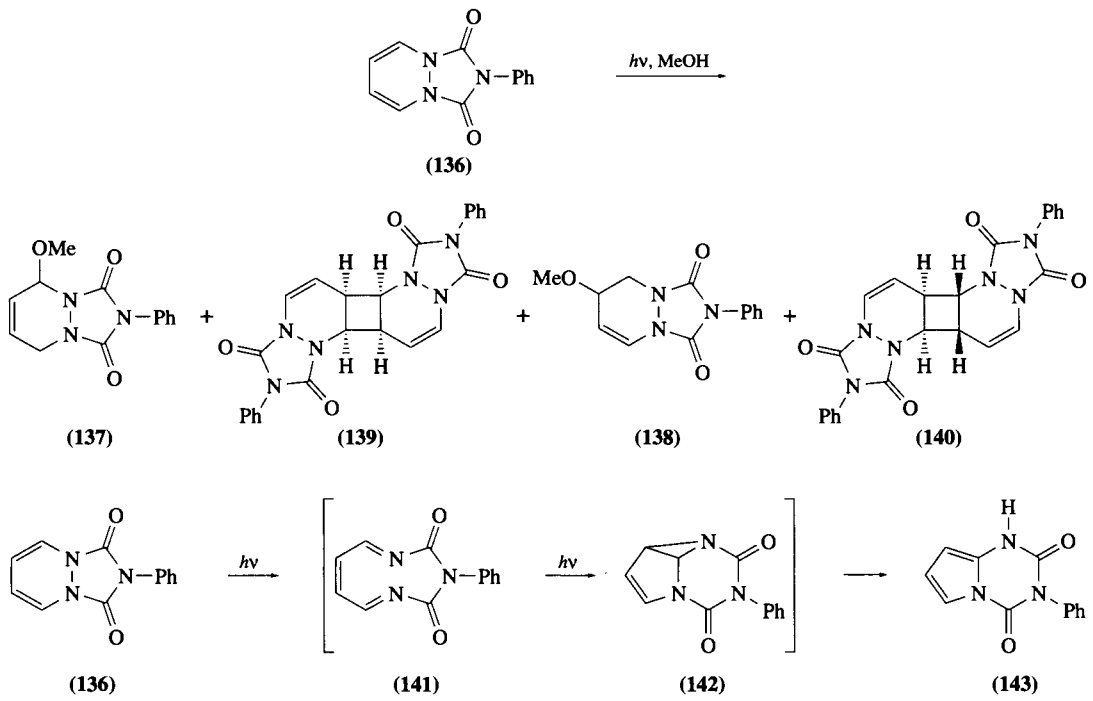


R	*Yield* (%)
H	10
COEt	30

R	*Yield* (%)
CO_2Et	60
COMe	67

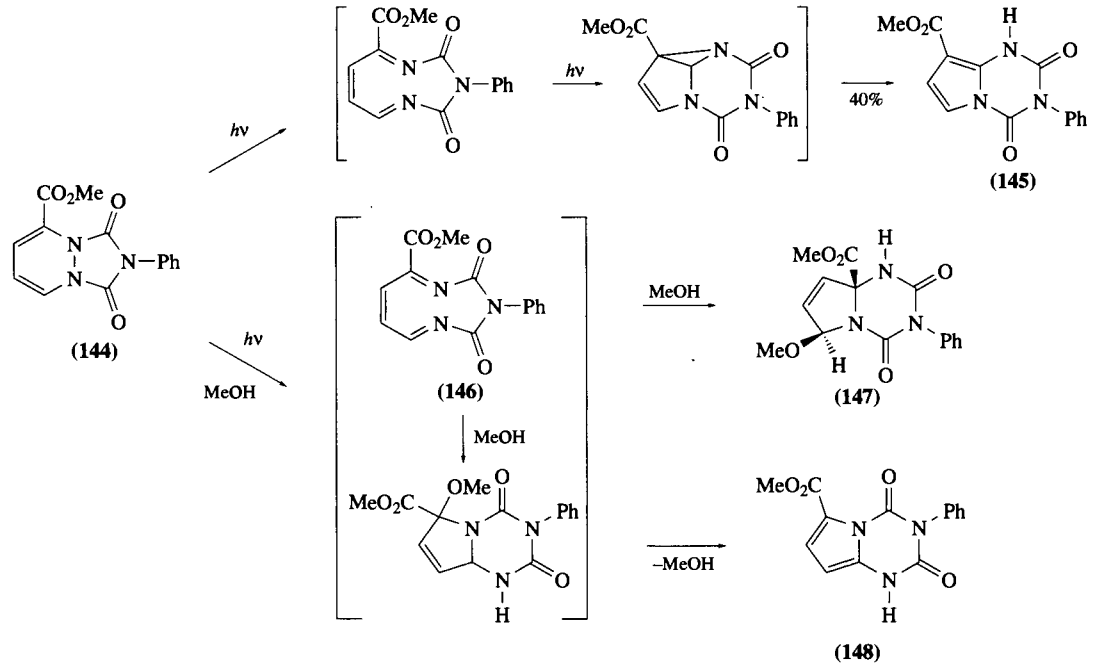
Scheme 20

as a main product (25%). Its formation involves electrocyclic ring opening to triazonine (**141**), followed by photorearrangement to (**142**) and aromatization through an aziridine ring opening (Scheme 21) ⟨85JOC5604⟩.



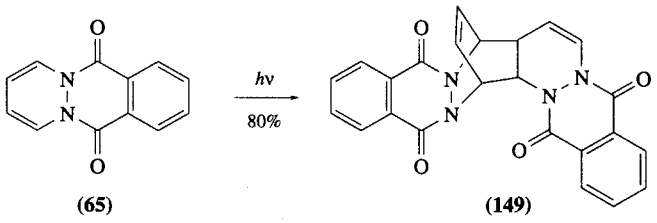
Scheme 21

The same reaction pathway is involved in photolysis of (**144**). When the reaction is performed in dichloroethane, (**145**) is obtained in 40% yield. In methanol, two products (**147**) and (**148**) are formed, both derived from common intermediate (**146**) (Scheme 22) ⟨84JOC587⟩.



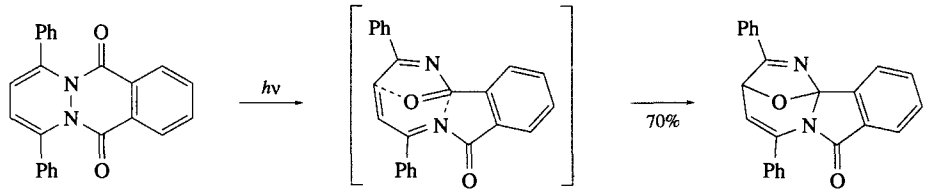
Scheme 22

Unlike reactions described above, photolysis of (**65**) in both methanol and dichloromethane produces high yields (80%) of an intermolecular (2 + 4) adduct (**149**) (Equation (12)) ⟨85JOC5604⟩.



(65) (149) (12)

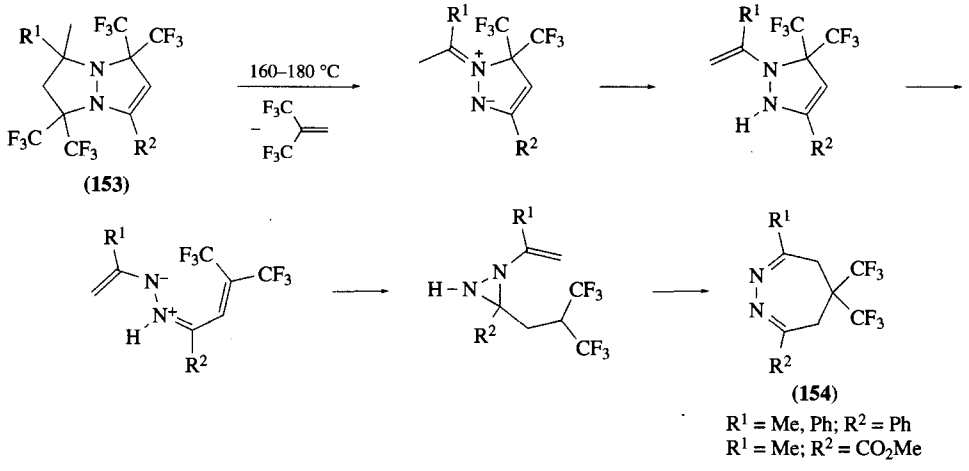
A quite different product (**152**) is formed in 70% yield by photolysis of diphenyl derivative (**150**). Formation of this compound is explained as a result of an electrocyclic conrotatory ring opening leading to (**151**) and subsequent Diels–Alder-like intramolecular cycloaddition of a carbonyl group to the aza diene moiety. The possibility of this unusual Diels–Alder-like reaction is explained by a favorable position of the CO group in (**151**) (Scheme 23) ⟨86JOC3123⟩.



(150) (151) (152)

Scheme 23

Thermolysis of (**153**) causes elimination of 3,3,3-trifluoro-2-trifluoromethylpropene to give (**154**). On the other hand, the similar vinyl derivative (**155**) gives pyrazole (**156**) (Scheme 24) ⟨82LA1741⟩.

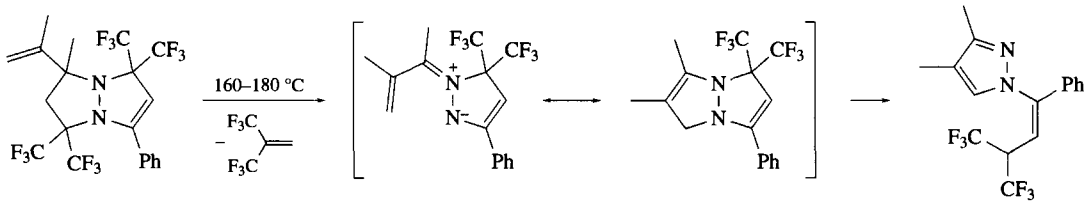


(153)

(154)

R^1 = Me, Ph; R^2 = Ph

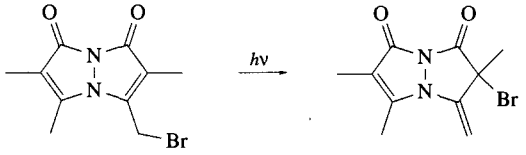
R^1 = Me; R^2 = CO_2Me



(155) (156)

Scheme 24

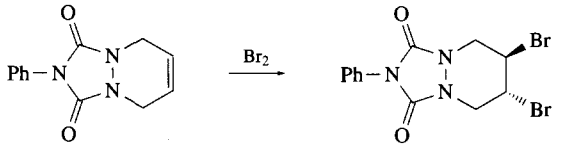
Finally, photolytic isomerization of bromomethyl derivative (**12**) gives exomethylene derivative (**157**) (Equation (13)) ⟨81JOC1666⟩.



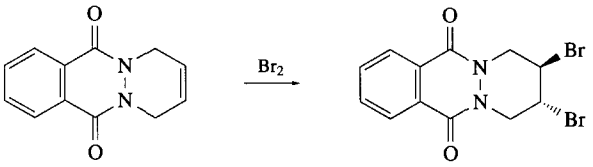
(12) (157) (13)

8.31.7.3 Electrophilic Addition

Compounds (**158**) and (**160**) easily add bromine to give (**159**) and (**161**), respectively (Equations (14) and (15)) ⟨85JOC5604⟩.



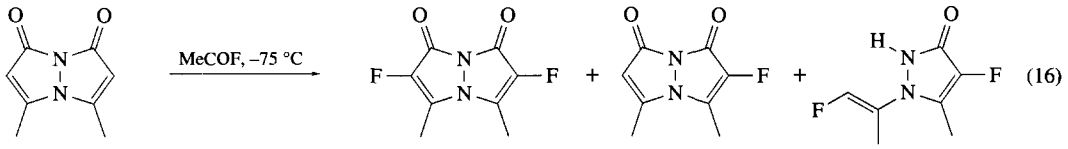
(158) (159) (14)



(160) (161) (15)

8.31.7.4 Electrophilic Substitution

Fluorination of (**162**) with acetyl hypofluorite gives a mixture as shown in Equation (16) ⟨85JOC4152⟩.



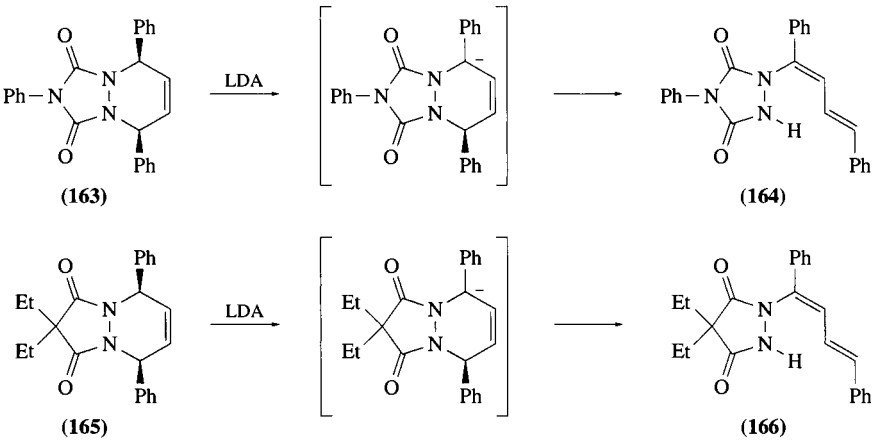
(162) 25% 5% 50% (16)

8.31.7.5 Nucleophilic Attack at Carbon—Deprotonation

Treatment of (**163**) and (**165**) with LDA gives intermediate carbanions which then provide ring opening products (**164**) and (**166**), respectively (Scheme 25) ⟨87JOC101⟩.

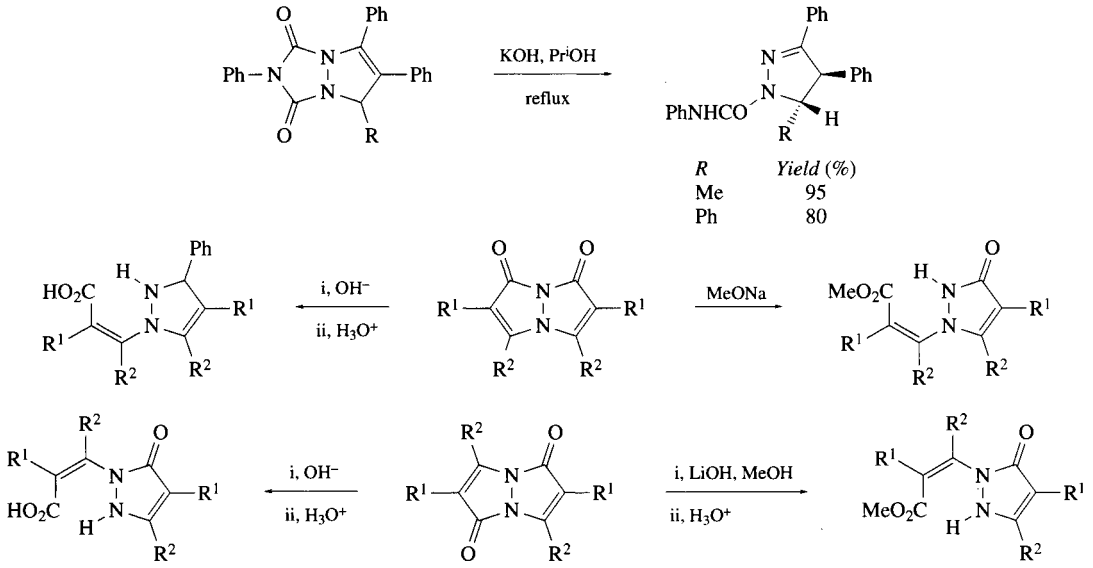
8.31.7.6 Nucleophilic Attack at Carbon—Hydrolysis

Some compounds having one or more carbonyl groups adjacent to a ring junction nitrogen atom undergo alkaline hydrolysis or alcoholysis to provide ring opened compounds ⟨80JA4983, 84CPB930, 90JOC2478⟩. Selected examples are given in Scheme 26.



(163) (164) (165) (166)

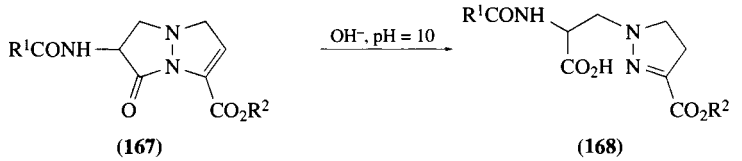
Scheme 25



R	*Yield* (%)
Me	95
Ph	80

Scheme 26

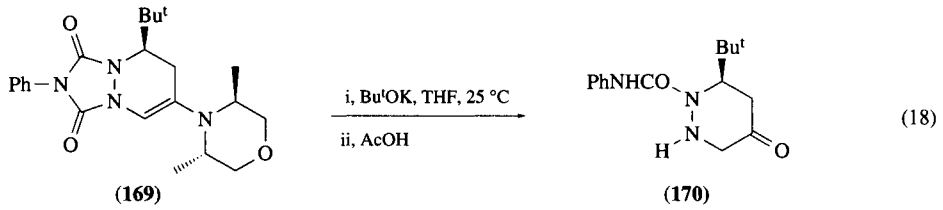
Some compounds are quite sensitive to hydrolysis, for example compounds (**167**) upon treatment with hydroxide ions at pH 10 undergo rapid and selective hydrolysis providing (**168**) (Equation (17)) ⟨87JOC4007⟩.



(17)

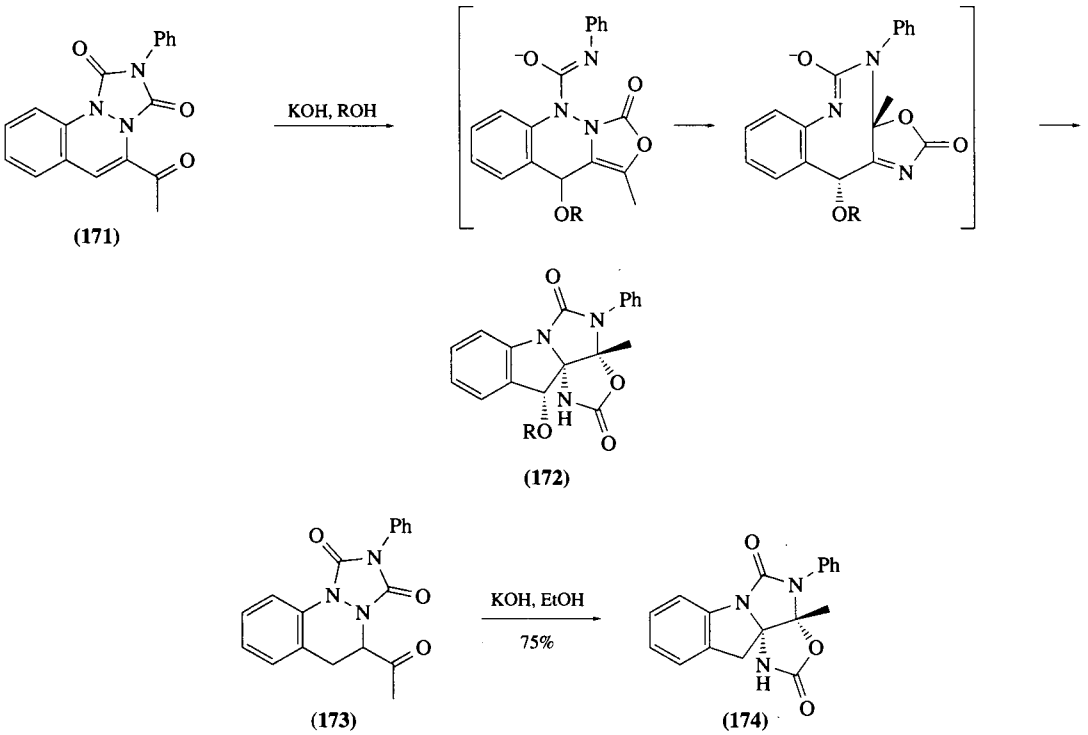
(167) (168)

Reaction of (**169**) with potassium *t*-butylate in THF followed by acidic workup affords hexahydropyridazinone (**170**) (Equation (18)) ⟨94S66⟩.



(169) (170) (18)

Alcoholysis of urazole (**171**) in the presence of KOH affords oxazolidinone derivatives (**172**) in moderate yields. The reaction proceeds via ring opening by Michael addition followed by participation of the carbonyl group and final skeleton rearrangement. The corresponding dihydro derivative (**173**), which is not able to undergo the Michael addition, gives a similar product (**174**) under the same conditions (Scheme 27) ⟨91JCS(P1)2883, 94JCS(P1)2335⟩.



(171) (172) (173) (174)

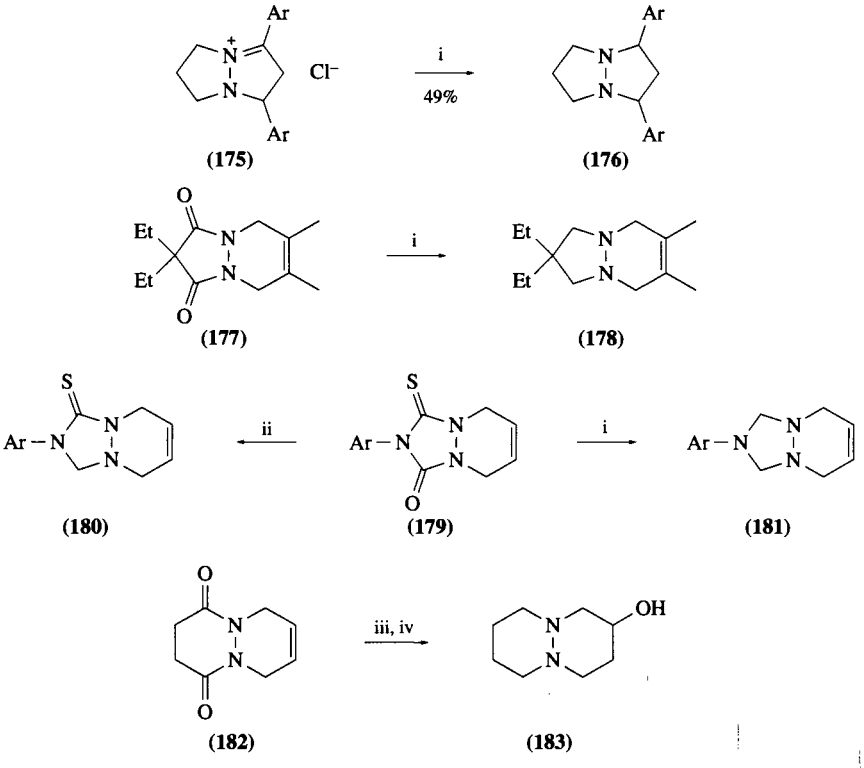
Scheme 27

8.31.7.7 Reduction

LAH reduction of quaternary chloride (**175**) in THF provides (**176**) in 49% yield ⟨68JOC3941⟩. LAH reduction of unsaturated dioxo derivative (**177**) yields the corresponding unsaturated compound (**178**) ⟨72JHC41⟩. Reduction of oxo-thioxo derivative (**179**) with a limited amount of LAH does not affect the thioxo group and the corresponding thioxo derivative (**180**) is isolated. Excess of LAH then provides (**181**) ⟨64ZOB390⟩. Borane reduces CO bonds and also attacks the C=C bond in (**182**) so that subsequent oxidation with hydrogen peroxide provides (**183**) (Scheme 28) ⟨81BRP2105707, 92BMC1293⟩.

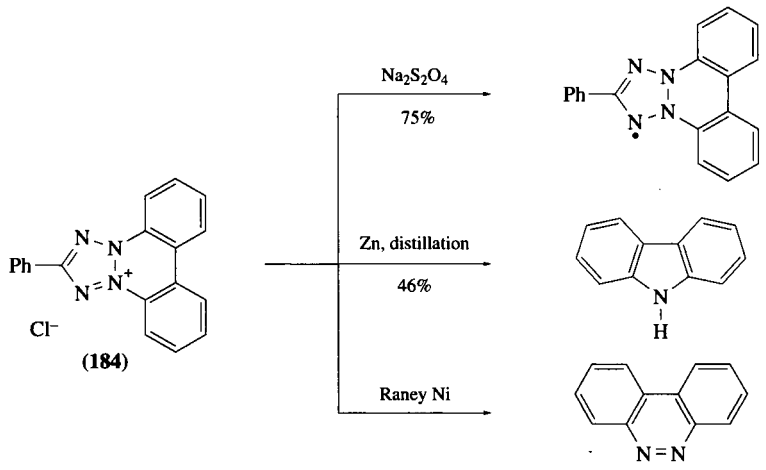
Reduction of quaternary chloride (**184**) and its derivatives has been studied and the results are summarized in Scheme 29 ⟨49CB195, 52LA(578)1, 54LA(590)216, 55CB1595⟩.

Catalytic hydrogenation of (**185**) under rather forcing conditions (palladium, isopropanol, 80 °C, 48 h) yields 10% of the product of N—N bond fission (**186**) (Equation (19)) ⟨80JA4983⟩.

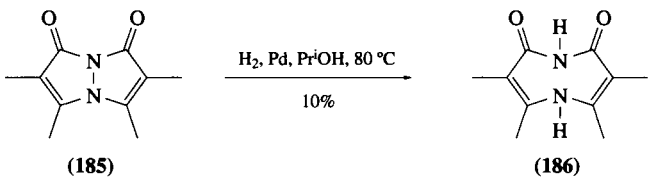


i, LAH (excess), THF, reflux; ii, LAH (1 equiv.), THF, reflux; iii, BH_3, THF; iv, H_2O_2, NaOH

Scheme 28



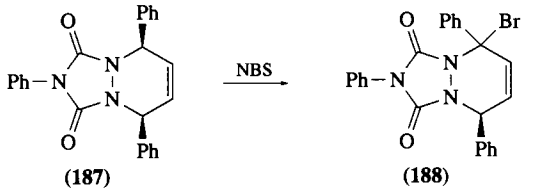
Scheme 29



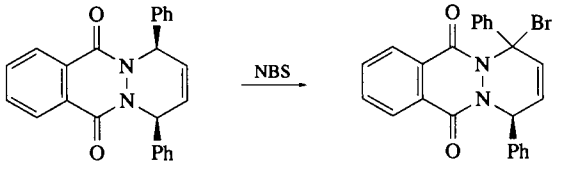
(19)

8.31.7.8 Radical Bromination

Radical bromination of (**187**) and (**189**) with NBS gives monobromination products (**188**) and (**190**) respectively (Equations (20) and (21)) ⟨86JOC3123, 87JOC101⟩.



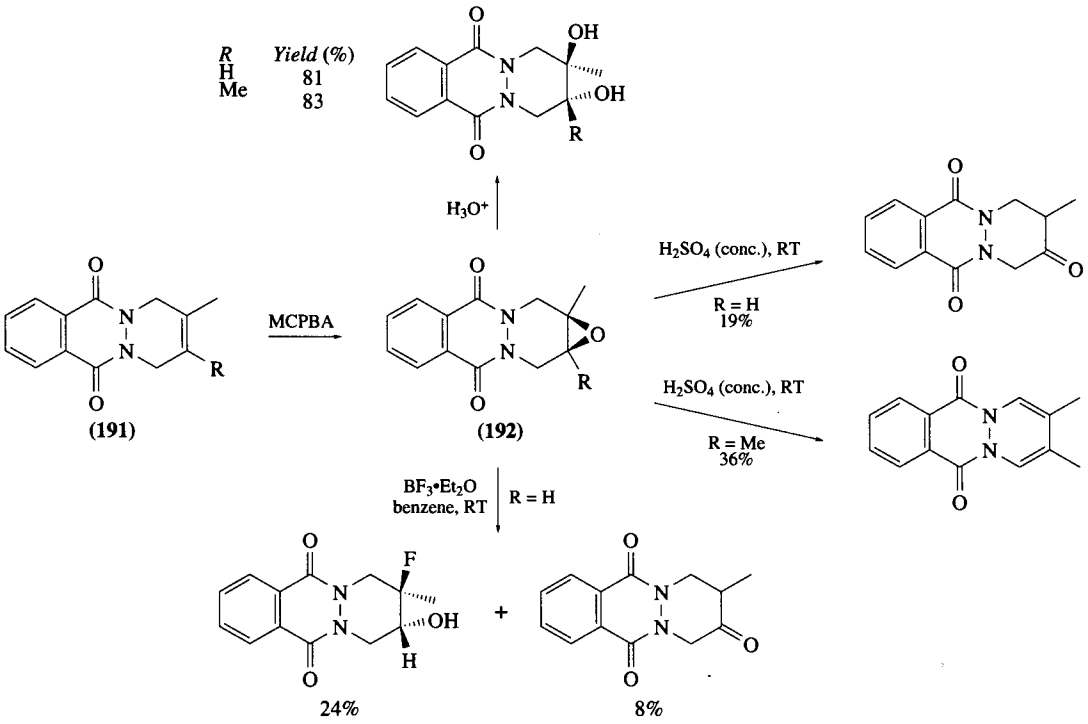
(187) (188) (20)



(189) (190) (21)

8.31.7.9 Oxidation

Peracid oxidation of (**191**) provides oxirane derivatives (**192**), which can be further transformed as is shown in Scheme 30 ⟨85JHC273⟩.



Scheme 30

8.31.8 REACTIVITY OF FULLY SATURATED COMPOUNDS

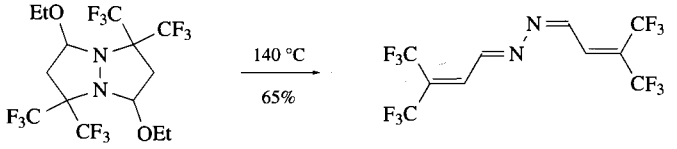
8.31.8.1 General Survey of Reactivity

This section covers fully saturated 5-5, 5-6, and 6-6 bicyclic structures including oxo, thioxo, and imino compounds as well as their benzo analogs. Reactions of the parent compounds without any

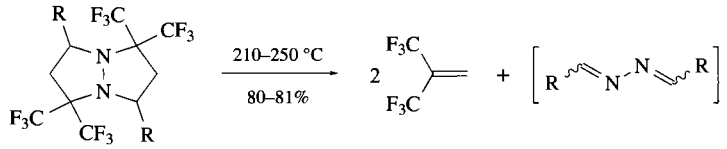
functional groups having only the ring junction nitrogen atoms are limited to *N*-alkylation and reductive N—N bond splitting leading to diazacycloalkanes. Quaternary salts often undergo Hofmann-type elimination reaction. Compounds containing one or more carbonyl groups adjacent to the ring junction nitrogen atoms can be reduced with LAH or diborane. Compounds having β-diketo groupings often have hydrogen atoms acidic enough to show reactions typical for β-diketones.

8.31.8.2 Thermal Reactions

Thermal decomposition of various trifluoromethyl substituted 5-5 bicyclic structures (mostly partially saturated ones) has been studied. Thermolysis of diethoxy derivative (**193**) provides 65% of diazatetraene (**194**) (Equation (22)) ⟨82LA853⟩. Another useful result (Equation (23)) dealing with fully saturated compounds is the finding that 3,3,3-trifluoro-2-trifluoromethyl-propene is formed in high yields by thermolysis of (**195**) ⟨71JCS(C)2404⟩.



(193) (194) (22)

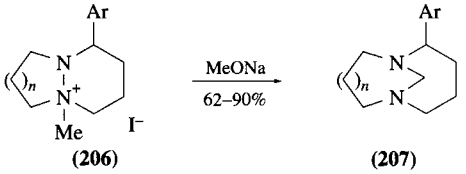


(195) (23)

8.31.8.3 Electrophilic Attack at Nitrogen, *N*-Alkylation

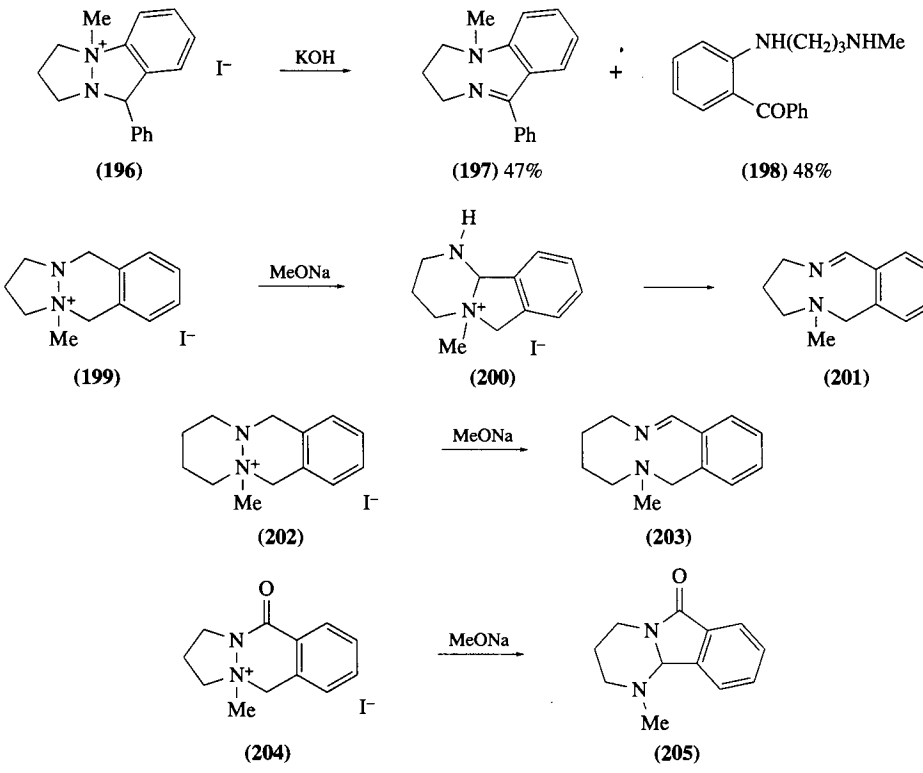
These compounds are usually easily alkylated with alkyl halides, often with methyl iodide, to the corresponding quaternary salts. Some of the salts are of interest as intermediates in the synthesis of medium-sized heterocycles. For example, quaternary salt (**196**) under alkaline treatment provides a mixture of (**197**) and (**198**) ⟨86H(24)3187⟩. Compound (**199**) boiled with sodium methoxide in methanol for 8 h provides a mixture from which 72% of (**200**) and 12% of the Hofmann-type elimination product (**201**) can be isolated. Prolonged heating causes conversion of (**200**) to (**201**) resulting in 75% yield of (**201**) ⟨72CPB1445, 74CPB2142⟩. The same reaction of the corresponding 6-6 fused halides (e.g., (**202**)) results in formation of only the Hofmann-type elimination products (e.g., (**203**)) ⟨69JOC2715, 72CPB1445⟩. These Hofmann-type elimination products can be easily reduced with sodium borohydride ⟨72CPB1445, 74CPB2142⟩ or catalytically hydrogenated ⟨69JOC2715⟩. Oxo derivative (**204**) gives only the product of rearrangement (**205**) under similar conditions (Scheme 31) ⟨70CPB1526, 72CPB69⟩.

Interestingly, 5-5 or 5-6 bicyclic derivatives (**206**), lacking the fused benzene ring, treated with sodium methoxide provide (**207**) (Equation (24)) ⟨69JOC2720⟩. Treatment of quaternary iodide (**208**) with potassium *t*-butoxide provides rearranged isoindole (**209**) (Equation (25)) ⟨74CPB2142⟩.

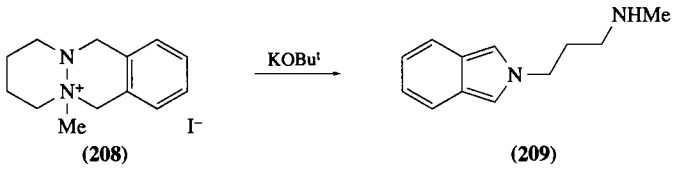


(206) (207) (24)

n = 1,2; Ar = *p*-anisyl



Scheme 31



(25)

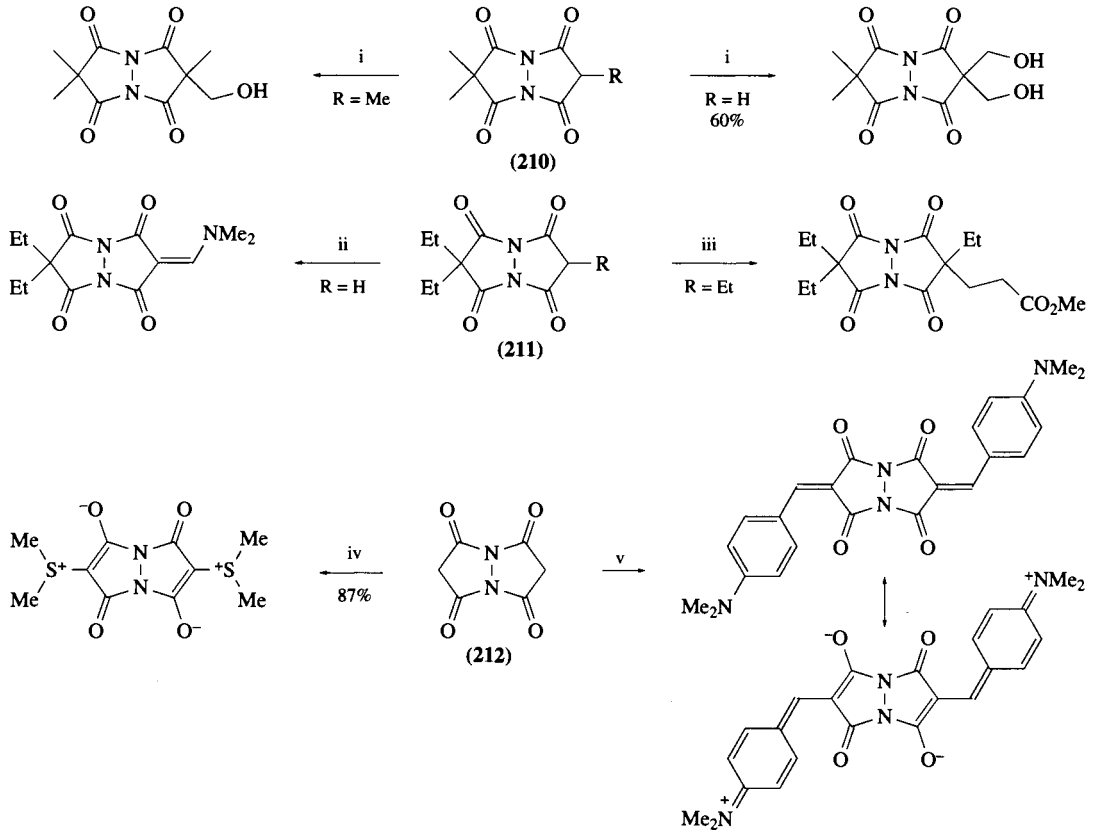
8.31.8.4 Electrophilic Attack at Carbon

Tetraoxo derivatives of 5-5 ring type (e.g., (**210**)–(**212**)) have very acidic hydrogen atoms. Reactivity of these tetrones as nucleophiles is well documented and it is summarized in Scheme 32 ⟨66AP(299)441, 78TL543, 86AP(319)646⟩.

Bicyclic pyrazolidine derivatives (**213**) and (**215**) can be converted into diazo compounds (**214**) and (**216**), respectively, on treatment with tosyl azide in the presence of triethylamine in dichloromethane or acetonitrile ⟨87JCS(P1)885⟩. This diazo transfer reaction is initiated by an electrophilic attack of tosyl azide on the carbanion generated from the respective bicyclic compounds (Scheme 33).

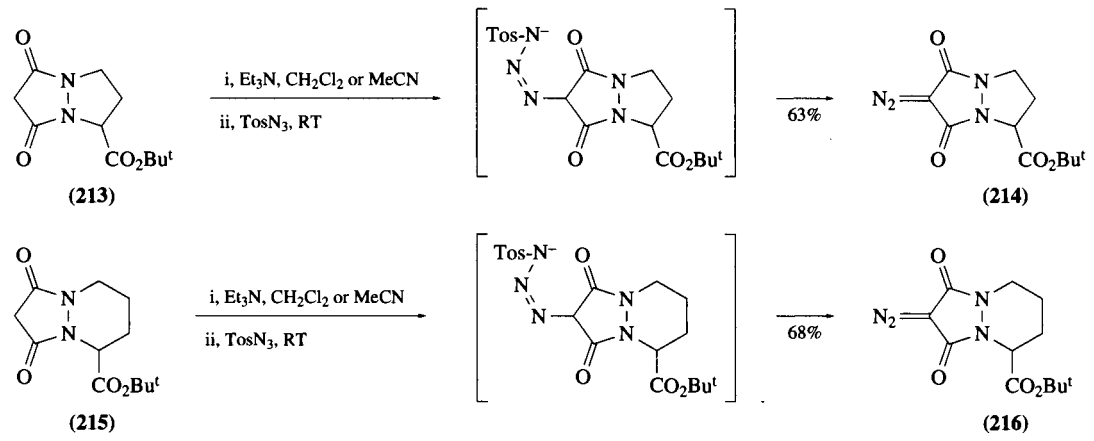
8.31.8.5 Nucleophilic Attack at Carbon

Dioxo derivative (**217**) under alkaline conditions undergoes a ring opening reaction leading to (**218**) (Equation (26)) ⟨69LA(724)150⟩.

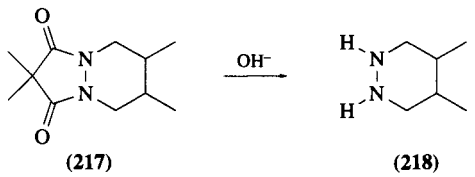


i, CH_2O, H^+; ii, DMF, Ac_2O, reflux; iii, $CH_2{=}CH{-}CO_2H$; iv, DMSO; v, 4-dimethylaminobenzaldehyde

Scheme 32



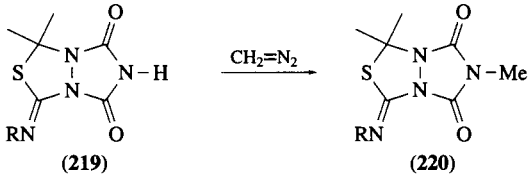
Scheme 33



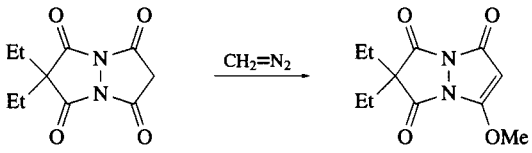
(26)

8.31.8.6 Nucleophilic Attack at a Hydrogen Attached to a Ring Carbon or Ring Nitrogen

Reaction of cyclic lactams with diazomethane is supposed to involve deprotonation in the first step. Treatment of (**219**) with diazomethane leads to the formation of *N*-methylated products (**220**) in nearly quantitative yields (Equation (27)) ⟨84S771⟩. On the other hand, tetrone (**221**) provides *O*-alkylated product (**222**) under the same conditions (Equation (28)) ⟨66AP(299)441⟩. *C*-Alkyl derivative (**224**) is obtained by treatment of the sodium salt of (**223**) with methyl iodide (Equation (29)) ⟨78TL543⟩.



(219) (220) (27)



(221) (222) (28)

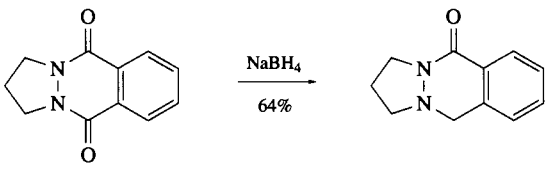


(223) (224) (29)

8.31.8.7 Reduction

Probably the most studied reaction of keto derivatives of this class having the oxo group adjacent to a ring junction nitrogen atom is their reduction with LAH which is summarized in Scheme 34 ⟨63JA3052, 65CB3228, 66JOC1311, 67JA4875, 69HCA1672, 69LA(724)150, 70FES305, 72JHC41, 78TL543, 84CB1659⟩. Some benzo derivatives have also been reduced in the same way ⟨69JOC2715, 70CPB1526, 72CPB1445⟩. Interestingly, *N*-unsubstituted derivative (**225**) is split with LAH into triazoline (**226**) and benzylmethylamine ⟨57HCA852⟩.

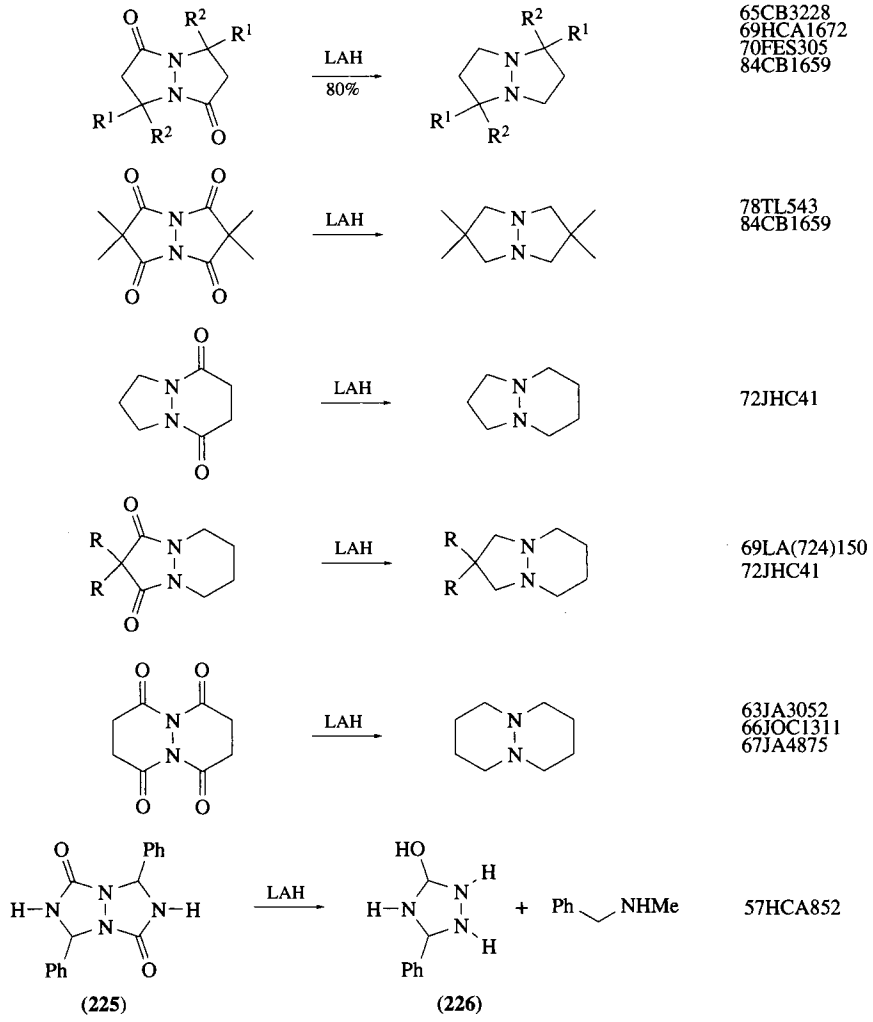
Sodium borohydride reduces only one carbonyl group in (**227**) to provide a good yield of (**228**) (Equation (30)) ⟨70CPB1526⟩.



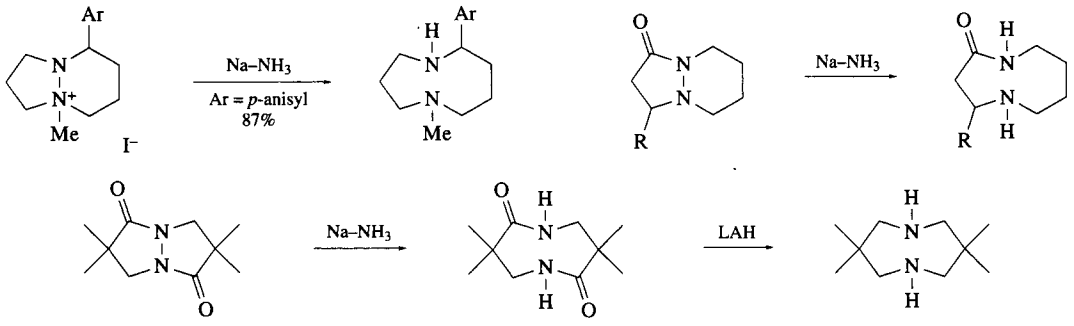
(227) (228) (30)

Reductive cleavage of the N—N bond in bicyclic systems containing a ring junction hydrazine subunit presents a facile route to medium-sized heterocycles containing two or more nitrogen atoms

〈69JOC2720, 79JOC4473, 80TL3493, 81JA461〉. Selected examples are given in Scheme 35. Sodium in ammonia also splits the N—N bond in similar 6-6 diketo derivatives 〈90SL148〉.



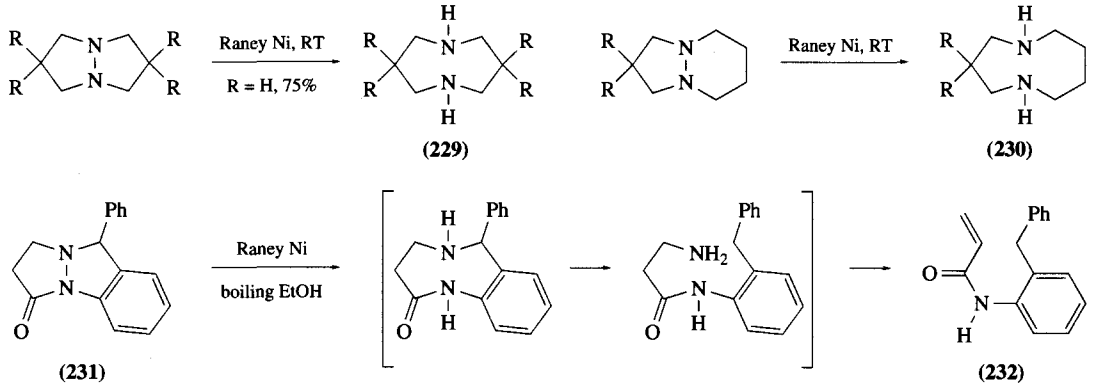
Scheme 34



Scheme 35

Hydrogenation on Raney nickel at room temperature has proved to be very useful for splitting of the N—N bond in neutral bicycles of this type. Diazacyclooctanes (**229**) 〈58CB1982, 65CB3228,

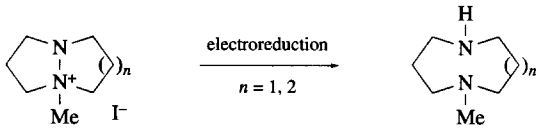
84CB1659〉 and diazacyclononanes (**230**) 〈58CB1982, 72JHC41〉 can be prepared in good yields by this method (Scheme 36). Treatment of (**231**) with Raney nickel in refluxing ethanol surprisingly provides (**232**) as the sole reaction product which could be isolated in 23% yield 〈91T9599〉. The supposed reaction intermediates are shown in Scheme 36.



(229) (230) (231) (232)

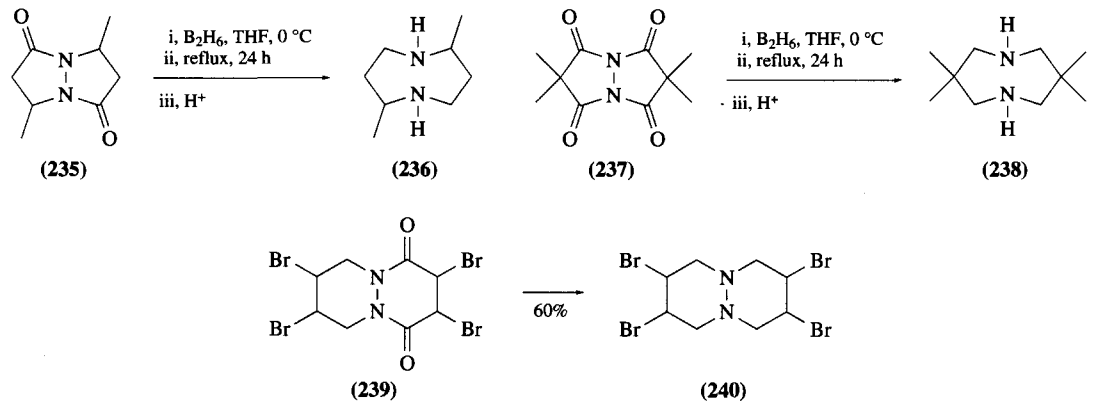
Scheme 36

Electroreductive cleavage of (**233**) in methanol provides (**234**) in 55% ($n = 1$) and 15% ($n = 2$) yields (Equation (31)) 〈78LA1505〉.



(233) (234) (31)

Diborane reduction is summarized in Scheme 37. Diketo bicycles of this type in some instances provide products of the carbonyl group reduction and N—N bond splitting. For example, dioxo derivative (**235**) and tetraoxo derivative (**237**) provide (**236**) and (**238**), respectively, in high yields 〈78TL543, 79JOC4473〉. On the other hand, tetrabromo compound (**239**) is reduced to (**240**) which is isolated in 60% yield 〈75JOC47〉.

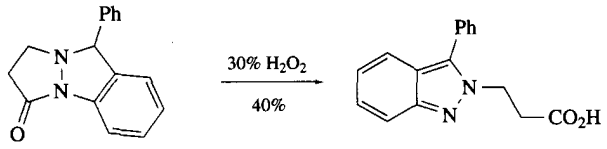


(235) (236) (237) (238) (239) (240)

Scheme 37

8.31.8.8 Oxidation

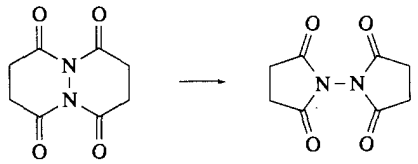
Oxidative ring cleavage of (**231**) with hydrogen peroxide provides 40% yield of the indazole (**241**) (Equation (32)) ⟨91T9599⟩.



(231) (241) (32)

8.31.8.9 Rearrangement Reactions

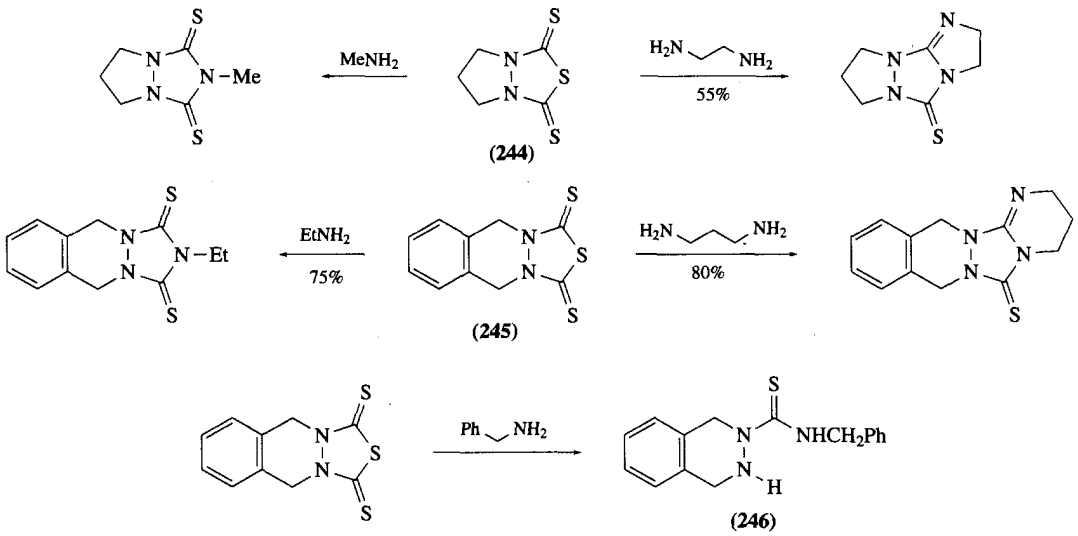
Tetrone (**242**) undergoes an interesting rearrangement to *N,N'*-bissuccinimide (**243**) (Equation (33)) either on heating or on reaction with succinyl chloride or hydrogen chloride in dioxane ⟨63JA3052, 67JA4875⟩.



(242) (243) (33)

8.31.8.10 Other Reactions

Compounds having in their structure the 1,3,4-thiadiazoledithione moiety (e.g. (**244**) and (**245**)) easily react with methyl or ethyl amine to yield the corresponding triazole derivatives. When 1,2- or 1,3-diaminoalkanes are used, additional five-membered or six-membered fused rings are formed ⟨92BMC1293, 94PHA489⟩. Interestingly, some amines (e.g., benzyl amine or isopropyl amine) provide only corresponding ring-opened derivatives (**246**) (Scheme 38) ⟨94PHA489⟩.



Scheme 38

8.31.9 REACTIVITY OF SUBSTITUENTS

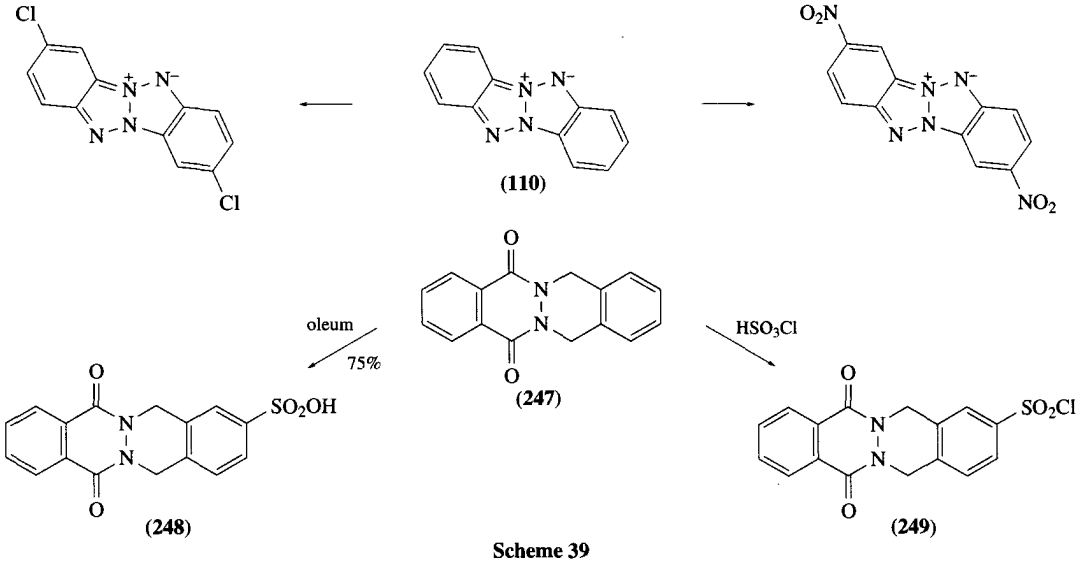
8.31.9.1 General Survey

This subsection contains some more or less general reactions of substituents of 5-5, 5-6, and 6-6 bicyclic compounds containing two ring-junction nitrogen atoms described in the literature. Since substituents removed from the bicyclic moiety by three or more saturated carbon atoms are not usually influenced by the moiety in their reactivity, such substituents are not treated here.

8.31.9.2 Fused Benzene Rings

8.31.9.2.1 Electrophilic attack at carbon

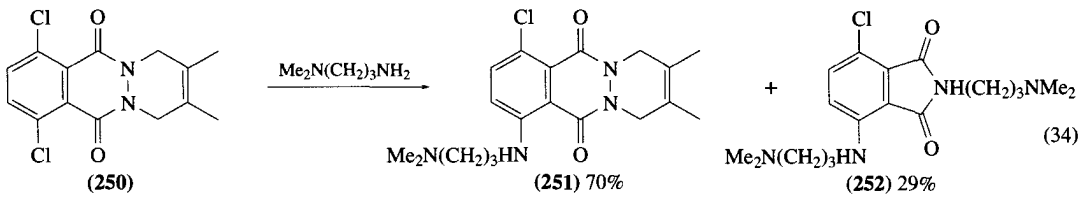
As was mentioned in Section 8.31.6.4, electrophilic attack at carbon of conjugated mesomeric betaines is very easy. Dibenzo derivative (**110**) having no hydrogen atom at the heteropentalene moiety can undergo electrophilic substitution only on phenyl rings. Halogenation and nitration of the compound lead to the corresponding disubstituted derivatives (Scheme 39) ⟨67JA2618⟩. In dibenzo derivative (**247**), electrophilic substitution occurs in the benzene ring without adjacent carbonyl groups. Thus sulfonation with oleum gives (**248**) and reaction with chlorosulfonic acid provides (**249**) ⟨84ZOR1575⟩.



Scheme 39

8.31.9.2.2 Nucleophilic displacement reactions

Halogen atoms activated by carbonyl groups adjacent to the benzene ring can be, in some cases, displaced with nucleophiles. For example, compound (**250**) treated with *N,N*-dimethylaminopropyl amine gives the product of monosubstitution (**251**) together with the rearrangement 2 : 1 product (**252**). No product of normal disubstitution is formed (Equation (34)) ⟨92CPB2905⟩.

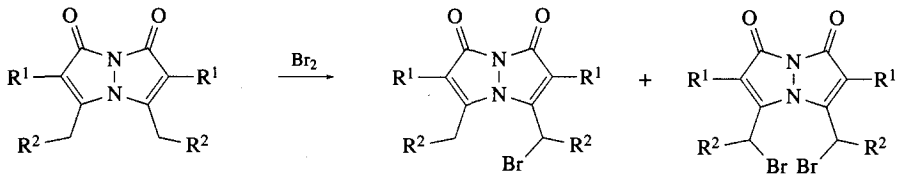


(34)

8.31.9.3 Alkyl Groups

8.31.9.3.1 Electrophilic attack at carbon

Reactivity of methyl groups in bimanes has been extensively studied. From the products of such reactions, halomethyl derivatives are of great interest for their reactivity and for the properties of these reaction products. Bromination of β-alkyl *syn*-bimanes provides moderate yields of monobromobimanes together with low amounts of the corresponding dibromoalkyl compounds (Equation (35)) ⟨80JA4983⟩.

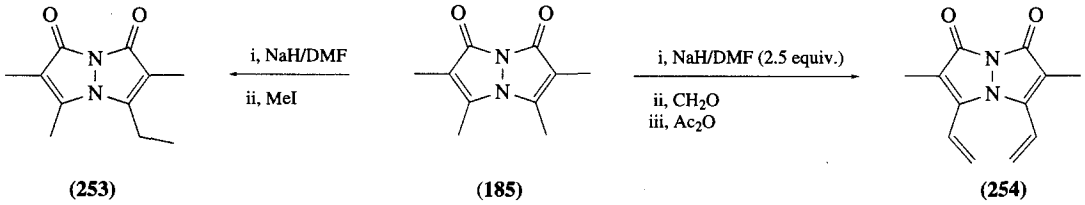


R^1 = Me, Cl; R^2 = H, Me

(35)

8.31.9.3.2 Nucleophilic attack at hydrogen attached to carbon

A methyl group on carbon adjacent to the ring junction nitrogen in bimane (**185**) is active enough to form an anion when treated with sodium hydride in DMF. This fact can be used for the synthesis of the ethyl derivative (**253**) as well as the vinyl derivative (**254**) as is shown in Scheme 40 ⟨90JA7305⟩.



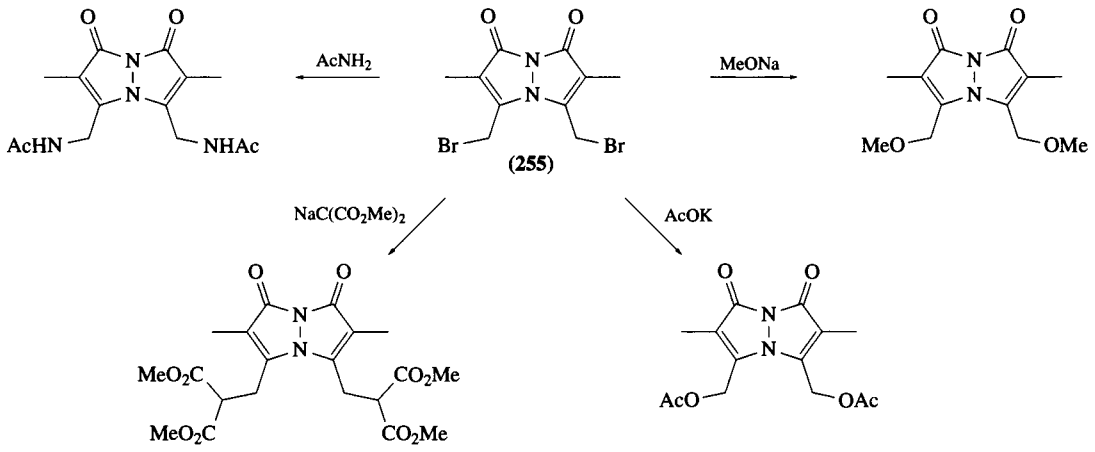
Scheme 40

8.31.9.4 Haloalkyl Groups

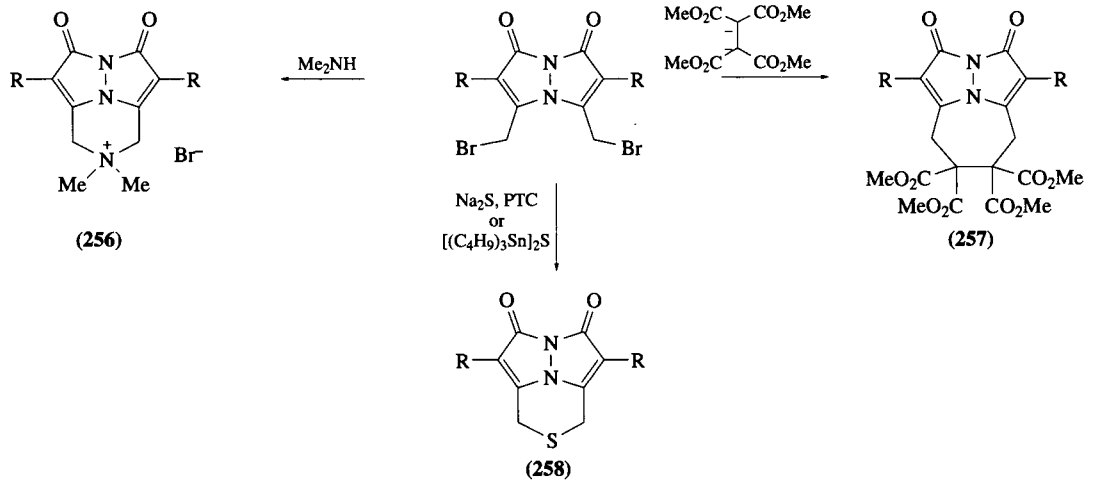
8.31.9.4.1 Nucleophilic displacement reactions

Bimanes containing one or two bromomethyl groups are very sensitive to nucleophilic substitution ⟨81JOC1666, 86JA4527⟩. Selected examples of reactivity of compound (**255**) are mentioned in Scheme 41.

This type of bifunctional compound has a tendency to form additional bridged rings, for example, quaternary bromide (**256**) is formed with dimethylamine ⟨81JOC1666⟩. Similar bridged tricyclic compounds (**257**) and (**258**) have been prepared (Scheme 42) ⟨90JA7315, 90JA7320⟩.



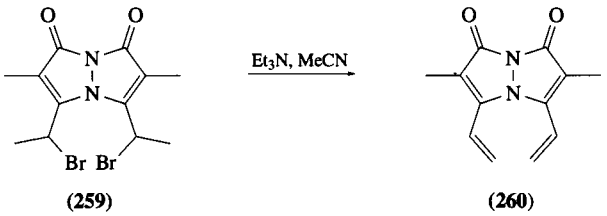
Scheme 41



Scheme 42

8.31.9.4.2 Dehydrohalogenation

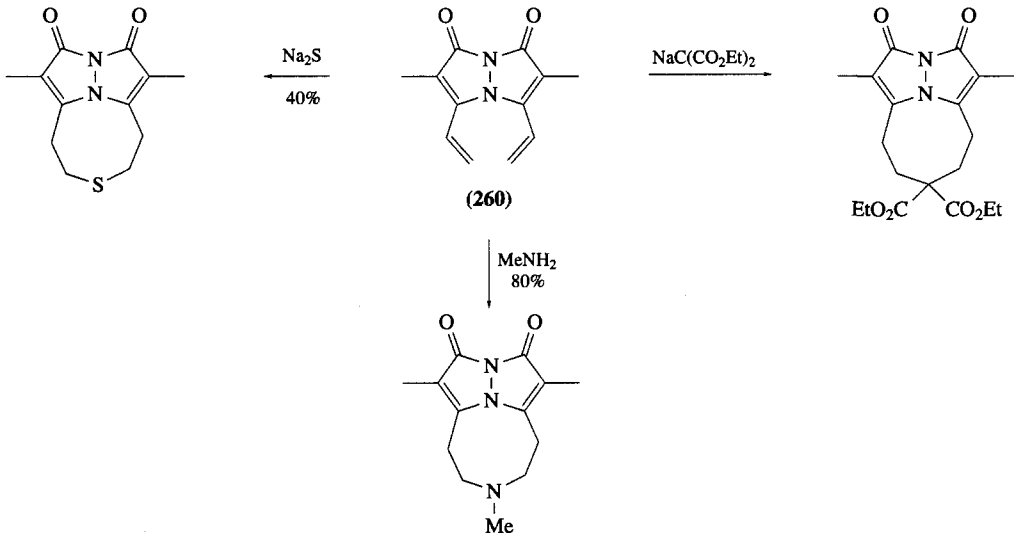
Bromoethyl bimanes (e.g., (**259**)) are easily dehydrobrominated to the corresponding vinyl derivatives which are useful intermediates for the synthesis of bridged bimanes (Equation (36)) ⟨90JA7305⟩.



(36)

8.31.9.5 Vinyl Group

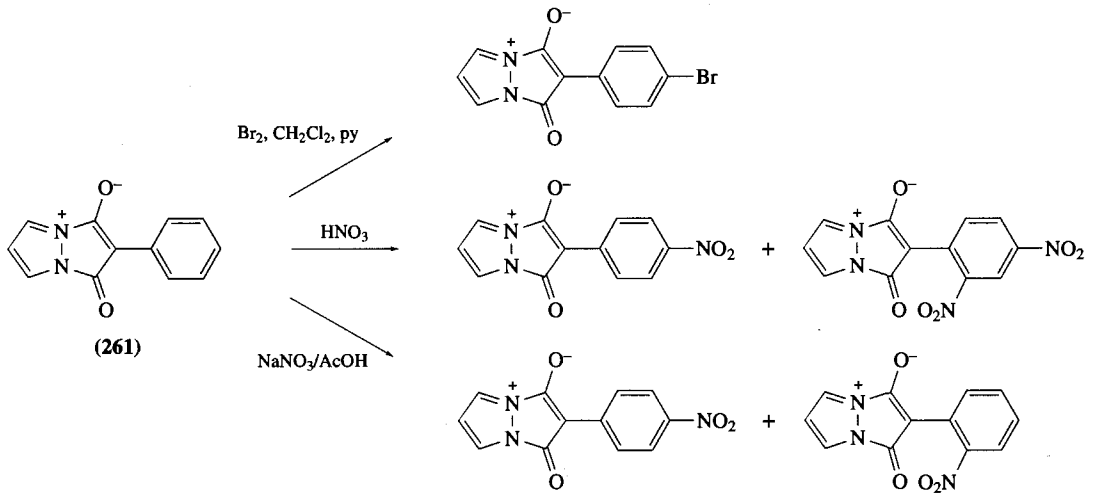
Vinyl bimanes (e.g., (**260**)) have been used for the synthesis of bridged bimanes with eight-membered rings. Typical reactions of (**260**) are summarized in Scheme 43 ⟨90JA7305⟩.



Scheme 43

8.31.9.6 Aryl Groups

The 2-phenyl derivative (**261**) undergoes ready electrophilic substitution in the phenyl ring; selected examples are given in Scheme 44 ⟨88JOC2898⟩.

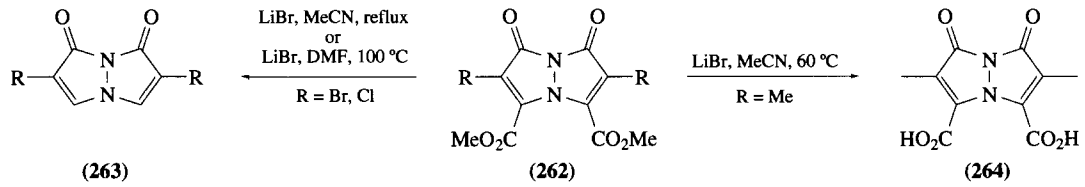


Scheme 44

8.31.9.7 Carboxylic Acids and Esters

8.31.9.7.1 Decarboxylation

Bimane esters (**262**) are stable toward hydrobromic acid in acetic acid even at reflux temperature. Nevertheless, lithium bromide in acetonitrile or DMF causes a dealkylation–decarboxylation reaction leading to the corresponding compounds (**263**). In some cases (e.g., for R = Me) the ester is reactive enough that the reaction can be carried out at 60 °C and the resulting dicarboxylic acid (**264**) is stable enough for isolation (Scheme 45) ⟨82JOC214⟩.

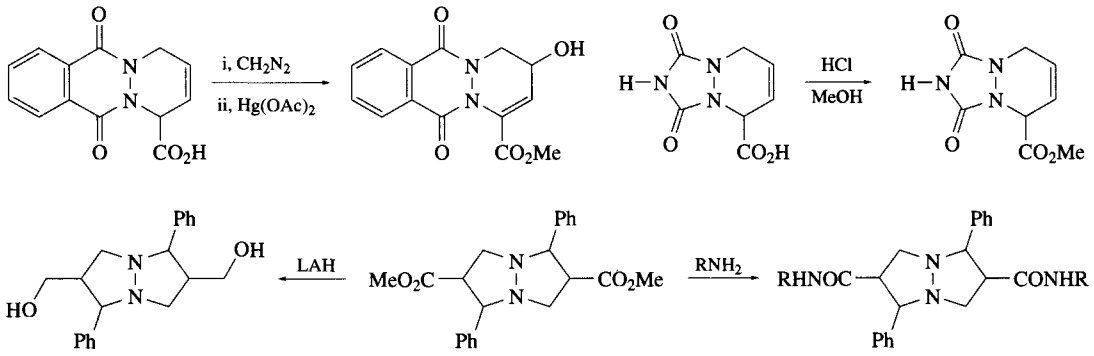


(263) (262) (264)

Scheme 45

8.31.9.7.2 Esterification

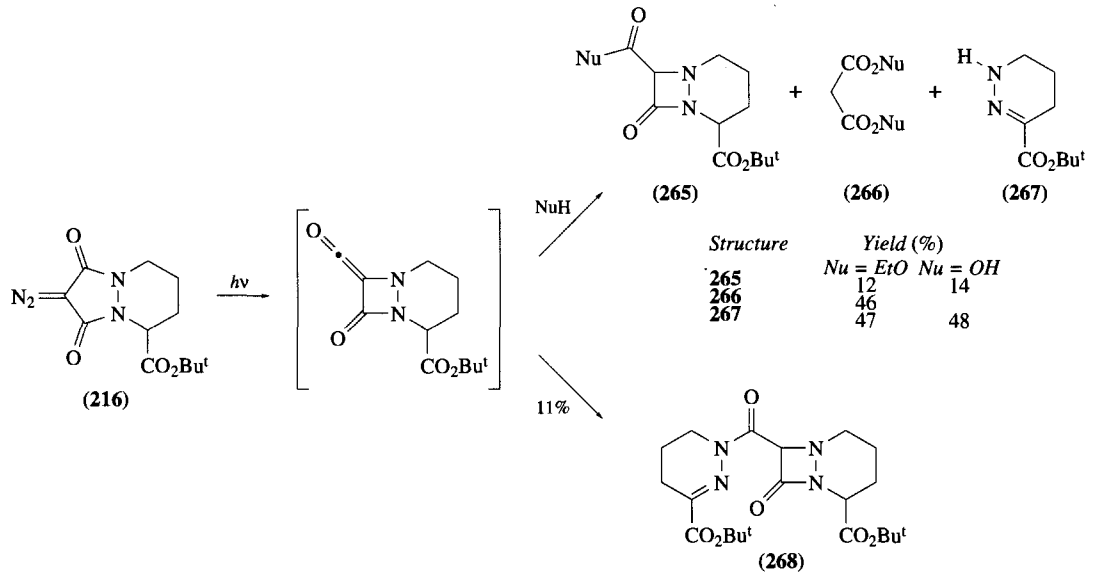
Carboxylic acids can be esterified by the usual methods as shown in Scheme 46 ⟨77H(7)119, 84JCS(P1)155⟩. In general, behavior of the esters is unsurprising. LAH reduction and reaction with primary amines are shown in Scheme 46 as examples ⟨57HCA852⟩.



Scheme 46

8.31.9.8 Diazo Group

Photochemical ring contraction of etheral solutions of diazo compound (**216**) in the presence of nucleophiles (e.g., ethanol or water) provides low yields of the products (**265**). Higher yields of products of splitting (**266**) and (**267**) can be detected (Scheme 47). The pyridazine (**267**), formed in the reaction, is itself sufficiently nucleophilic to intercept the ketene intermediate when the reaction is performed without any nucleophile. Compound (**268**) is then obtained in 11% yield. No product of the ring contraction is formed when 5-5 bicyclic diazo derivative compound (**214**) is similarly treated ⟨87JCS(P1)885⟩.



(216) (265) (266) (267) (268)

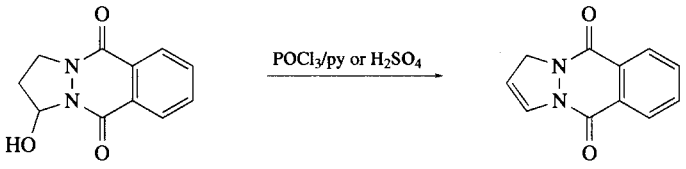
Structure	*Yield (%)*	
	Nu = EtO	*Nu = OH*
265	12	14
266	46	
267	47	48

Scheme 47

8.31.9.9 Hydroxy and Oxo Groups

8.31.9.9.1 Dehydration

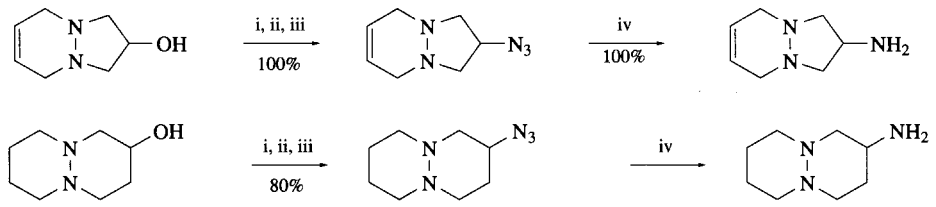
Some hydroxy derivatives (e.g., (**269**)) are easily dehydrated to the corresponding unsaturated analogs. The reaction sometimes occurs spontaneously, sometimes sulfuric acid or phosphorus trichloride in pyridine is used (Equation (37)) ⟨70CPB1526⟩.



(269) (37)

8.31.9.9.2 Nucleophilic attack at hydrogen attached to oxygen

Compounds having hydroxy groups at the β position to a ring junction nitrogen atom are nearly quantitatively transferred under conditions typical for the Mitsunobu reaction to the corresponding azides which can be reduced with LAH to amines in high yields. Examples are given in Scheme 48 ⟨81BRP2105707, 92BMC1293⟩.

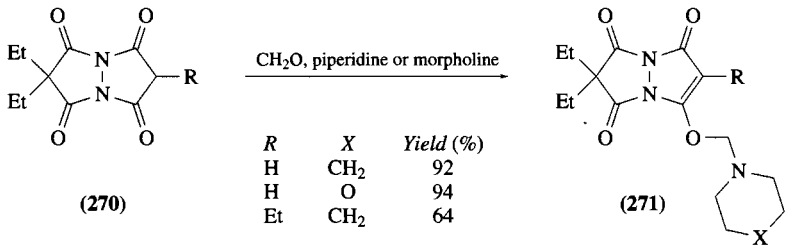


i, Ph_3P; ii, diethyl azodicarboxylate; iii, HN_3; iv, LAH

Scheme 48

8.31.9.9.3 Electrophilic reaction

Tetrones (**270**) react with cyclic amines (piperidine, morpholine) and formaldehyde in their enol forms and provide good yields of the respective derivatives (**271**) (Equation (38)) ⟨66AP(299)441⟩.

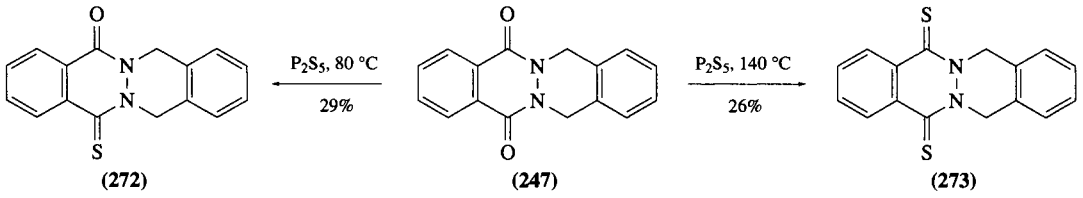


R	*X*	*Yield* (%)
H	CH_2	92
H	O	94
Et	CH_2	64

(270) (271) (38)

8.31.9.9.4 Nucleophilic displacement reaction

Phosphorus pentasulfide is a useful reagent for converting a carbonyl group into a thiocarbonyl group. Dioxo derivative (**247**) can be transformed at 80 °C to oxo-thioxo derivative (**272**) and at 140 °C to the corresponding dithioxo compound (**273**) (Scheme 49) ⟨84ZOR1575⟩.



(272) (247) (273)

Scheme 49

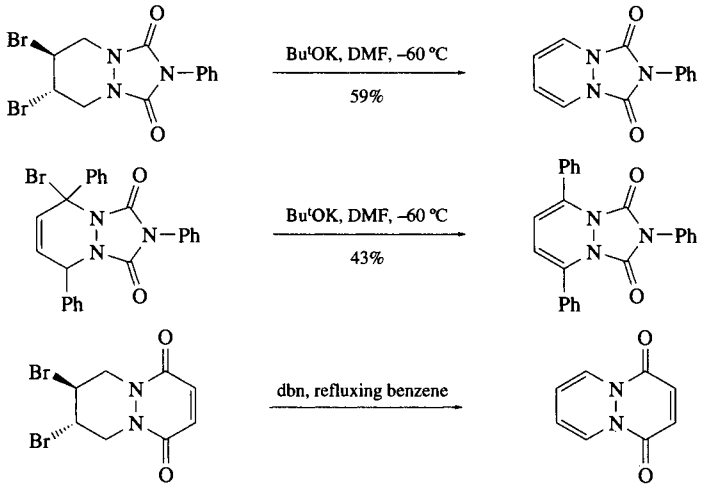
8.31.9.10 Halogen Atoms

8.31.9.10.1 Reductive dehalogenation

Hydrogenolysis of halogen over palladium or platinum, which is usual for aromatic compounds, is described also for both *syn*- and *anti*-halogenated bimanes. For example, catalytic hydrogenation of *syn*-(Cl,Me)B over palladium in acetic acid proceeds easily in two stages. The product of total dehalogenation *syn*-(H,Me)B is obtained in 55% yield ⟨80JA4983, 82JOC214⟩.

8.31.9.10.2 Dehydrohalogenation

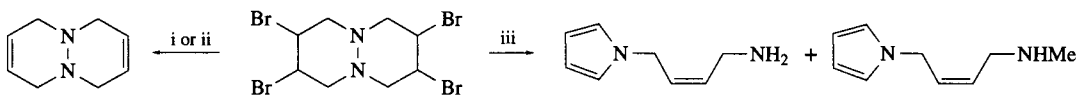
Elimination of hydrogen halides is usually a base catalyzed process. Selected examples are given in Scheme 50 ⟨72TL1885, 85JOC5604, 87JOC101⟩.



Scheme 50

8.31.9.10.3 Dehalogenation

Tetrabromo derivative (**240**) treated with methyl lithium in benzene or LAH in THF undergoes a dehalogenation reaction leading to (**274**). When the reaction with methyl lithium is performed in ether, a mixture of pyrroles (**275**) and (**276**) is formed (Scheme 51) ⟨75JOC47⟩.



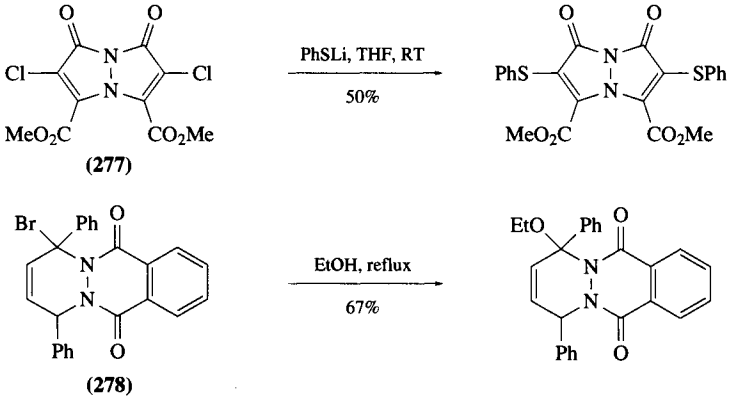
(274) (240) (275) (276)

i, MeLi, benzene; ii, LAH, THF; iii, MeLi, ether

Scheme 51

8.31.9.10.4 Nucleophilic displacement reactions

Replacement of both chloro atoms in (**277**) by PhS^- takes place when the compound is treated with lithium thiophenolate in THF at room temperature ⟨82JOC214⟩. Benzo derivative (**278**) heated to reflux in ethanol gives the corresponding ethoxy derivative in 67% yield (Scheme 52) ⟨86JOC3123⟩.



(277) (278)

Scheme 52

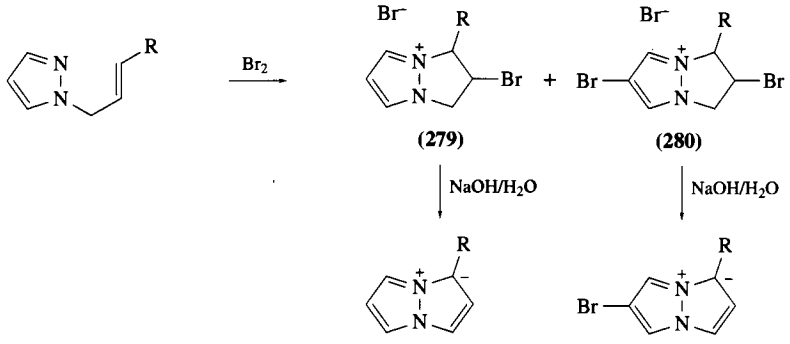
8.31.10 SYNTHESIS OF CONJUGATED HETEROCYCLIC MESOMERIC BETAINES

8.31.10.1 Pyrazolo[1,2-*a*]pyrazole

8.31.10.1.1 Ring syntheses by formation of one bond

(i) Bond formation α to the ring junction nitrogen atom

Bromination of *N*-allylpyrazoles followed by heating of the crude reaction mixture leads to salts (**279**) and (**280**) which under alkaline conditions provide the corresponding pyrazolo[1,2-*a*]pyrazoles (Scheme 53). The parent bicyclic compound and its derivatives containing electron donating substituents were prepared by this route ⟨65JA4393, 65JA5256, 66JA1992, 66JA5588⟩. Corresponding benzo and dibenzo derivatives have not been reported.

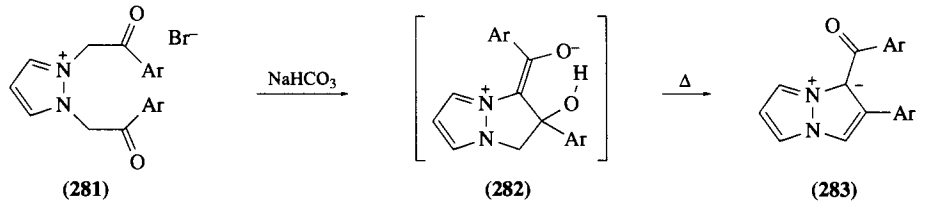


(279) (280)

Scheme 53

(ii) Bond formation β to the ring junction nitrogen atom

Pyrazole is first converted to 1,2-diphenacyl pyrazolium salts (**281**) by reaction with the appropriate phenacyl bromide. The salts undergo cyclization to (**283**) when treated with aqueous sodium hydrogen carbonate. In some cases intermediates (**282**) are intercepted and prolonged heating is necessary for the conversion to (**283**) (Scheme 54) ⟨63CI(L)1462, 65JA528⟩.



(281) (282) (283)

Scheme 54

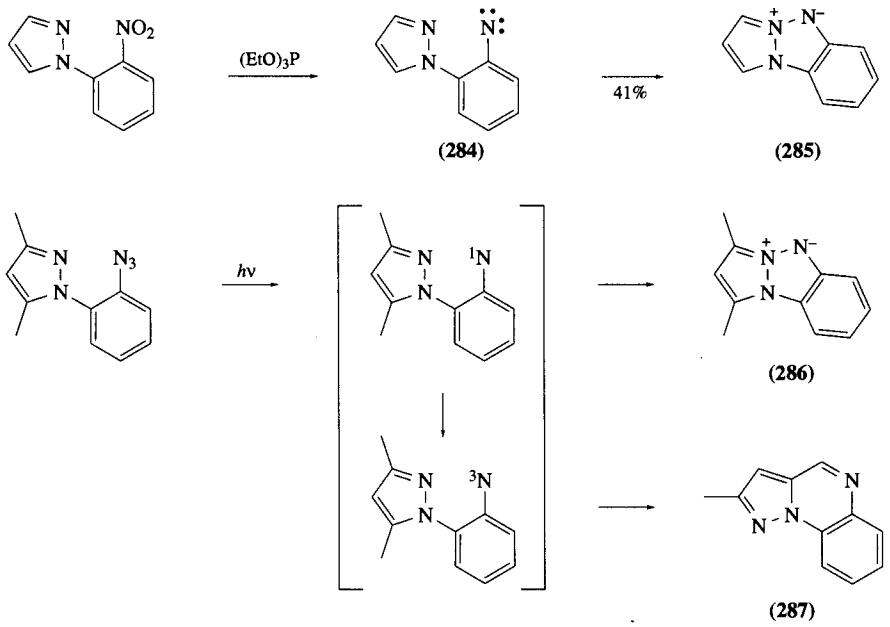
8.31.10.2 Pyrazolo[1,2-*a*][1,2,3]triazole

8.31.10.2.1 Ring syntheses by formation of one bond

(i) Bond formation α to the ring junction nitrogen atom

Monobenzo derivatives (**285**) can be prepared by an electrophilic attack of singlet nitrenes (**284**) on the pyrazole nitrogen atom. The nitrenes are usually generated either by reduction with triethylphosphite ⟨65JHC218, 72OPP273, 74JCS(P1)1970, 76TL925, 80JCS(P1)982, 81CL331, 83JOC1080⟩, or by thermolysis or photolysis of the corresponding azides ⟨76TL925, 80JCS(P1)982, 81CL331⟩. Photolysis of 1-(2-azidophenyl)-3,5-dimethylpyrazole leads to singlet nitrene which as an electrophile provides (**286**). Triplet nitrene abstracts a hydrogen from the methyl group and affords pyrazolo[1,2-*a*]quinoxaline (**287**) (Scheme 55).

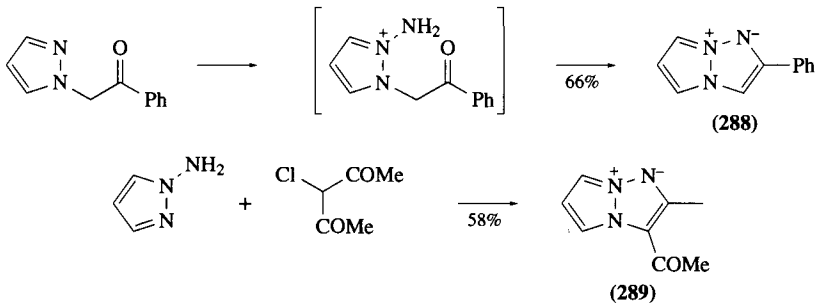
Dibenzo derivatives are formed in a similar manner ⟨71JHC707, 74CL951⟩.



Scheme 55

(ii) Bond formation β to the ring junction nitrogen atom

The 2-phenyl derivative (**288**) is obtained in 66% yield by *N*-amination of 1-phenacyl pyrazole followed by base-catalyzed cyclodehydration ⟨75MI 831-01, 78TL1291⟩. Treatment of 1-amino pyrazole with 3-chloropentane-2,4-dione provides the corresponding 1-acetyl-2-methyl derivative (**289**) (Scheme 56) ⟨78TL1291⟩.

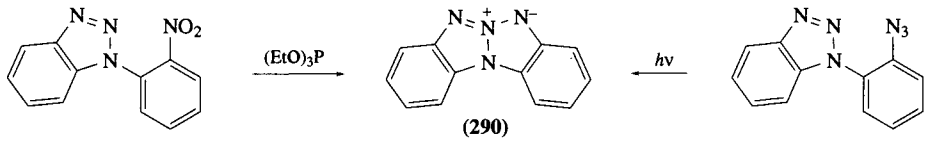


Scheme 56

8.31.10.3 1,2,3-Triazolo[1,2-*a*][1,2,3]triazole

8.31.10.3.1 Ring syntheses by formation of one bond

Dibenzo derivative (**290**) can be prepared by reductive cyclization of the corresponding 2-nitrophenyl benzotriazole with triethyl phosphite or photochemically from the corresponding azide (Scheme 57) ⟨67JA2618, 67JA2633⟩. The monobenzo derivative is similarly accessible ⟨67JA2633⟩.

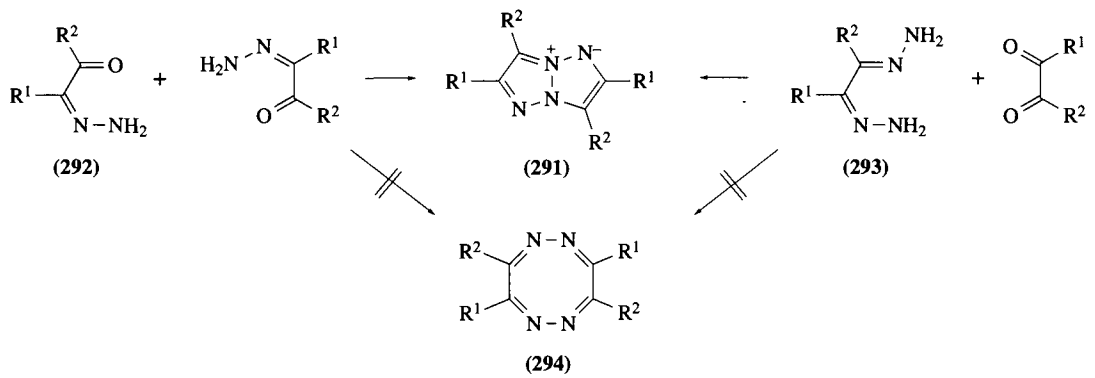


Scheme 57

8.31.10.4 1,2,3-Triazolo[2,1-*a*][1,2,3]triazoles

8.31.10.4.1 Ring syntheses from acyclic precursors

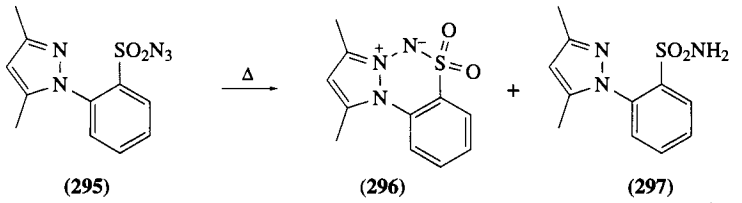
There are two principal methods leading to triazolo[2,1-*a*][1,2,3]triazoles (**291**) starting from different acyclic precursors. The first method is based on thermal dehydration of acyl hydrazones (**292**). The same products can be obtained by reaction of dihydrazones (**293**) with the corresponding diketones. These reactions were first reported in 1956 and structure (**294**) was erroneously assigned to the products ⟨56AG580, 56AG680, 60AG563⟩. It seems to be reasonable that this structure is first formed and rearranged to the more stable structure (**291**) (Scheme 58).



Scheme 58

8.31.10.5 Pyrazolo[1,2-*c*][1,2,3,4]thiatriazine

Only the benzo analog of this bicyclic structure is known, in the form of its *S,S*-dioxide (**296**). It is formed as a main product of thermal cyclization of pyrazole (**295**) in chlorobenzene (isolated yield of 23%) together with 8% of the corresponding sulfonamide (**297**) (Equation (39)) ⟨80JCS(P1)982⟩.



(295) (296) (297) (39)

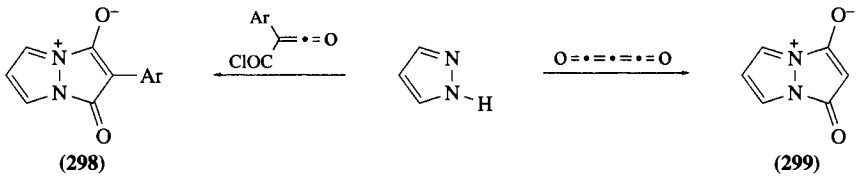
8.31.11 SYNTHESIS OF CROSS-CONJUGATED MESOMERIC BETAINES

8.31.11.1 Mesomeric 1-Oxo-1*H*-pyrazolo[1,2-*a*]pyrazol-4-ium-3-olates

8.31.11.1.1 Ring syntheses by formation of two bonds

(i) From [3 + 2] atom fragments, both adjacent to ring junction nitrogen atoms

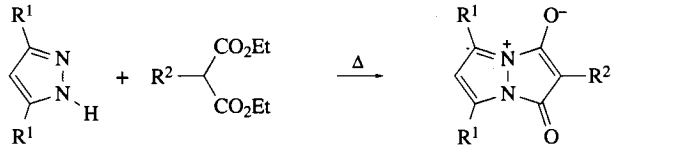
Mesomeric oxo-pyrazolo[1,2-*a*]pyrazol-4-ium-3-olates were first described independently by Potts ⟨80JA3971⟩ and Friedrichsen ⟨80ZN(B)1002⟩. The first syntheses of these compounds started from chlorocarbonylketenes (Scheme 59). These effective bielectrophiles react with the 1,2-binucleophilic system of pyrazole to form mesomeric betaines (**298**). Benzo analogs can also be prepared from indazoles by this method ⟨80JA3971, 82JOC295, 83JCS(P1)11⟩. The parent compound (**299**) is prepared by a similar reaction of pyrazole with carbon suboxide as the 1,3-bielectrophile (Scheme 59) ⟨88JOC2889⟩.



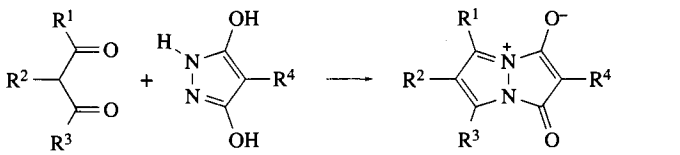
(298) (299)

Scheme 59

Thermal condensation of pyrazoles with substituted diethyl malonates or triethyl methanetricarboxylate provides an easy way to 2-substituted derivatives (**300**). Yields range between 30% and 60% and combined with an easy availability of the malonates this approach could be attractive (Equation (40)) ⟨89S629⟩. An alternative approach starting from 3,5-dihydroxypyrazoles and 1,3-dicarbonyl compounds is applicable for a wide range of substituents (Equation (41)) ⟨82JOC295⟩.



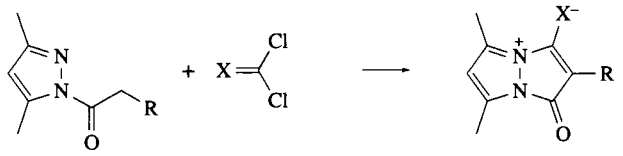
R^1 = H, Me; R^2 = Ph, CO_2Et (**300**) (40)



(41)

(ii) From [4 + 1] atom fragments, one adjacent to a ring junction nitrogen atom

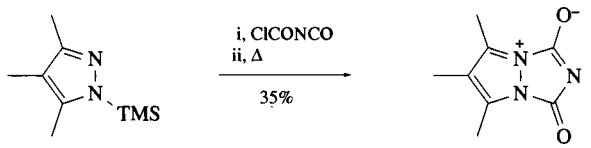
A different approach employs reaction of 1-acetyl pyrazoles (**301**) with 1,1-dielectrophiles (e.g., phosgene). Variation of the one-carbon electrophiles allows the introduction of other exocyclic groups to position 3 (Equation (42)). This procedure seems to be limited to 3,5-disubstituted 1-acyl pyrazoles ⟨84JOC3672, 88JOC2889⟩.



(301) X = O, S, *N*-tosyl (42)

8.31.11.2 Mesomeric 1-Oxo-1*H*-pyrazolo[1,2-*a*][1,2,4]triazol-4-ium-3-olates

Whereas direct reaction of 3,4,5-trimethyl pyrazole with chlorocarbonyl isocyanate is unsuccessful ⟨77AG789⟩, treatment of its activated trimethylsilyl derivative (**302**) with this 1,3-bielectrophile, followed by heating, yields (**303**) in 35% yield (Equation (43)) ⟨83H(20)23⟩.



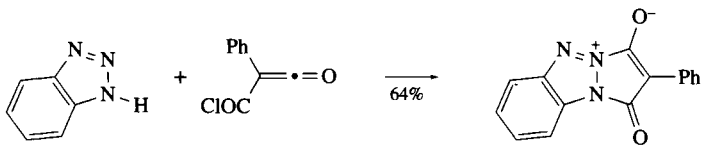
(302) (303) (43)

8.31.11.3 Mesomeric 7-Oxo-7*H*-pyrazolo[1,2-*a*][1,2,4]triazol-4-ium-5-olates

Mesomeric 7-oxo-7*H*-pyrazolo[1,2-*a*][1,2,4]triazol-4-ium-5-olates were prepared in a manner similar to the corresponding pyrazolo[1,2-*a*]pyrazole derivatives, by reaction of triazoles with chlorocarbonylketenes ⟨88JOC2889⟩.

8.31.11.4 Mesomeric 7-Oxo-7*H*-pyrazolo[1,2-*a*][1,2,3]triazol-4-ium-5-olates

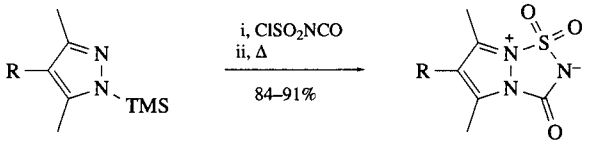
Though the bicyclic ring system has not been reported, the corresponding benzo analog (**304**) is formed in 64% yield by treatment of benzotriazole with chlorocarbonylphenylketene (Equation (44)) ⟨88JOC2889⟩.



(304) (44)

8.31.11.5 Mesomeric 3-Oxo-3*H*-pyrazolo[1,2-*b*][1,2,3,5]thiatriazol-8-ium-1-olates

This mesomeric betaine structure is known only in the form of its *S,S*-dioxides (**305**). They are prepared in good yields from corresponding trimethylsilyl pyrazoles and chlorosulfonyl isocyanate and subsequent heating to 60 °C (Equation (45)) ⟨83H(20)845⟩.

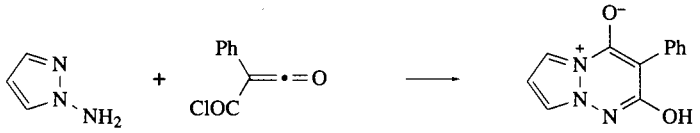


(45)

(305)

8.31.11.6 Mesomeric 2-Hydroxypyrazolo[1,2-*a*][1,2,3]triazin-5-ium-4-olates

By analogy with the formation of oxo-pyrazolo[1,2-*a*]pyrazol-4-ium-3-olates from pyrazole and chlorocarbonylphenylketene (see Scheme 59), 1-aminopyrazole provides the 5-6 bicyclic mesomeric betaine (**306**) (Equation (46)) ⟨83H(20)1271⟩.



(46)

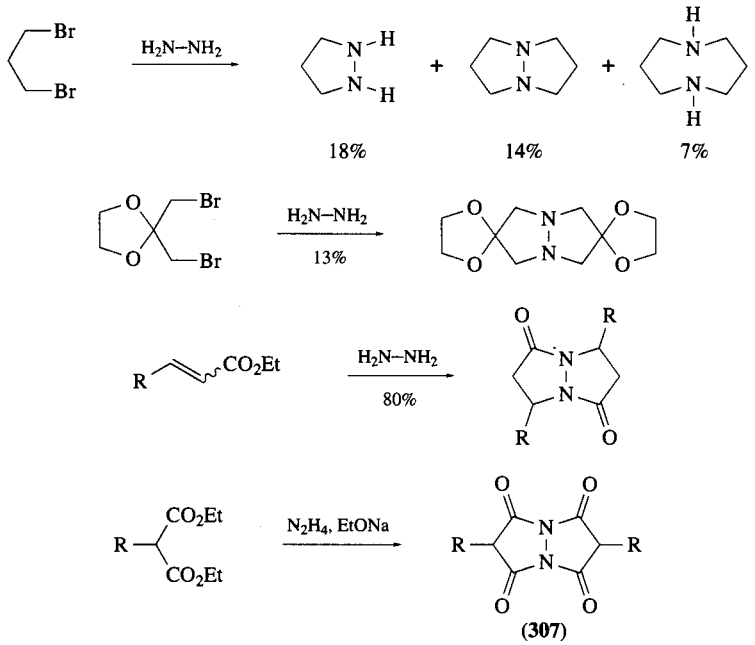
(306)

8.31.12 SYNTHESIS OF 5-5 RING SYSTEMS EXCEPT MESOMERIC BETAINES

8.31.12.1 Pyrazolo[1,2-*a*]pyrazole

8.31.12.1.1 Ring synthesis from nonheterocyclic precursors

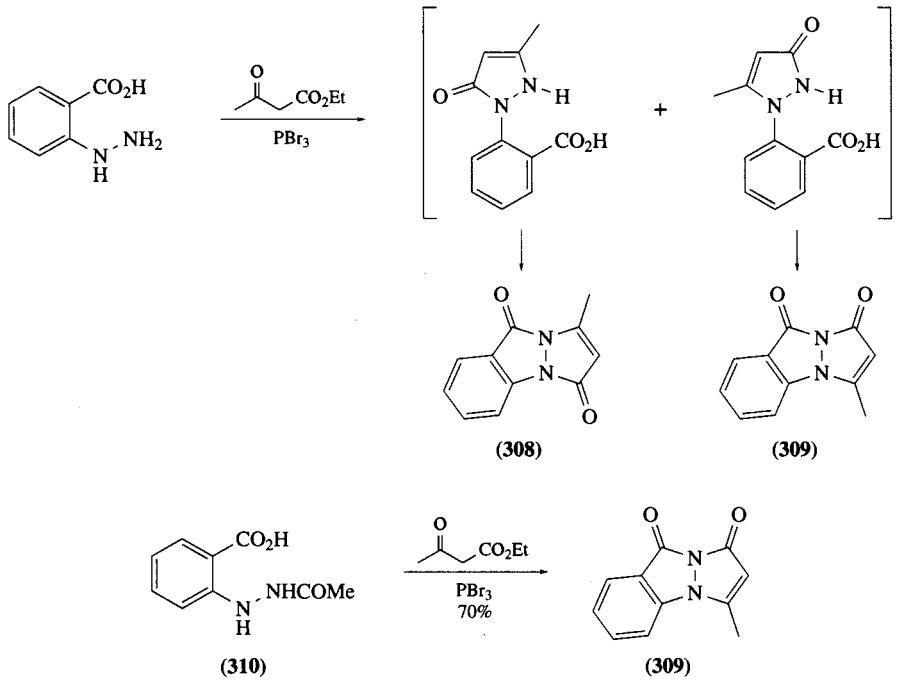
Direct alkylation of hydrazine generally leads to quaternary salt formation. Alkylation of hydrazine with 1,3-dihalopropane derivatives under various conditions provides mixtures in which quaternary salts predominate. Depending on the reaction conditions, low yields of the corresponding bicyclic products are formed ⟨43JA29, 70BSF696⟩. Reaction of hydrazine with acrylic acid or esters is an alternative route to this bicyclic system providing these compounds in good yields ⟨58CB1982, 65CB3228⟩. Cinnamic acid provides only small yields of the corresponding bicycles ⟨69HCA1672⟩. Reaction of two equivalents of alkyl malonate with one equivalent of hydrazine provides the tetrone system (**307**). Dialkyl malonates provide only the corresponding dioxo pyrazolidines (Scheme 60) ⟨32JA3674⟩.



(307)

Scheme 60

Benzo derivatives (**308**) and (**309**) were prepared by Michaelis ⟨10LA(373)148, 10LA(373)202⟩ by heating a mixture of 2-hydrazinobenzoic acid and ethyl acetoacetate with phosphorus tribromide. When the acetyl derivative (**310**) is used, only isomer (**309**) is isolated (Scheme 61) ⟨57T201⟩.



Scheme 61

8.31.12.1.2 Ring synthesis by formation of one bond

(i) Bond formation α to the ring junction nitrogen atom

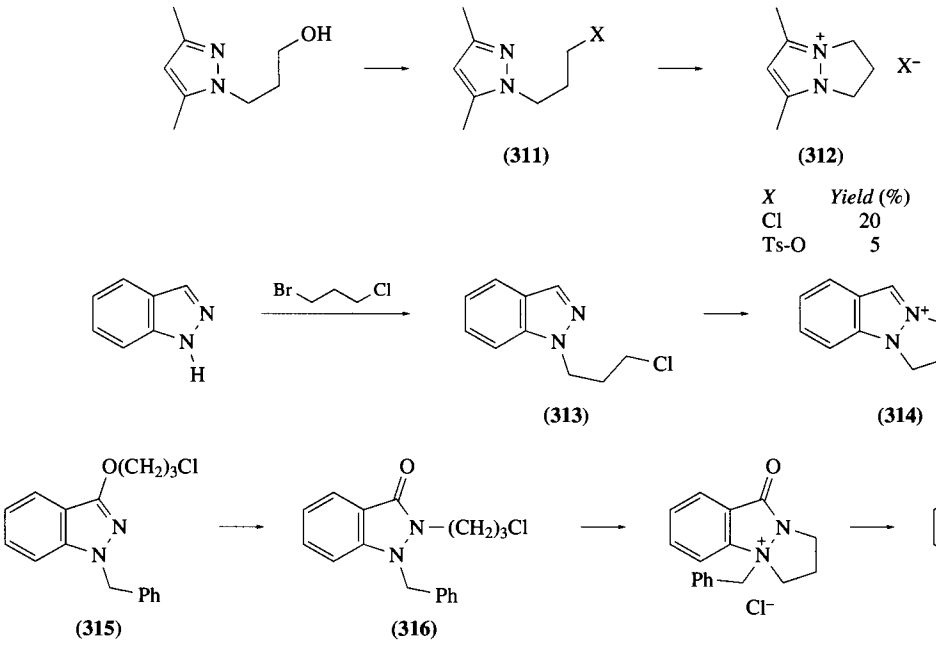
Intramolecular cyclization of suitable *N*-(halopropyl)-pyrazole (**311**) and -indazole (**313**) provides low yields of the corresponding quaternary salts (**312**) and (**314**), respectively ⟨69BSF2064, 82LA420, 86YZ1002⟩. Similarly, 2,3-dibromopropyl derivatives provide corresponding 2-bromo salts ⟨65JA5256⟩. Heating of 1-benzyl-3-(3-chloropropoxy)indazole (**315**) leads first to a Claisen-type rearrangement product (**316**) which on further heating provides (**317**) via the corresponding quaternary salt (Scheme 62) ⟨68MI 831-02⟩.

Benzo derivatives (**320**) have been prepared by nonaqueous diazotization of amino pyrazole (**318**) with isopentyl nitrite in the presence of bromine ⟨87JHC267⟩. The intermediacy of (**319**) was proved by its isolation, and its subsequent thermal cyclization then provided (**320**) (Scheme 63).

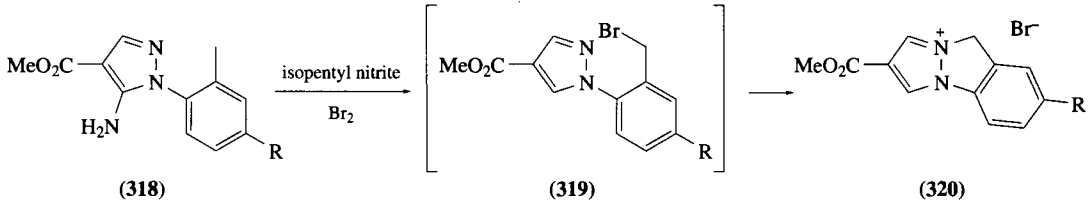
(ii) Bond formation β to the ring junction nitrogen atom

An efficient and regioselective method for the synthesis of pharmaceutically important intermediates (**323**) has been developed. It is based on the intramolecular Wadsworth–Horner–Emmons condensation of monocyclic compound (**322**), which is available by a selective stepwise functionalization of pyrazolidinone (**321**) (Scheme 64). The overall yield is about 25% ⟨90TL2805⟩.

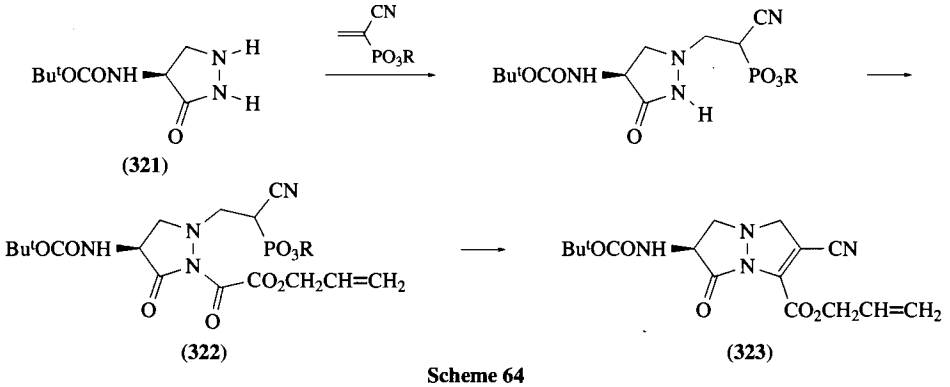
A novel synthesis of similar compounds (**324**) or (**325**), which is depicted in Scheme 65, has been recently reported. The reaction proceeds via *N*-hydrazinium intermediates and gives the products in 94% and 68% yields, respectively ⟨94RTC145⟩.



Scheme 62



Scheme 63

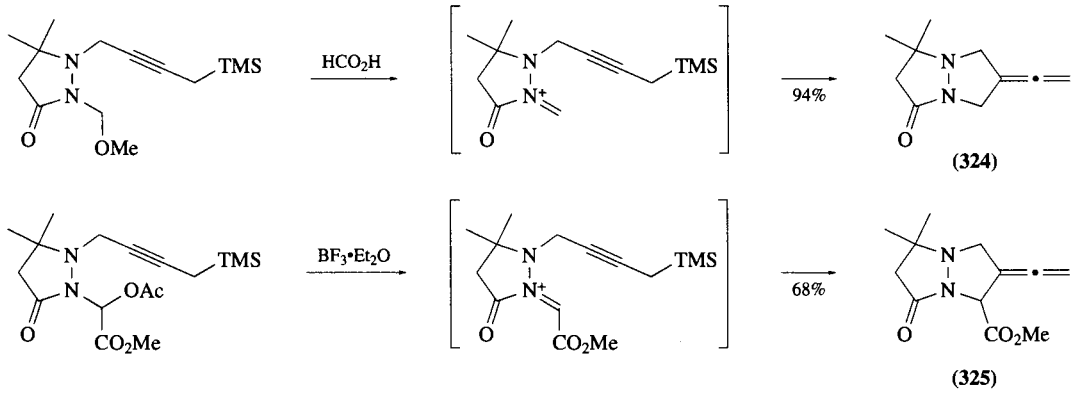


Scheme 64

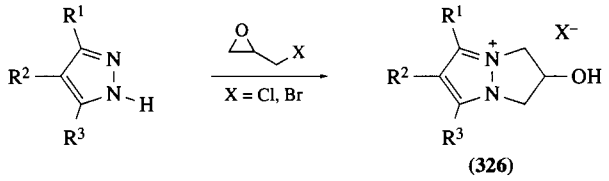
8.31.12.1.3 Ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

Treatment of pyrazole derivatives with epihalohydrins yields the corresponding 2-hydroxy derivatives (**326**) (Equation (47)) ⟨71JHC489, 90UKZ1096⟩. This method can also be used for synthesis of the corresponding benzo derivatives from indazoles ⟨71JHC489⟩.

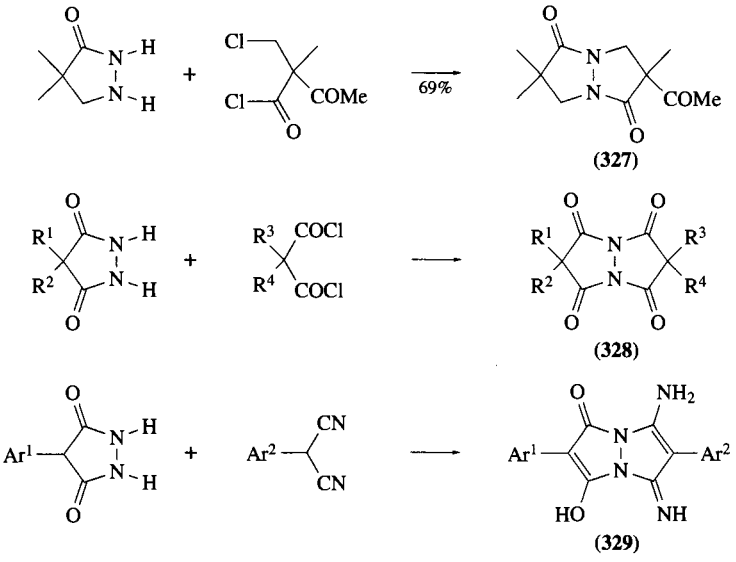


Scheme 65



(47)

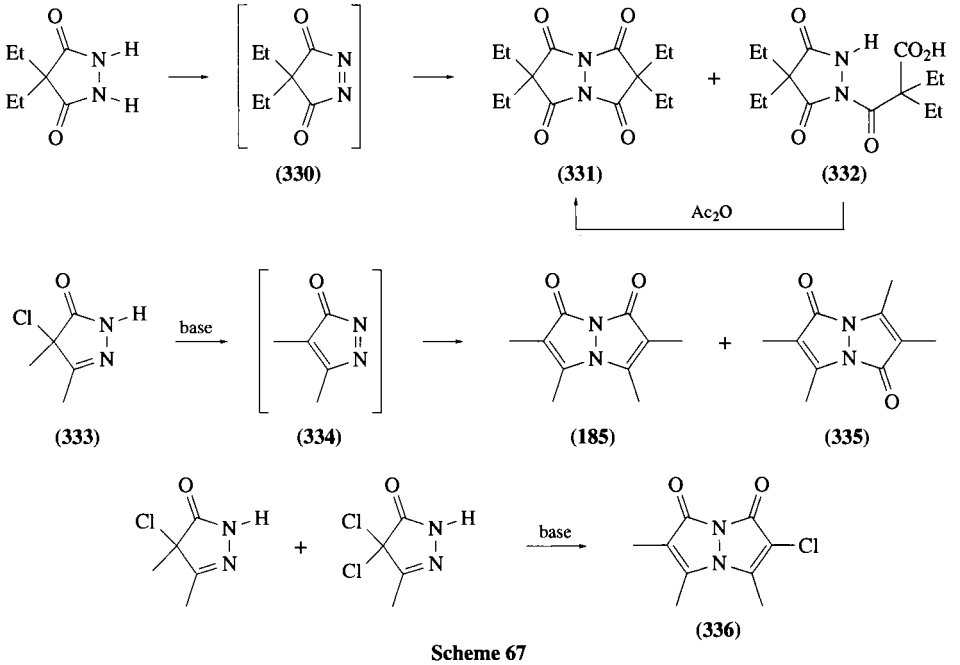
Reaction of mono- or disubstituted 3-chloropropionyl chlorides with pyrazolidin-3-ones is a versatile route to the corresponding derivatives (**327**) ⟨79JOC4473⟩. Similarly, substituted malonyl dichlorides react with pyrazolidinediones providing tetrones (**328**) ⟨66AP(299)441, 68BSF4210, 86AP(319)70, 86AP(319)646⟩. Heating of arylpyrazolidinediones with aryl malonodinitriles affords 30–39% of (**329**) whereas alkyl substituted or unsubstituted malononitriles do not yield bicyclic compounds (Scheme 66) ⟨86S239⟩.



Scheme 66

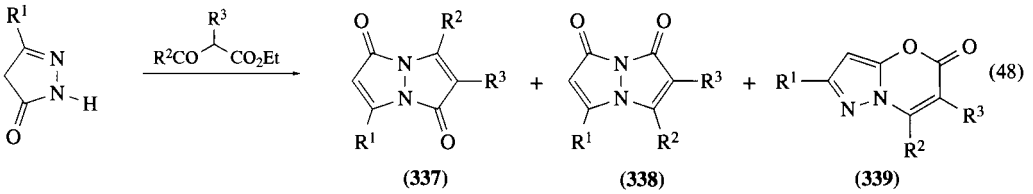
Tetrone derivative (**331**) is one of the products of decomposition of (**330**) which takes place when this reactive intermediate is generated *in situ* and then the solution is left at room temperature. Diethyl malonic acid and pyrazole derivative (**332**) are additional products of this decomposition. Pyrazole derivative (**332**) treated with acetic anhydride provides tetrone derivative (**331**) ⟨69JOC3181⟩. Species (**334**), similar to (**330**), is supposed to be an intermediate in the treatment of chloropyrazolinone (**333**) with a base leading to a mixture of corresponding bimanes (**185**) and (**335**)

〈78JA6516, 80JA4983〉. Mixed bimanes (e.g., (**336**)) can be obtained when a mixture of two different chloropyrazolinones are used (Scheme 67).



Scheme 67

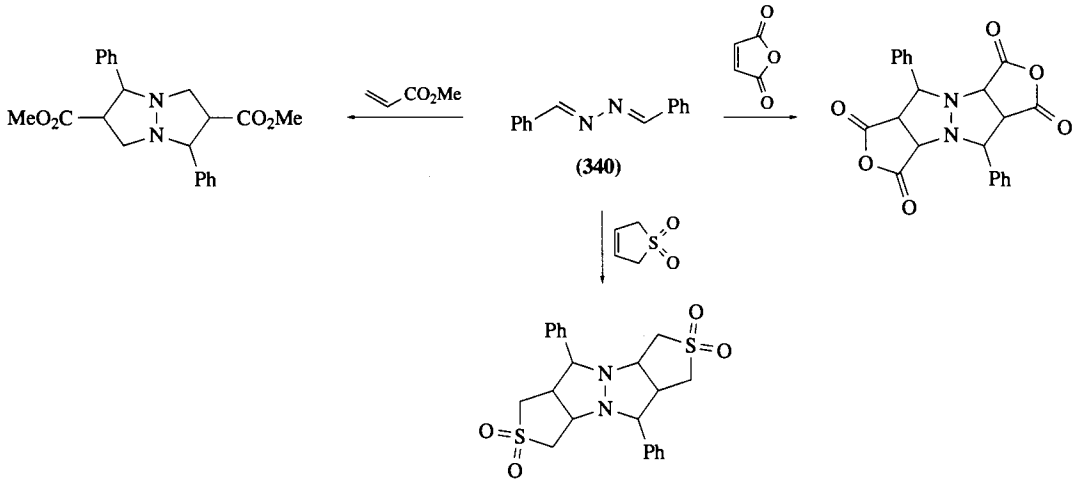
Low yields of bicyclic bimanes are formed by treatment of pyrazolidin-3-ones with acetoacetates 〈80JA4983〉. Much better yields are obtained with acetoacetates substituted at the position 2 with electron attracting substituents, for instance ester or acyl groups. *anti*-Isomers (**337**) are predominant products, *syn*-isomers (**338**) and pyrazolo[5,1-*b*][1,3]oxazines (**339**) are minor products (Equation (48)) 〈84CPB930〉.



(ii) From [3 + 2] atom fragments, one bond adjacent to ring junction nitrogen atom

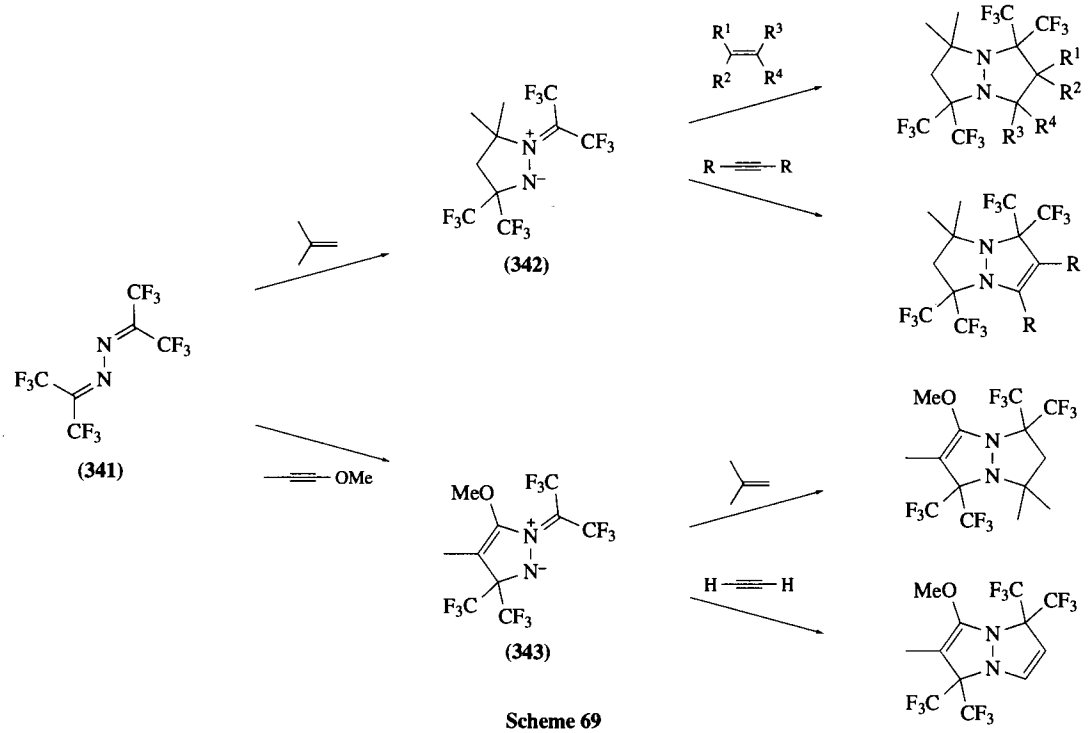
Extensive studies of the criss-cross addition (see Section 8.31.12.5.2) have shown that this reaction is general for the reaction of azines of aromatic aldehydes (e.g., benzaldazine (**340**)) with various electron deficient alkenes in which the double bond is terminal (e.g., methyl acrylate, acrylonitrile) 〈57HCA852, 87JOC2277〉, or in which allylic substituents do not sterically hinder the reaction, for example maleic anhydride 〈42RTC892, 57HCA852〉 or sulfolene 〈93PS(84)17〉 (Scheme 68).

Hexafluoroacetone azine (**341**), as an electron-deficient azine, was found capable of reaction with electron-rich terminal alkenes and alkynes under both thermal (160–180 °C) and photochemical conditions to give the corresponding 2 : 1 criss-cross adducts in yields higher than 80% 〈71JCS(C)2404, 72JCS(P1)1059〉. Electron-deficient alkenes and alkynes usually do not react under comparable conditions and both *cis* and *trans* nonterminal alkenes provide different products formally derived from the intermediacy of bis(trifluoromethyl)carbene 〈75JCS(P1)538〉. Burger *et al.* isolated, in 85% yield, a stable zwitterionic intermediate (**342**) from the intermolecular cycloaddition of one equivalent of 2-methylpropene onto (**341**) and determined its structure by x-ray analysis 〈74AG481, 74AG482, 74AG484, 75CB1460〉. Similar zwitterionic intermediates, e.g. (**343**), were also isolated from reactions



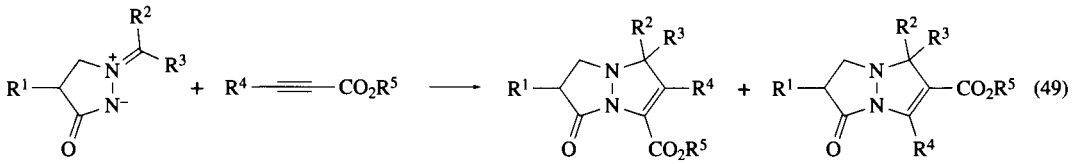
Scheme 68

of several alkynes with (**341**) ⟨79LA133⟩. This observation opened the way to a new variant called mixed criss-cross addition. Since these zwitterions also react with electron-deficient species, many different derivatives are thus available. Selected examples are given in Scheme 69 ⟨75CB1460, 79LA133⟩.



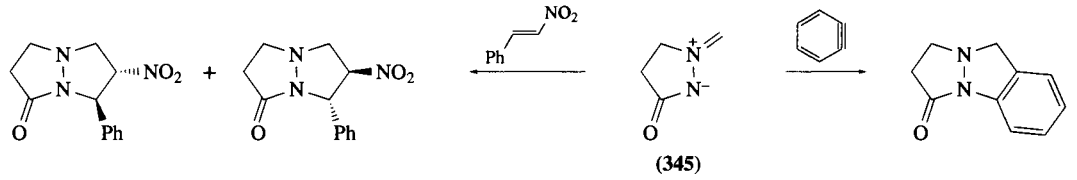
Scheme 69

The 3-oxo-1,2-pyrazolidinium ylides (**344**) are usually easily available by the reaction of corresponding pyrazolidin-3-one with aldehydes or ketones ⟨68CB3287⟩ or by an intramolecular dehydrohalogenation of β-chloropropionylhydrazones of the corresponding ketones ⟨81JA7743⟩. These species function as 1,3-dipoles in cycloaddition reactions with suitable alkynes. When unsymmetrical alkynes are used, mixtures of both possible products are usually obtained (Equation (49)) ⟨87JOC4007⟩.



(344) (49)

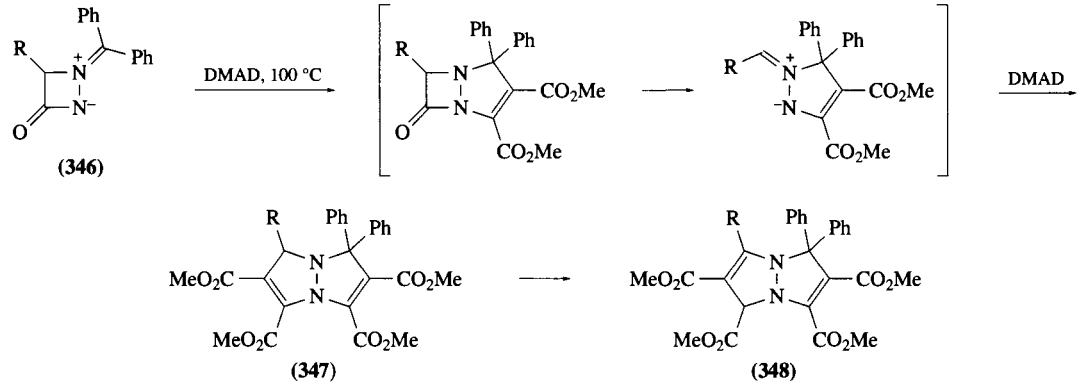
Cycloaddition of (**345**) and (*E*)-β-nitrostyrene gives stereospecifically the *trans*-adducts ⟨85TL5119⟩. The lower stereospecificity observed ⟨79JPR(321)555⟩ was explained as epimerization catalyzed by silica gel and small amounts of pyrazolidinone ⟨85TL5123⟩. Benzyne, generated by thermal decomposition of benzenediazonium-2-carboxylate, can also be used as 1,3-dipolarophile in the reaction with azomethine ylides (Scheme 70) ⟨91T9599⟩.



(345)

Scheme 70

Treatment of 3-oxo-1,2-diazetidinium ylides (**346**) with DMAD in methylene chloride at 100°C gives 77–90% of (**347**) which quantitatively isomerizes to (**348**) during crystallization from ethyl acetate or upon melting. The supposed mechanism is depicted in Scheme 71 ⟨81JA7659, 81JA7743⟩.

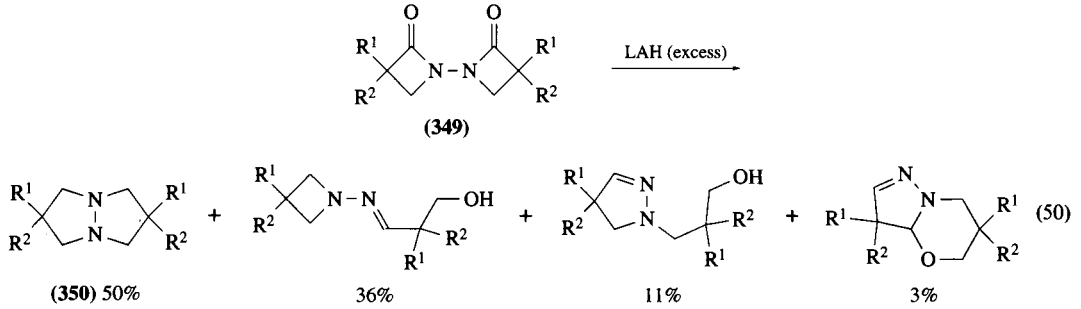


(346) (347) (348)

Scheme 71

8.31.12.1.4 Ring synthesis by transformation of an existing heterocycle

Bellasio and Gallo reported that reduction of (**349**) with LAH provided (**350**) as a product of reduction and rearrangement ⟨70FES295⟩. Three other minor products have also been identified (Equation (50)) ⟨84CB1659⟩.



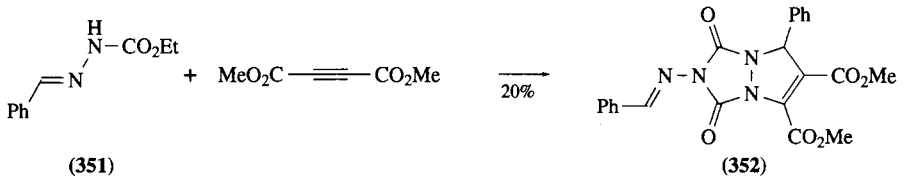
(349)

(**350**) 50% 36% 11% 3% (50)

8.31.12.2 Pyrazolo[1,2-*a*][1,2,4]triazole

8.31.12.2.1 Ring synthesis from nonheterocyclic precursors

Reaction of benzaldehyde ethyl carbazone (**351**) with DMAD in boiling xylene gives a mixture from which bicyclic compound (**352**) is isolated in 20% yield (Equation (51)) ⟨87T5873⟩.

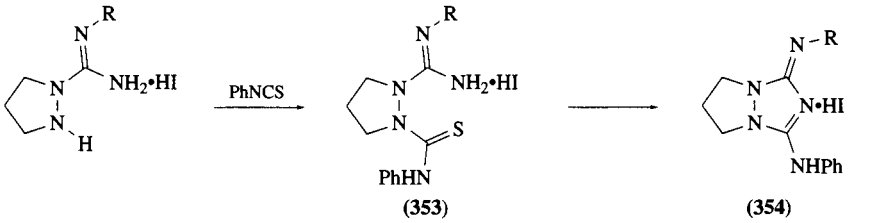


(51)

(351) (352)

8.31.12.2.2 Ring synthesis by formation of one bond

Hydroiodides of *N*-arylsubstituted or unsubstituted 1-amidino pyrazolidines treated with phenyl isothiocyanate provides hydroiodides (**353**) which cyclize into (**354**) by boiling in ethanol (Equation (52)) ⟨91PHA637⟩.



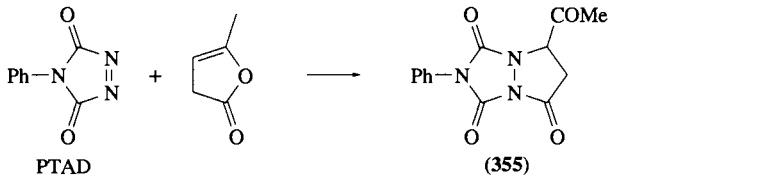
(52)

(353) (354)

8.31.12.2.3 Ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

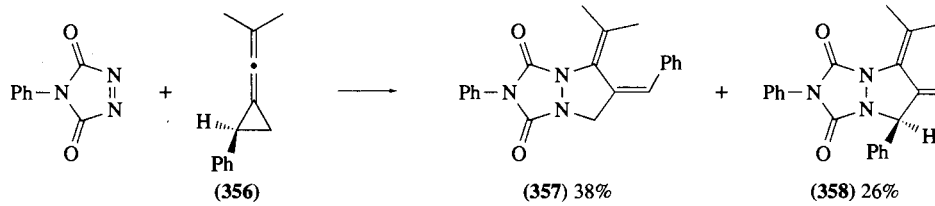
5-Methylfuran-2(3*H*)-one (α-angelica lactone) reacts with PTAD by an ene-type reaction involving acyl group transfer to yield (**355**) (Equation (53)) ⟨80JCS(P1)843⟩.



(53)

PTAD (355)

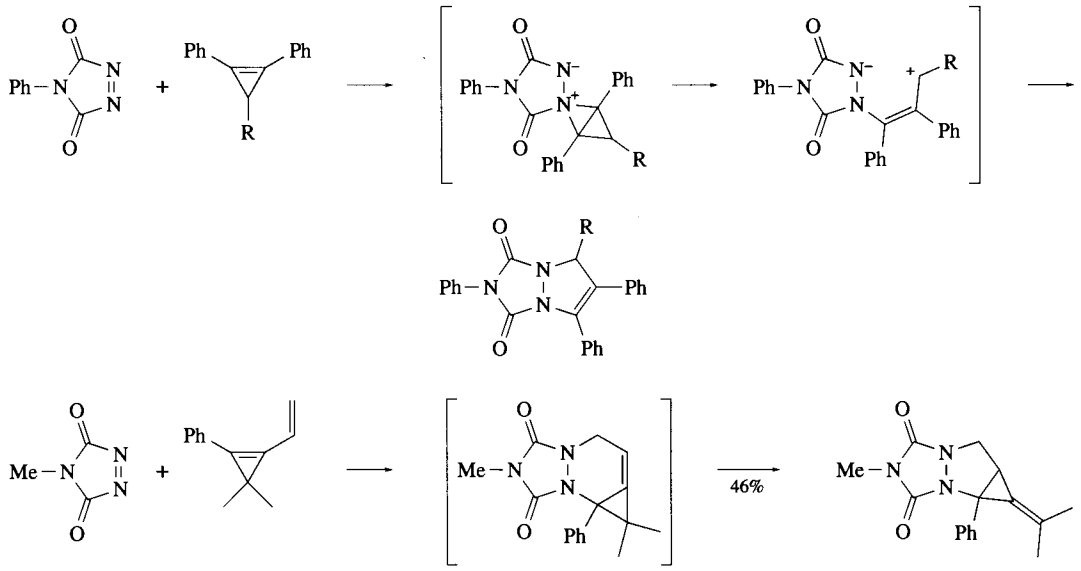
PTAD reacts with allenic cyclopropane derivative (**356**) to give high yields of a mixture in which pyrazolotriazoles (**357**) and (**358**) predominate (Equation (54)) ⟨71JA2562, 73JA1553, 74JA6220, 74JA6944⟩.



(54)

(356) (357) 38% (358) 26%

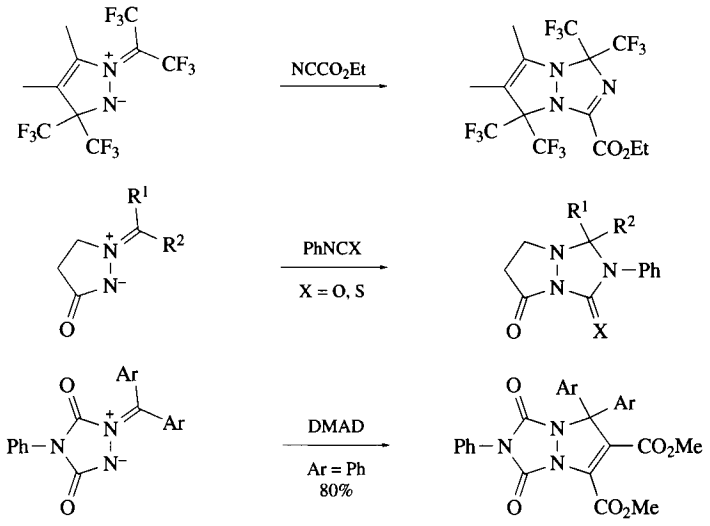
Various substituted diphenyl cyclopropenes react smoothly with PTAD to give good yields of the corresponding bicyclic compounds. Examples, together with the proposed mechanism, are shown in Scheme 72 ⟨90JOC2478⟩.



Scheme 72

(ii) From [3 + 2] atom fragments, one bond adjacent to a ring junction nitrogen atom

Azomethine imines are useful intermediates for the synthesis of these heterocycles. Selected examples are given in Scheme 73 ⟨68CB3287, 79LA133, 82ZOR1986⟩.

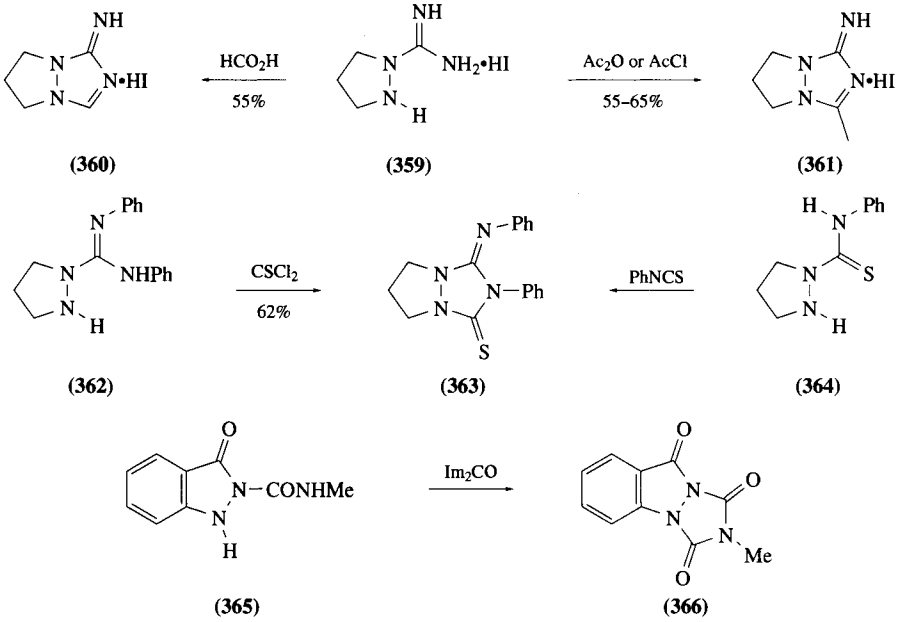


Scheme 73

(iii) From [4 + 1] atom fragments, one bond adjacent to a ring junction nitrogen atom

1-Amidinopyrazolidine (**359**) reacts easily with formic acid or acetic acid derivatives to form 1-imino substituted pyrazolo[1,2-*a*][1,2,4]triazoles (**360**) and (**361**), respectively. Similarly (**362**) reacts

with thiophosgene to provide (**363**). The same product is obtained by treatment of (**364**) with phenylisothiocyanate ⟨91PHA418, 91PHA637⟩. Other similar reactions have been described ⟨91PHA573⟩. Benzo derivative (**366**) is obtained by treatment of indazolone (**365**) with carbonyl diimidazole (Scheme 74) ⟨81LA1361⟩.



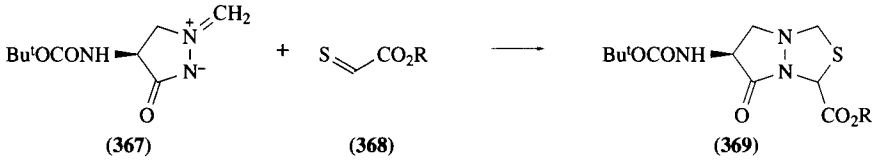
Scheme 74

8.31.12.3 Pyrazolo[1,2-*c*][1,3,4]thiadiazole

8.31.12.3.1 Ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments

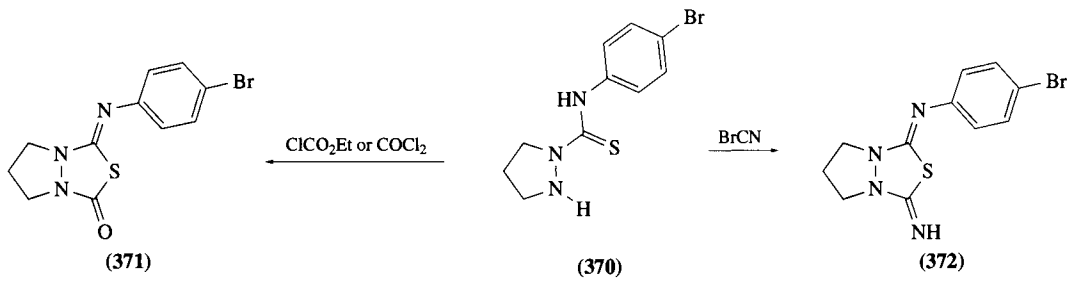
In situ generated thioaldehydes (**368**) undergo a 1,3-dipolar cycloaddition reaction with pyrazolidinium ylide (**367**) to produce bicyclic esters (**369**) (Equation (55)) ⟨88TL5061⟩.



(55)

(ii) From [4 + 1] atom fragments

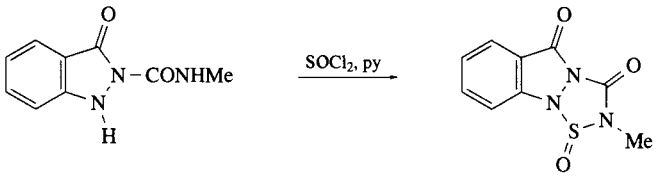
Pyrazolidine (**370**) treated with ethyl chloroformate, phosgene, or cyanogen bromide in the presence of triethylamine gives the respective bicyclic products (**371**) and (**372**) (Scheme 75) ⟨91PHA573, 94EUP600833⟩.



Scheme 75

8.31.12.4 Pyrazolo[1,2-*b*][1,2,3,5]thiatriazole

The parent bicyclic structure is not known but benzo derivative (**373**) can be prepared in 72% yield from indazole (**365**) by treatment with thionyl chloride in pyridine (Equation (56)) ⟨81LA1361⟩.



(56)

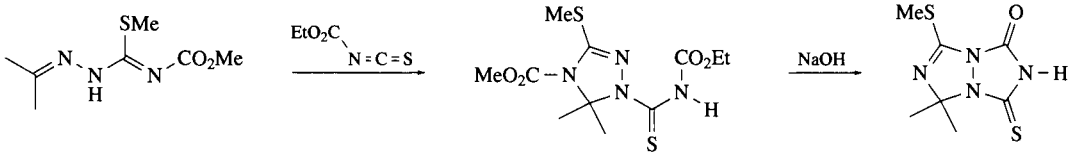
(365) (373)

8.31.12.5 1,2,4-Triazolo[1,2-*a*][1,2,4]triazole

8.31.12.5.1 Ring synthesis by formation of one bond

(i) Bond formation α to a ring junction nitrogen atom

Compound (**374**) treated with ethoxycarbonyl isothiocyanate provides intermediate (**375**) which upon treatment with sodium hydroxide cyclizes to (**376**) (Scheme 76) ⟨84JOC1703⟩.

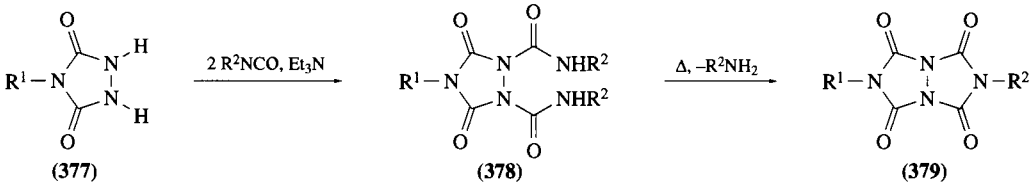


(374) (375) (376)

Scheme 76

(ii) Bond formation β to a ring junction nitrogen atom

Triazolinediones (**377**) treated with two equivalents of various isocyanates in the presence of tertiary amines provide intermediates (**378**). Thermolysis of these intermediates then provide tetrones (**379**) (Scheme 77) ⟨77CB1691⟩.



(377) (378) (379)

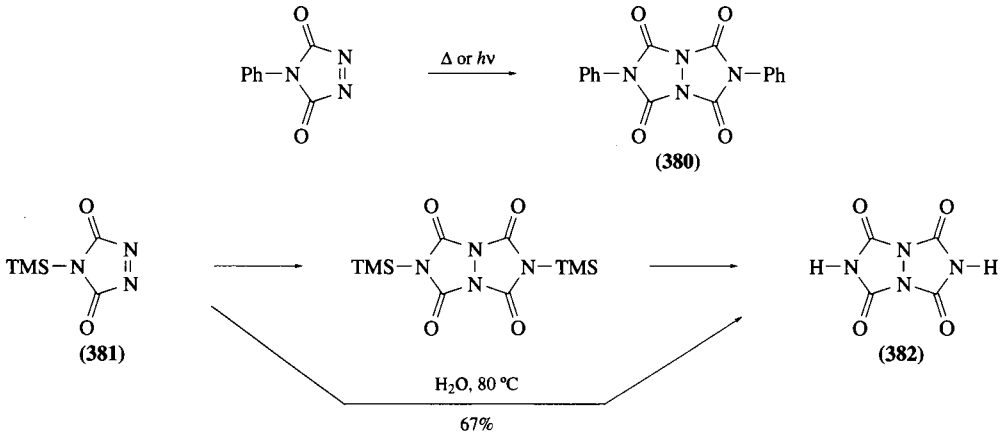
Scheme 77

8.31.12.5.2 Ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

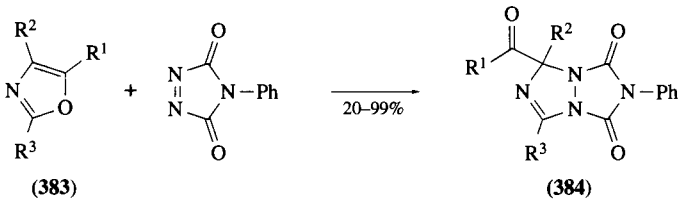
1,2,4-Triazolo[1,2-*a*][1,2,4]triazole (**380**) has been reported as a decomposition product of PTAD under photolytic or thermal conditions in various solvents ⟨12CB273, 76CC326, 77CB1699, 79CJC2727, 84JOC2579, 85JOC4589, 86JOC1563, 88AG703⟩. Catalytic activity of several agents has been described ⟨76CC326, 80ZOR2444, 86JOC1563⟩, in some instances, for example, with catalysis of potassium *t*-butoxide in DMSO, the yields are nearly quantitative. Similarly, thermolysis of other *N*-substituted

triazolinediones provides mixtures from which low to moderate yields of the corresponding symmetrically substituted tetraoxo triazolo[1,2-*a*][1,2,4]triazoles can be isolated ⟨75JOC1854⟩. For the synthesis of *N*-unsubstituted derivative (**382**) protection of this nitrogen atom is necessary. The compound is prepared in 67% yield from the *N*-trimethylsilyl precursor (**381**) (Scheme 78) ⟨88AG703⟩.



Scheme 78

Oxazoles (**383**) react with PTAD to give triazolotriazoles (**384**). Yields of the reaction are strongly dependent on the substitution (Equation (57)) ⟨84LA641, 88CL1551, 92BCJ2998⟩.



(57)

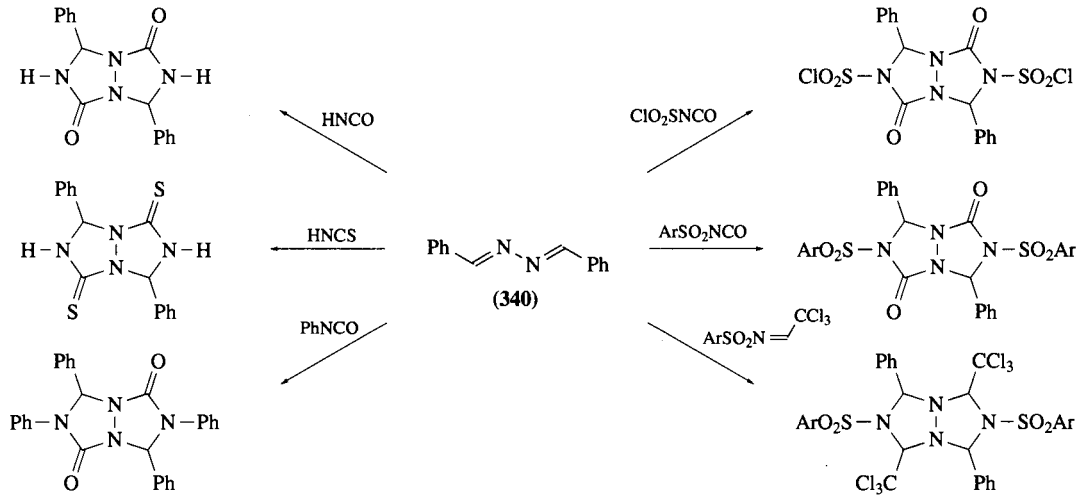
(ii) From [3 + 2] atom fragments, one bond adjacent to a ring junction nitrogen atom

In 1917 Bailey *et al.* ⟨17JA279, 17JA1322⟩ reported a new reaction of aromatic aldazines with two equivalents of isocyanic acid, isothiocyanic acid, and isocyanates leading to unexpected products. Though the benzaldazine (**340**) is in fact a 2,3-diaza analog of 1,4-diphenyl-1,3-butadiene, the addition reaction never took place either on the 1,4 or 1,2 positions but rather 1,3 and 4,2 positions of the conjugated double bonds of aromatic aldazines were attacked. Due to the pattern they named the reaction criss-cross addition. There are many examples of the reaction leading to the 1,2,4-triazolo[1,2-*a*][1,2,4]triazole moiety in the literature. These include reactions of chlorosulfonyl isocyanates ⟨77JCS(P1)47⟩, arylsulfonyl isocyanates ⟨67CB2938, 69MI 831-01⟩, and arylsulfonyl imines ⟨86ZOR2173, 89ZOR1695⟩ (Scheme 79).

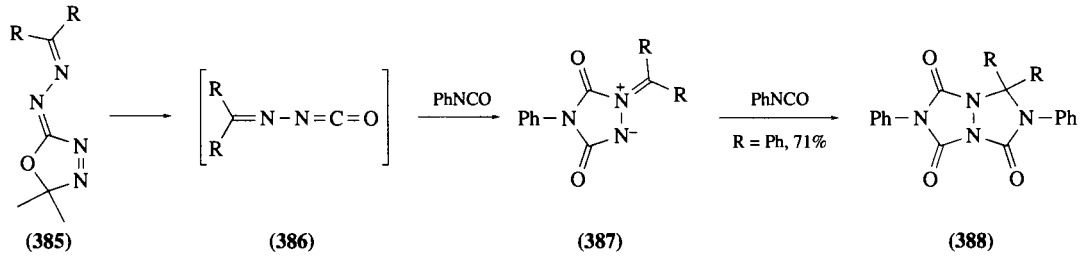
Azomethine imines (**387**) are intermediates of the thermolysis of 2-hydrazones (**385**) with isocyanates (Scheme 80). The starting compound first undergoes a 1,3-dipolar cycloreversion reaction to (**386**) which provides with phenyl isocyanate the azomethine imine (**387**) which subsequently reacts with the second equivalent of the isocyanate to give (**388**) ⟨76T2685⟩.

(iii) From [4 + 1] atom fragments

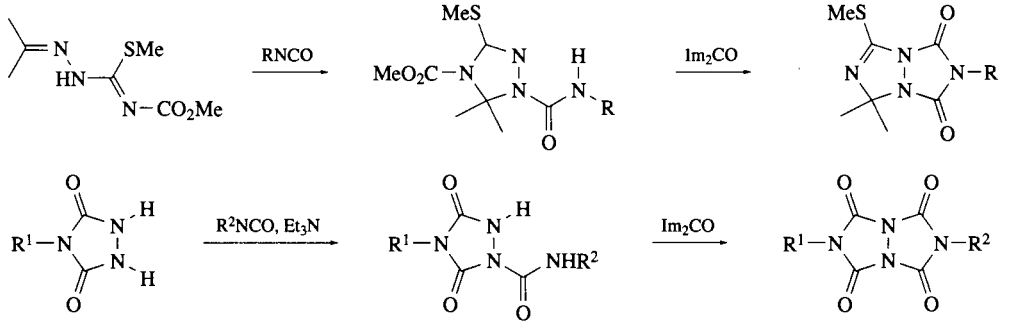
Suitable substituted triazole derivatives can be cyclized with phosgene or some of its substitutes (e.g., diphosgene, triphosgene, carbonyl diimidazole) to form the corresponding triazolotriazole derivatives. This approach can be demonstrated by reactions in Scheme 81 ⟨77CB1691, 84JOC1703⟩.



Scheme 79



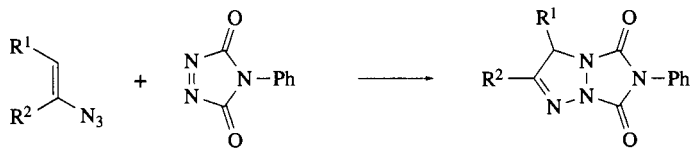
Scheme 80



Scheme 81

8.31.12.6 1,2,3-Triazolo[1,2-*a*][1,2,4]triazole

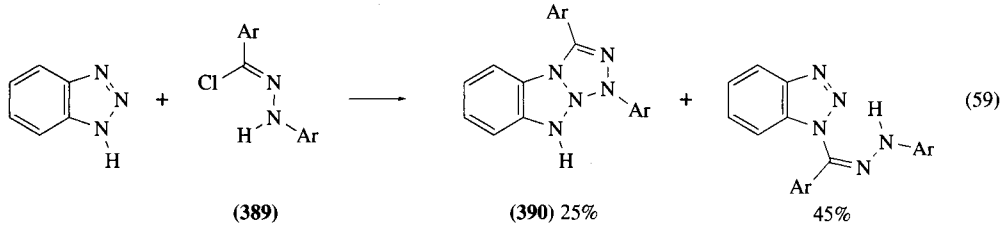
PTAD reacts readily at room temperature with vinyl azides to give 1,3-dipolar cycloaddition products of an intermediate vinyl nitrene with PTAD (Equation (58)). No addition of the azide 1,3-dipolar system to the N=N bond is observed ⟨76JOC2102⟩.



(58)

8.31.12.7 1,2,3-Triazolo[1,2-*a*]tetrazole

This bicyclic system has not been described but the corresponding benzo derivatives (i.e., tetrazolo[1,2-*a*]benzotriazoles (**390**)) can be isolated from the reaction mixture after treatment of benzotriazole with (**389**) in the presence of triethylamine (Equation (59)) ⟨84H(22)1561⟩.

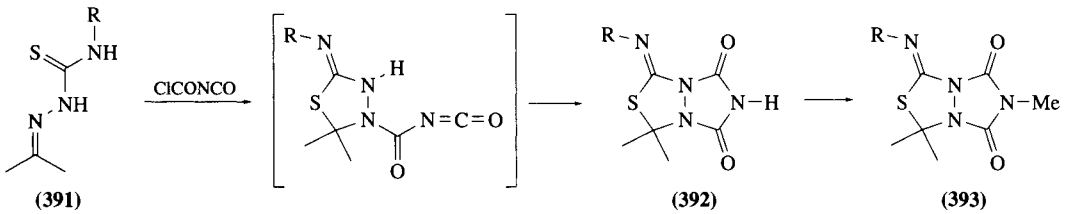


(389) (390) 25% 45% (59)

8.31.12.8 1,2,4-Triazolo[1,2-*c*][1,3,4]thiadiazole

8.31.12.8.1 Ring synthesis from nonheterocyclic precursors

Reaction of *N*-substituted thioamides (**391**) with chlorocarbonyl isocyanate at room temperature affords good yields of 1-imino derivative (**392**) which can be quantitatively *N*-methylated with diazomethane to (**393**) (Scheme 82) ⟨84S771⟩.



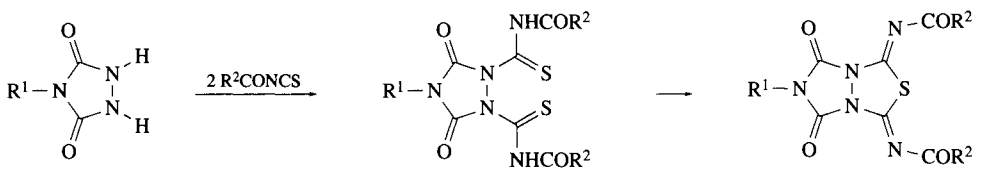
(391) (392) (393)

R	Yield (%)
Me	87
Ph	89

Scheme 82

8.31.12.8.2 Ring synthesis by formation of one bond

4-Substituted 1,2,4-triazolidine-3,5-diones treated with two equivalents of acyl isothiocyanates in the presence of triethylamine provide an easy way to this moiety via intermediates (**394**) (Scheme 83) ⟨77CB1691⟩.



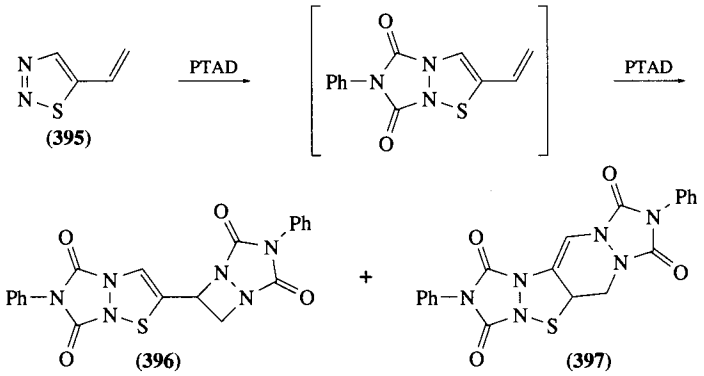
(394)

R^1	R^2	*Yield* (%)
Ph	OEt	35
Me	Ph	62

Scheme 83

8.31.12.9 1,2,4-Triazolo[1,2-*b*][1,2,3]thiadiazole

5-Alkenyl-1,2,3-thiadiazole (**395**) treated with PTAD provides a mixture from which (**396**) and the corresponding tetracyclic adduct (**397**) are isolated ⟨86LA1334⟩. The reaction involves annulation of one molecule of PTAD to the N=N double bond and either a 1,2- or 1,4-cycloaddition reaction of the second molecule of PTAD, respectively (Scheme 84).



Scheme 84

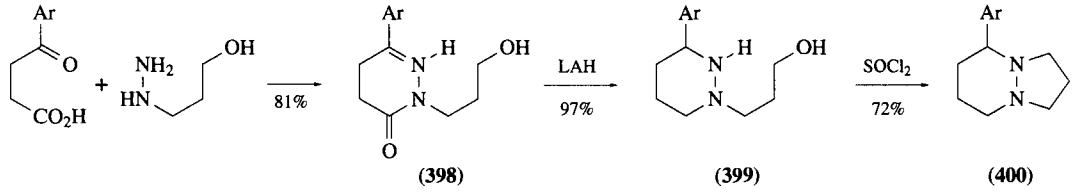
8.31.13 SYNTHESIS OF 5-6 RING SYSTEMS

8.31.13.1 Pyrazolo[1,2-*a*]pyridazine

8.31.13.1.1 Five-membered ring synthesis by formation of one bond

(i) Bond formation α to a ring junction nitrogen atom

3-Benzoylpropionic acids react with 3-hydrazinopropanol to give (**398**) which is reduced with LAH to (**399**). This intermediate is cyclized to (**400**) in 72% yield upon treatment with thionyl chloride (Scheme 85) ⟨69JOC2720⟩.



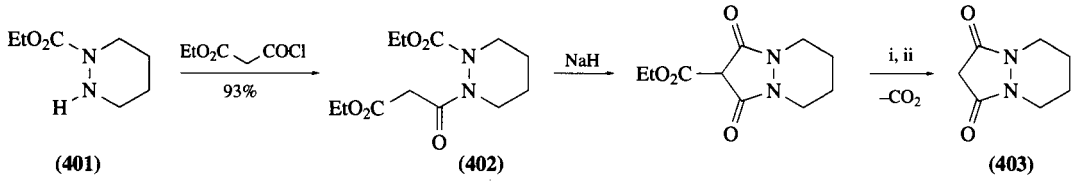
Scheme 85

(ii) Bond formation β to a ring junction nitrogen atom

Acylation of (**401**) with ethoxycarbonylacetyl chloride provides a high yield of (**402**) which treated with sodium hydride affords the corresponding product of intramolecular cyclization. Hydrolysis of this intermediate, which is used without isolation, is accompanied by decarboxylation to give dioxo derivative (**403**) in 60% yield (Scheme 86) ⟨87JCS(P1)877⟩.

8.31.13.1.2 Six-membered ring synthesis by formation of one bond

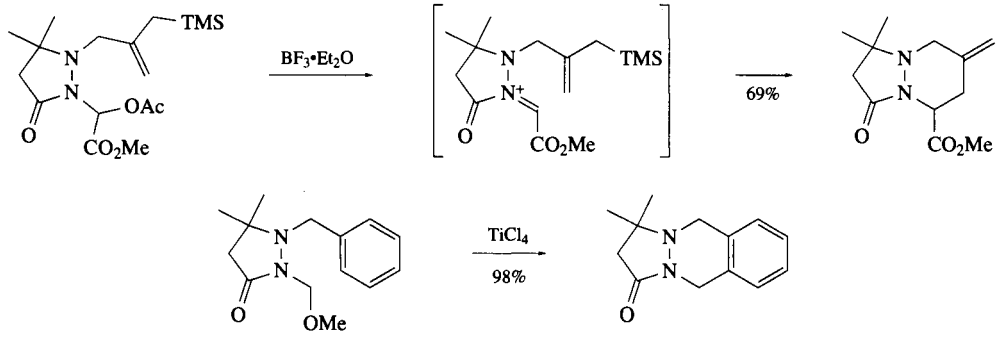
Similar methodology as used for the 5-5 fused pyrazolidinones (see Section 8.31.12.1.2) based on an acid-induced cyclization of exocyclic hydrazonium intermediates is also useful for the synthesis of similar 5-6 bicycles as is shown in Scheme 87 ⟨94RTC145⟩.



(401) (402) (403)

i, NaOH; ii, H_2O, Δ

Scheme 86

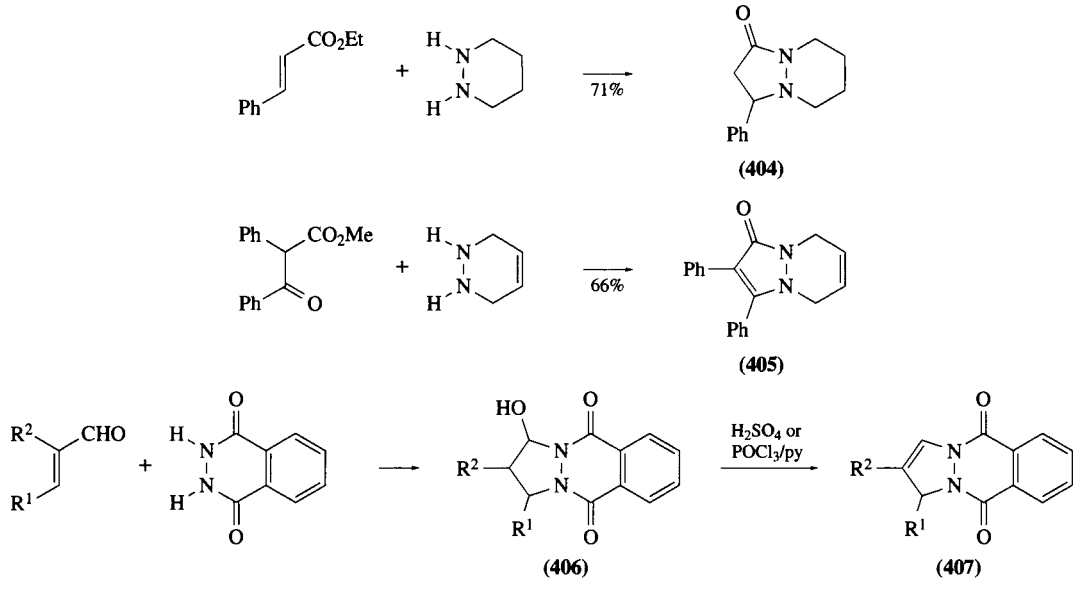


Scheme 87

8.31.13.1.3 Five-membered ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

Heating of piperidazine with ethyl cinnamate gives 71% of (**404**) ⟨80TL3493⟩. The unsaturated diphenyl derivative (**405**) is also easily available. Michael-type addition reaction of succinic and phthalic hydrazides to α,β-unsaturated aldehydes provides intermediates (**406**) ⟨68BSF4229⟩. In the case of phthalic hydrazide, the intermediate is then easily dehydrated to (**407**) ⟨67CPB949, 70CPB1526⟩. Cinnamaldehyde provides directly corresponding products of dehydration (Scheme 88) ⟨37JCS(C)16, 66JOC2867, 82ACH387⟩.



Scheme 88

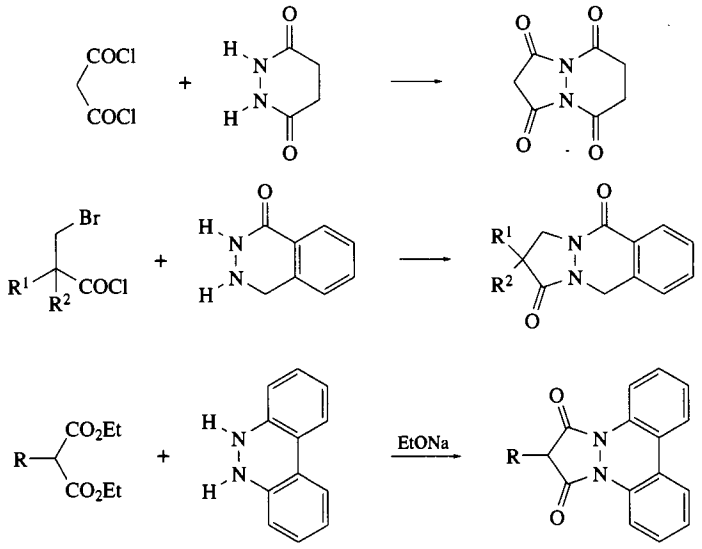
When epichlorohydrin is used for the cyclization reaction with piperidazine or tetrahydropyridazine, hydroxy derivatives (**408**) and (**409**) are formed, respectively (Scheme 89) ⟨81BRP2105707, 92BMC1293⟩.



(408) **(409)**

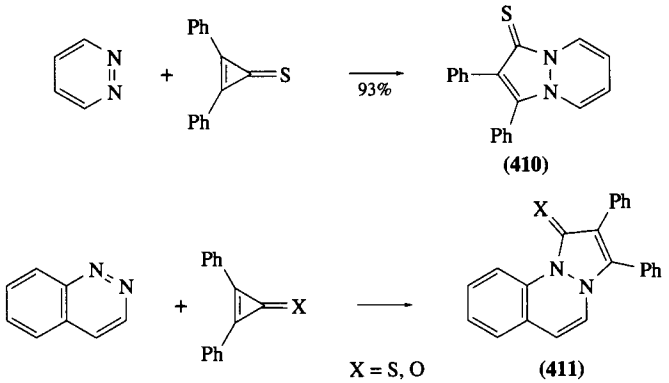
Scheme 89

Bifunctional agents such as maleic dihalides, β-bromopropionyl halides, and malonates can also be used for the syntheses leading to various bicyclic compounds as shown in Scheme 90 ⟨55HCA531, 65CR(261)1872, 70FES305⟩.



Scheme 90

Pyridazine and its benzo derivatives react with diphenylcyclopropene thione and/or diphenylcyclopropenone to yield (**410**) and (**411**), respectively (Scheme 91) ⟨71CJC3119⟩.

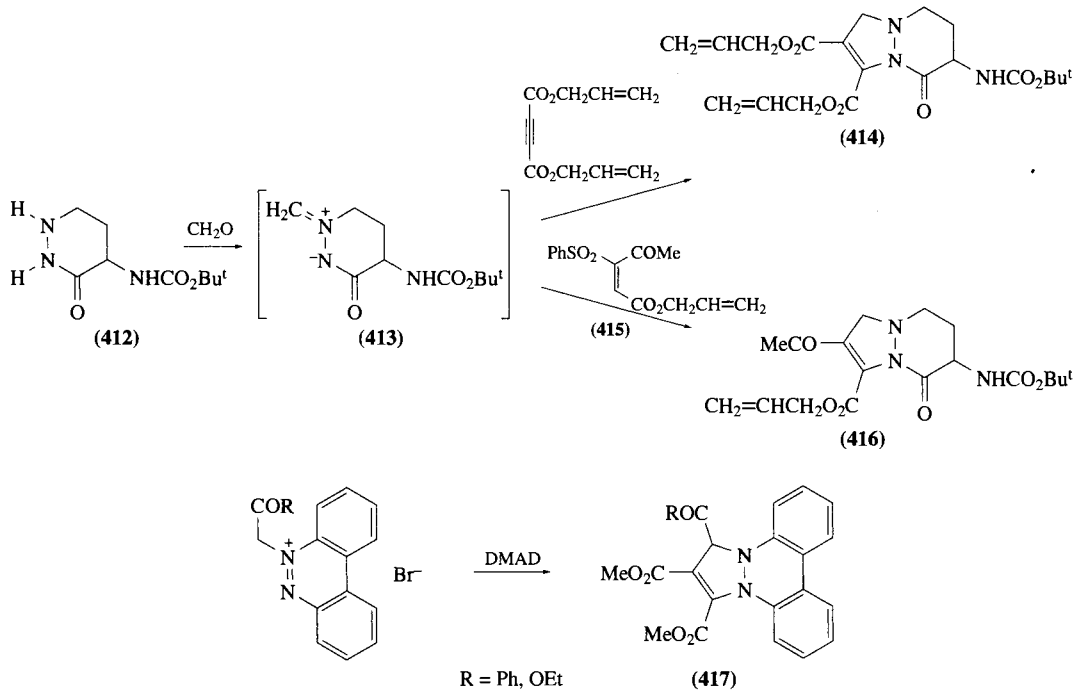


(410) **(411)**

Scheme 91

(ii) From [3 + 2] atom fragments, one bond adjacent to a ring junction nitrogen atom

Treatment of (**412**) with aqueous formaldehyde followed by heating generates ylide (**413**) which can be trapped by ethyne dicarboxylates to yield (**414**). The ylide similarly undergoes 1,3-dipolar cycloaddition with vinyl sulfone (**415**), followed by base catalyzed elimination to regioselectively give isomer (**416**) ⟨91JMC1732⟩. Benzo derivatives (**417**) are available similarly from benzocinnolinium bromides and DMAD (Scheme 92) ⟨74RRC1507, 76RRC1203⟩.



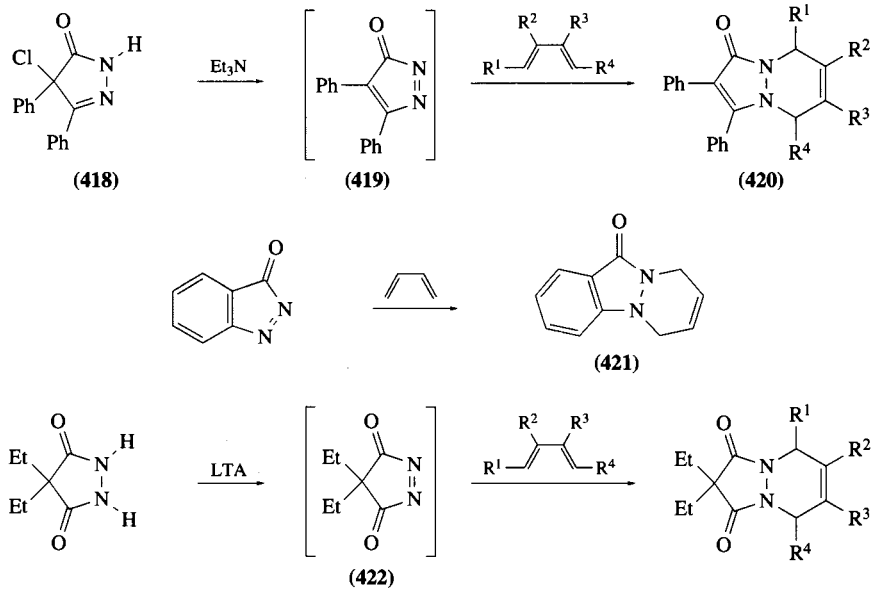
Scheme 92

8.31.13.1.4 Six-membered ring synthesis by formation of two bonds

(i) From [4 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

The Diels–Alder reaction of pyrazolones and pyrazolinediones with various dienes represents an easy and efficient route to this bicyclic system. Unstable dienophile (**419**), when generated *in situ* by elimination from halopyrazolone (**418**), can be trapped with butadiene or its derivatives to yield compounds (**420**) ⟨66JOC2867⟩. Intermediates similar to (**419**) can also be generated through oxidation of substituted pyrazolin-3-ones with lead tetraacetate (LTA) ⟨67JOC3321, 79AQ927, 85JCS(P1)71, 92T3775⟩. Similarly, benzo derivative (**421**) can be prepared in low yields ⟨62CI(L)93, 85TL5707⟩. Oxidation of 4,4-diethyl pyrazoline-3,5-dione with LTA or *t*-butyl hypochlorite provides (**422**) which is also a strong dienophile as evidenced by its easy reaction with various dienes (Scheme 93) ⟨69JOC3181, 69LA(724)150⟩.

Diesters, diacid dichlorides and dihaloalkanes react with pyrazolidine or its derivatives to give varying yields of products containing the pyrazolo[1,2-*a*]pyridazine moiety. For example, pyrazolidine reacts with diethyl succinate ⟨62HCA37, 72JHC41⟩. Alkylation of pyrazoles with *cis*-1,4-dichloro-2-butene under PTC conditions also gives products of intramolecular cyclization ⟨89KGS497⟩.

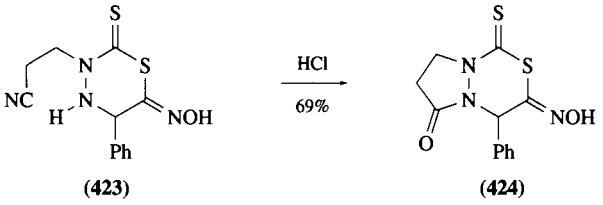


Scheme 93

8.31.13.2 Pyrazolo[1,2-*c*][1,3,4]thiadiazine

8.31.13.2.1 Five-membered ring synthesis by formation of one bond

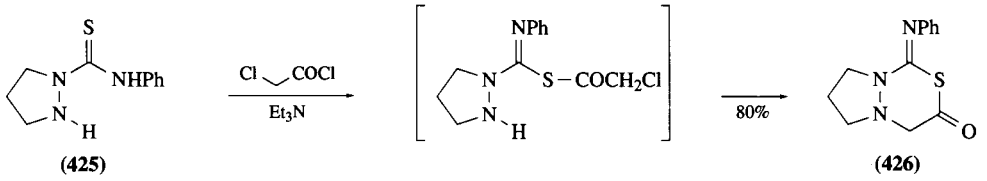
Thiadiazine (**423**), which is easily available in low yields from the reaction of 3-hydrazinopropionitrile, carbon disulfide and nitrostyrene, heated under acidic conditions provides a 69% yield of (**424**) (Equation (60)) ⟨73LA944⟩.



(60)

8.31.13.2.2 Six-membered ring synthesis by formation of two bonds

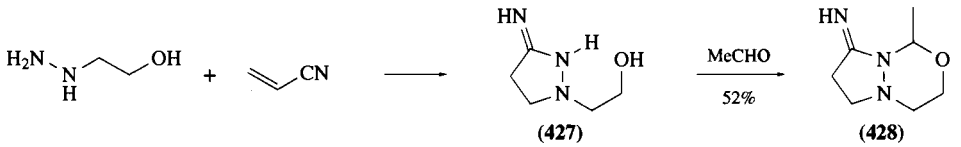
Phenyl thiocarbamoyl pyrazolidine (**425**) treated with chloroacetyl chloride in the presence of triethylamine gives good yields of (**426**) (Scheme 94) ⟨91PHA573⟩.



Scheme 94

8.31.13.3 Pyrazolo[1,2-*c*][1,3,4]oxadiazine

Hydroxyethyl pyrazolidine (**427**), which is easily available from the reaction of 2-hydroxyethylhydrazine with acrylonitrile, reacts with acetaldehyde at room temperature to provide 52% of bicyclic imine (**428**) (Scheme 95) ⟨86ZOR2271⟩.

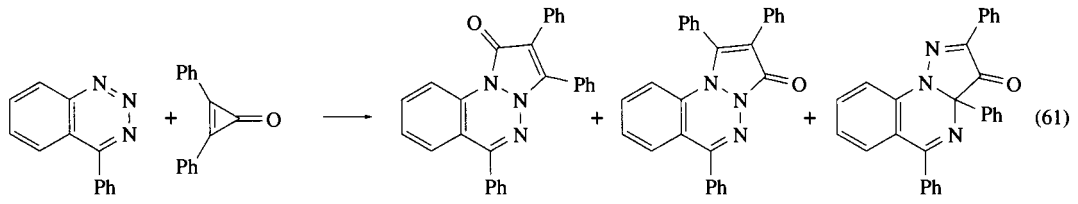


(427) (428)

Scheme 95

8.31.13.4 Pyrazolo[1,2-*a*][1,2,3]triazine

Only benzo derivatives of pyrazolo[1,2-*a*][1,2,3]triazine are known. 4-Phenyl-1,2,3-benzotriazine reacts with diphenylcyclopropenone to give several possible products, two of them being of this type (Equation (61)) ⟨80CC808⟩.

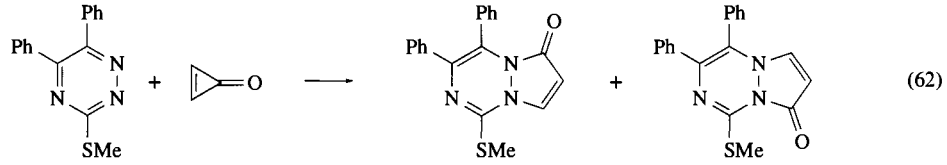


38% 8% 5% (61)

8.31.13.5 Pyrazolo[1,2-*a*][1,2,4]triazine

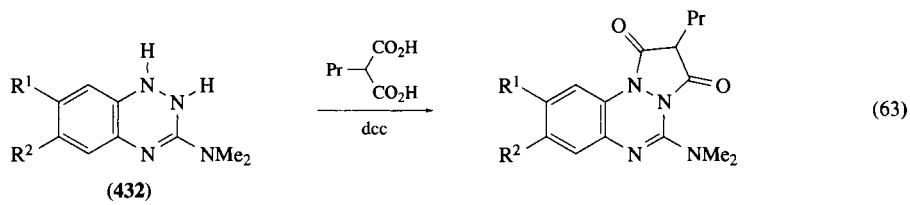
8.31.13.5.1 Five-membered ring synthesis by formation of two bonds

Unsubstituted cyclopropenone reacts with the N=N bond of some 1,2,4-triazines to provide pyrazolo[1,2-*a*][1,2,4]triazinones in low yields. In the case of (**429**), a mixture of both possible adducts (**430**) and (**431**) is formed (Equation (62)) ⟨94AP(327)477⟩.



(**429**) (**430**) 23% (**431**) 23% (62)

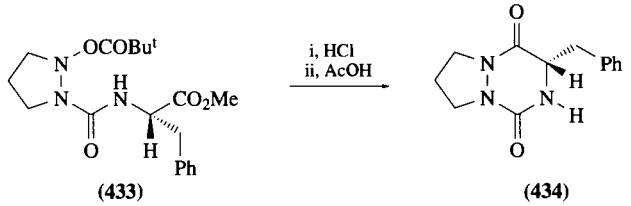
Synthesis of benzo derivatives has been studied in connection with biological activity of azapropazone (see Section 8.31.15.2). This synthesis is based on the reaction of (**432**) with propyl malonic acid using the DCC method (Equation (63)) ⟨72HCA1031⟩.



(**432**) (63)

8.31.13.5.2 Six-membered ring synthesis by formation of one bond

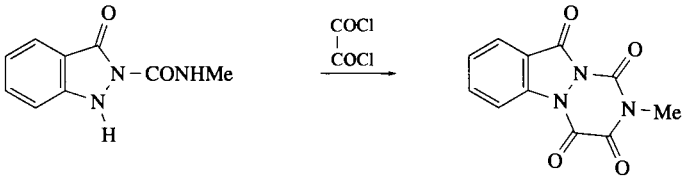
After deprotection of (**433**) with dry hydrogen chloride in dioxane, intramolecular cyclization to (**434**) is achieved by prolonged treatment with acetic acid at 70 °C (Equation (64)) ⟨94JCS(P1)1611⟩.



(433) (434) (64)

8.31.13.5.3 Six-membered ring synthesis by formation of two bonds

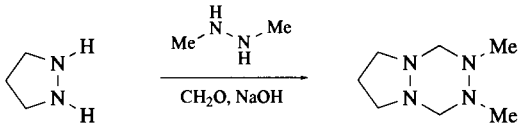
Benzo derivative (**435**) is prepared in 70% yield from indazolone (**365**) and oxalyl chloride (Equation (65)) ⟨81LA1361⟩.



(365) (435) (65)

8.31.13.6 Pyrazolo[1,2-*a*][1,2,4,5]tetrazine

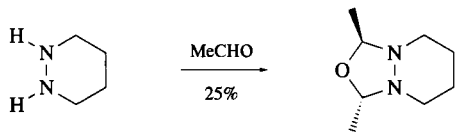
Treatment of pyrazolidine with 1,2-dimethylhydrazine and formaldehyde under alkaline conditions provides a low yield of (**436**) (Equation (66)) ⟨79CB853⟩.



(436) (66)

8.31.13.7 1,3,4-Oxadiazolo[3,4-*a*]pyridazine

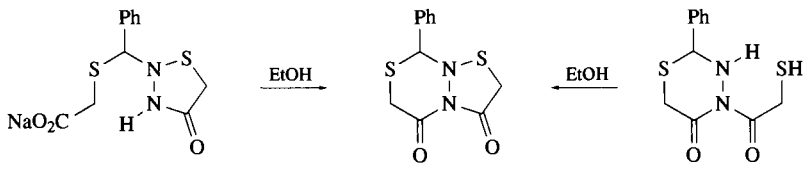
Piperidazine treated with acetaldehyde provides a 25% yield of *trans* isomer (**437**) (Equation (67)) ⟨72JA7108⟩. Similarly, 4-tetrahydropyridazine and butyryl aldehyde gives 30% yield of the corresponding bicyclic compound ⟨64RTC877⟩.



(437) (67)

8.31.13.8 1,2,3-Thiadiazolo[2,3-*c*][1,3,4]thiadiazine

Heating of (**438**) or (**440**) in polar solvents (e.g., in ethanol) provides (**439**) (Scheme 96) ⟨65G1258⟩.



(438) (439) (440)

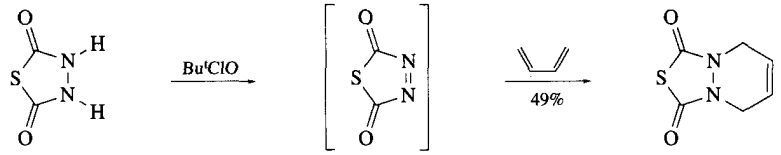
Scheme 96

8.31.13.9 1,3,4-Thiadiazolo[3,4-*a*]pyridazine

8.31.13.9.1 Ring synthesis by formation of two bonds

(i) From [4 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

Compound (**441**) oxidized *in situ* with *t*-butyl hypochlorite in the presence of butadiene gives 49% of (**443**) via intermediate (**442**) (Scheme 97) ⟨74JOC2951⟩.



(441) (442) (443)

Scheme 97

(ii) From [5 + 1] atom fragments, one bond adjacent to a ring junction nitrogen atom

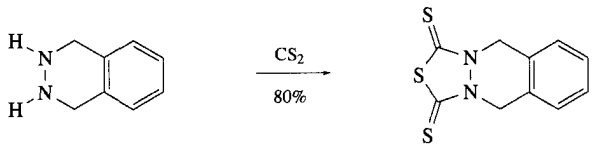
Thiocarbamoyl tetrahydrophthalazines (**444**) treated with thiophosgene under mild conditions provide the corresponding imino-substituted compounds (**445**) (Equation (68)) ⟨94PHA419⟩.



(444) (445) (68)

8.31.13.9.2 Ring synthesis by formation of three bonds

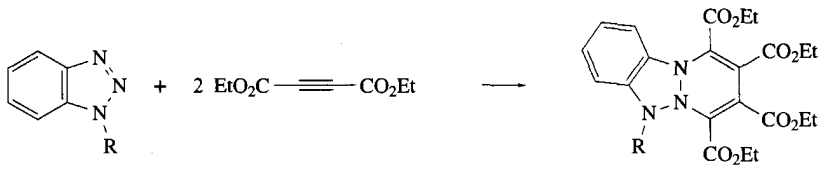
1,3-Dithiacarbonyl derivative (**446**) can be easily prepared in 80% yield by treatment of tetrahydrophthalazine with carbon disulfide (Equation (69)) ⟨94PHA419⟩.



(446) (69)

8.31.13.10 1,2,3-Triazolo[1,2-*a*]pyridazine

This ring system is present in the 5-alkyl-5*H*-pyridazo[1,2-*a*]benzotriazole tetraester (**447**), which is formed by treating 1-alkyl benzotriazole with two molar equivalents of diethyl ethynedicarboxylate (Equation (70)) ⟨72JCS(P1)2182⟩.

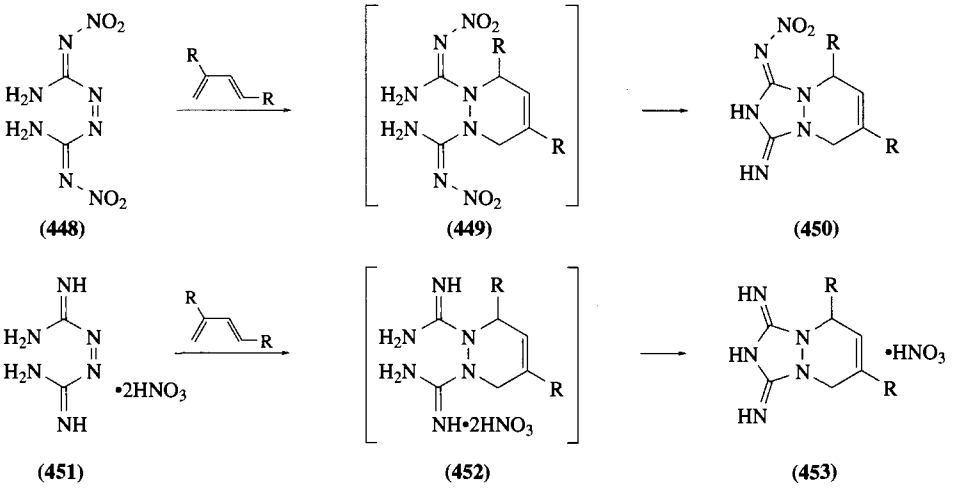


(447) (70)

8.31.13.11 1,2,4-Triazolo[1,2-*a*]pyridazine

8.31.13.11.1 Synthesis from nonheterocyclic precursors

The Diels–Alder reaction of azo-bis-formamidine derivatives (**448**) and (**451**) with simple dienes provides (**450**) and (**453**) probably via intermediates (**449**) and (**452**), respectively (Scheme 98) ⟨52CJC62, 52JOC1666⟩.

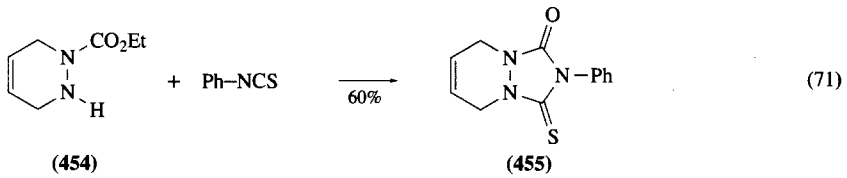


Scheme 98

8.31.13.11.2 Five-membered ring synthesis by formation of two bonds

(i) From [3 + 2] atom fragments, one bond adjacent to a ring junction nitrogen atom

Phenyl isothiocyanate treated with (**454**) provides 60% yield of oxo-thioxo derivative (**455**) (Equation (71)) ⟨64ZOB390⟩.



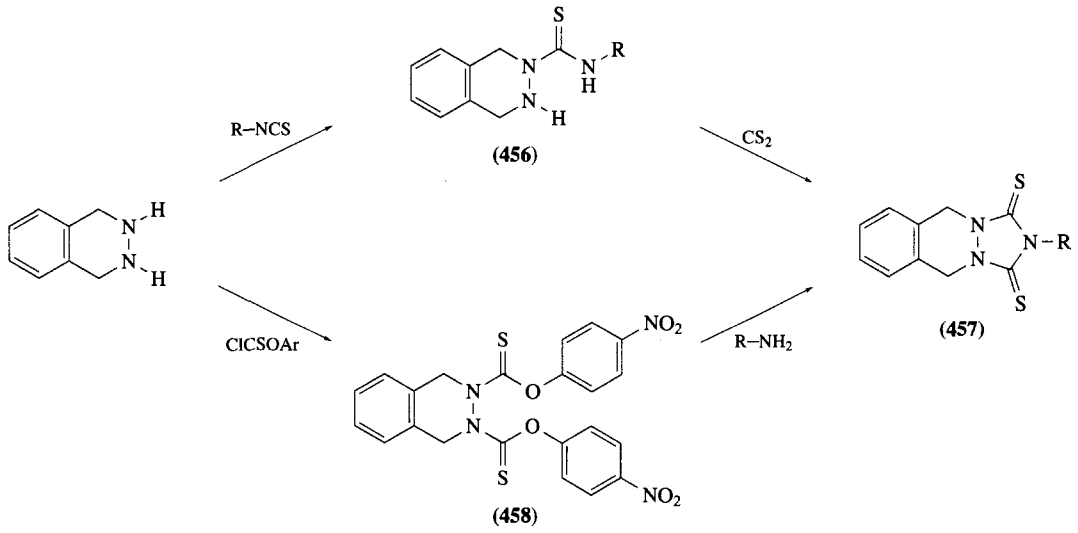
(71)

(ii) From [4 + 1] atom fragments, one bond adjacent to a ring junction nitrogen atom

Tetrahydrophthalazine treated with isothiocyanates provides (**456**) which treated with carbon disulfide affords (**457**) (Scheme 99) ⟨94PHA419, 94PHA489⟩.

(iii) From [4 + 1] atom fragments, no bonds adjacent to ring junction nitrogen atoms

Compound (**458**), which is easily available by treatment of tetrahydrophthalazine with the corresponding aryl chlorothioformate, can react with primary amines to provide compounds (**457**) (Scheme 99) ⟨94PHA489⟩.

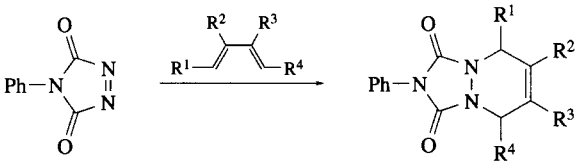


Scheme 99

8.31.13.11.3 Six-membered ring synthesis by formation of two bonds

(i) From [4 + 2] atom fragments, both bonds adjacent to ring junction nitrogen atoms

PTAD is well known as a powerful dienophile that reacts intermolecularly with various dienes at −78 °C to −50 °C as evidenced by the immediate discharge of the red color ⟨62TL615⟩. There are many other examples of the Diels–Alder addition of TADs, especially PTAD, to various dienes (Equation (72)). Selected examples are given in Table 6. The reaction generally provides high yields of the 1,4-adducts and is often used for intercepting labile dienes of natural origin and/or for their structure elucidation ⟨80HCA860, 91HCA2035⟩.



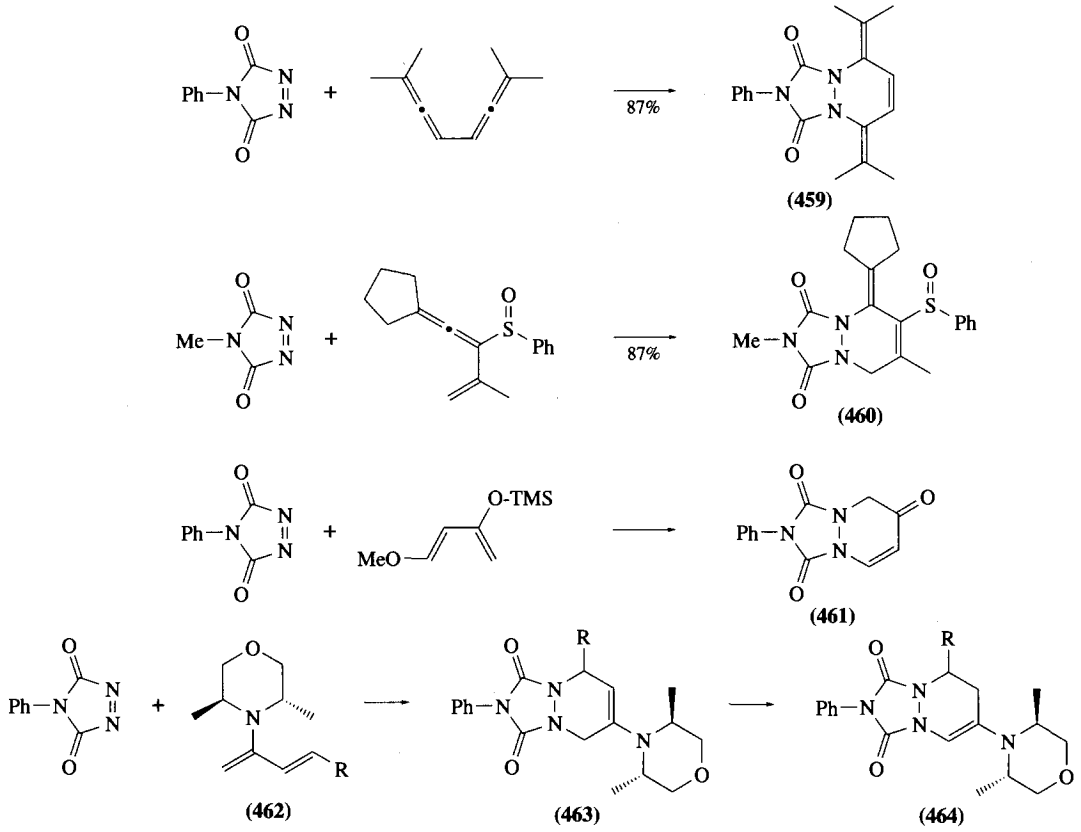
(72)

Table 6 Reaction of PTAD with dienes (Equation (72)).

R^1	R^2	R^3	R^4	*Yield* (%)	*Ref.*
H	H	H	H		62TL615
				61	67JCS(C)1905
Me	H	H	H	96	87JA6376
H	N_3	N_3	Me	92	87AG(E)879
COOH	H	H	H	93	76JCS(P1)2390
MeO	H	MeO	H	82	82JOC4774
Me	H	H	$(CH_2)_3SePh$	89	90JOC1786
H	Me_3SiO	Me_3SiO	H	90	88CB185
Ph	H	H	$C[P(O)(OMe)_2]{=}N^+{=}N^-$	72	85T2625

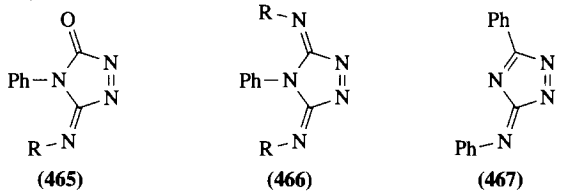
The bicyclic structure (**459**), containing two exocyclic double bonds, is formed in the Diels–Alder reaction of 2,7-dimethyl-2,3,5,6-octatetraene with PTAD ⟨78JCS(P1)1568⟩. Similarly, MTAD reacts at subambient temperatures with vinylsulfoxy allenes to give the corresponding Diels–Alder adducts (e.g., (**460**)) ⟨94JHC871⟩. PTAD also reacts with electron-rich dienes, for example 1,3-dimethoxy-1,3-butadiene provides the corresponding adduct in 82% yield ⟨82JOC4774⟩. 1-Methoxy-3-trimethylsilyl-1,3-butadiene reacts rapidly at room temperature to give after the work-up enone (**461**) in 84%

yield ⟨85JCS(P1)71⟩. The 2-morpholino-1,3-butadiene (**462**) reacts with PTAD to give primary adduct (**463**) which isomerizes to the more stable isomer (**464**), where two nitrogen atoms are in conjugation with the double bond (Scheme 100) ⟨94S66⟩.



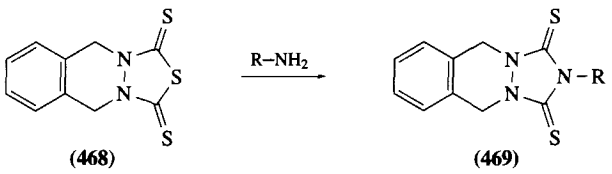
Scheme 100

Whereas triazolinediones react with dienes spontaneously to form 1,4-adducts, the same reaction with (**465**), (**466**) and (**467**) requires the presence of two molar equivalents of boron trifluoride etherate ⟨74CB454⟩.



8.31.13.11.4 Ring synthesis from other heterocycles

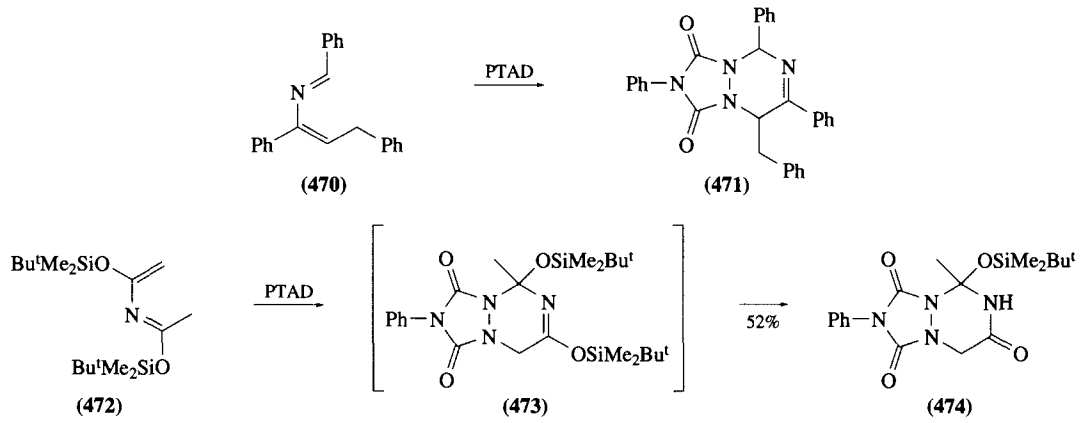
Thiadiazolophthalazine (**468**) treated with sufficiently basic primary aliphatic amines (e.g., methylamine or ethylamine) provides high yields of triazolo analogs (**469**) (Equation (73)) ⟨94PHA489⟩.



(73)

8.31.13.12 1,2,4-Triazolo[1,2-*a*][1,2,4]triazine

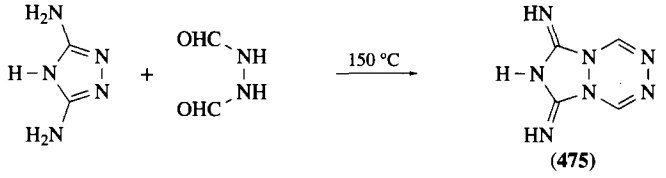
Triphenyl aza pentadiene (**470**) reacts with PTAD to give the Diels–Alder adduct (**471**) ⟨75CJC355⟩. Aza pentadiene (**472**) reacts with PTAD via the Diels–Alder adduct (**473**), which, in this case, cannot be isolated, giving bicyclic structure (**474**) (Scheme 101) ⟨87HCA1255⟩.



Scheme 101

8.31.13.13 1,2,4-Triazolo[1,2-*a*][1,2,4,5]tetrazine

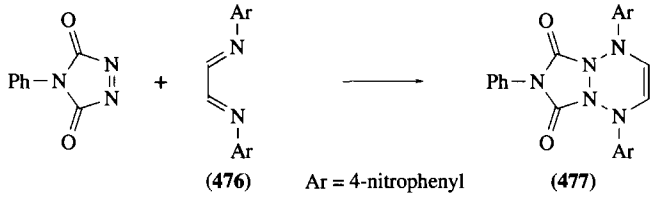
Condensation of 3,5-diamino-1,2,4-triazole with diformylhydrazine yields a white solid which was assigned structure (**475**) (Equation (74)) ⟨52G735⟩.



(74)

8.31.13.14 1,2,4-Triazolo[1,2-*b*][1,2,3,4]tetrazine

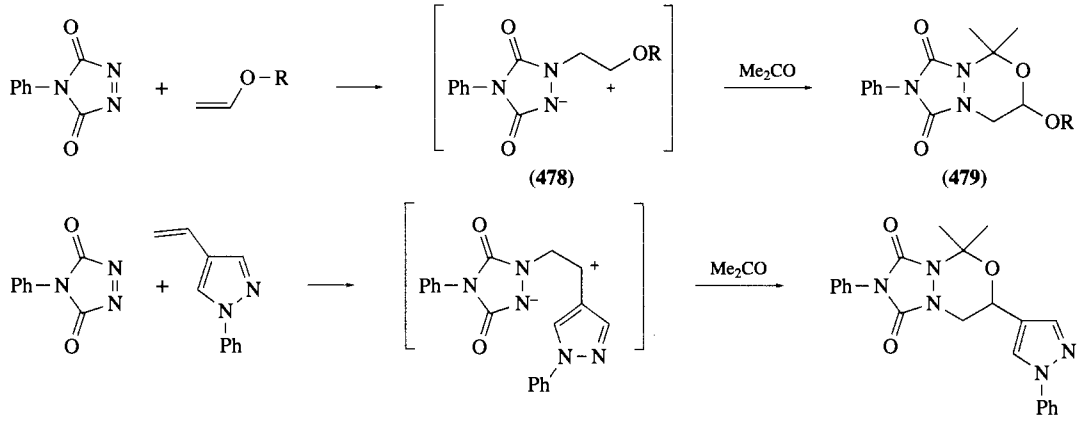
The Diels–Alder reaction of PTAD with diazadiene (**476**) provides (**477**) (Equation (75)) ⟨82IJC589⟩.



(75)

8.31.13.15 1,2,4-Triazolo[1,2-*c*][1,3,4]oxadiazine

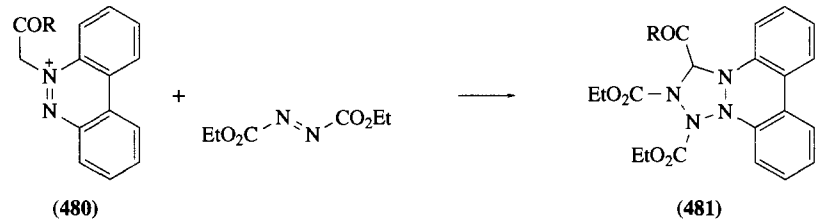
PTAD reacts spontaneously with vinyl ethers to give 1,4-dipoles (**478**) which are able to react with weakly dipolarophilic alkyl ketones to form (**479**), together with a polymeric material ⟨71JOC2838, 83JOC822⟩. A similar reaction takes place when 1-phenyl-4-vinylpyrazole is treated with PTAD at −60 °C in acetone (Scheme 102) ⟨85TL6357⟩.



Scheme 102

8.31.13.16 Tetrazolo[1,2-*a*]pyridazine

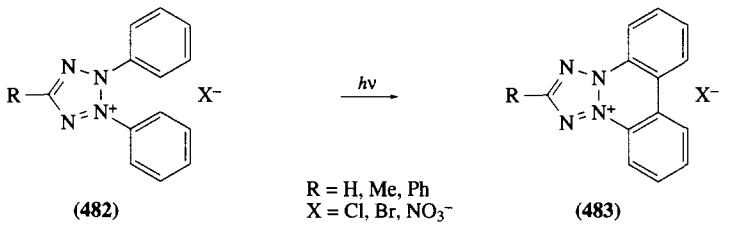
Only the corresponding dibenzo derivatives have been reported. Benzocinnolinium salts (**480**; R = Ph, OEt) react easily with diethyl azodicarboxylate via the corresponding azomethine imines by a 1,3-dipolar cycloaddition mechanism to give (**481**) (Equation (76)) ⟨74RRC1507, 76RRC1203⟩.



(76)

8.31.13.17 Tetrazolo[2,3-*a*]pyridazine

This bicyclic ring system has not been described but the corresponding dibenzo analogs (benzo[*c*]tetrazolo[2,3-*a*]cinnolines) are known. Photocyclization reaction of the starting 2,3-diphenyltetrazolium salts (**482**) in alcoholic solutions provides the corresponding tetracyclic salts (**483**) (Equation (77)) ⟨48ZN(B)377, 49CB195, 54LA(590)216, 55CB1284, 55CB1595⟩.



(77)

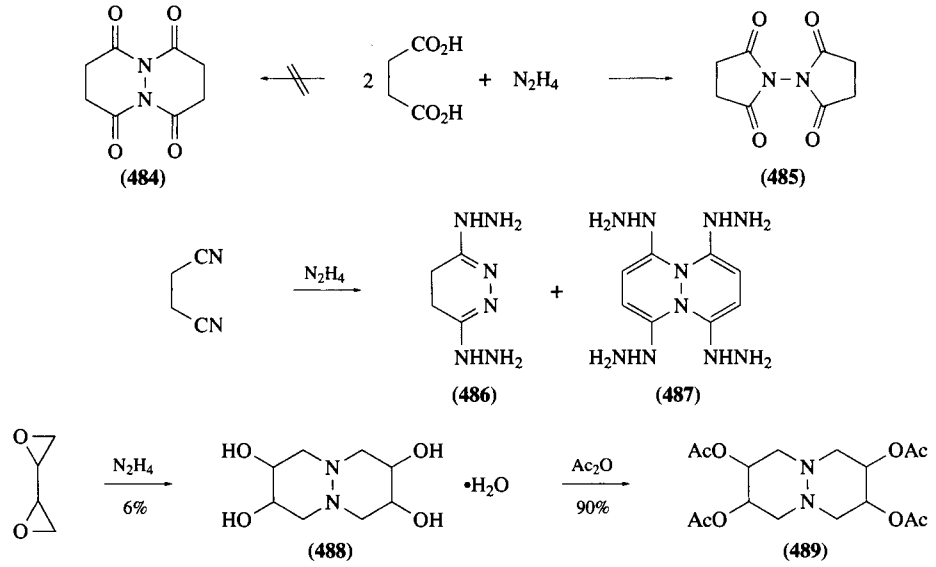
8.31.14 SYNTHESIS OF 6-6 RING SYSTEMS

8.31.14.1 Pyridazino[1,2-*a*]pyridazine

8.31.14.1.1 Synthesis from nonheterocyclic precursors

Heating of a 2:1 molar ratio mixture of succinic acid and hydrazine with or without polyphosphoric acid gives high yields of a crystalline product which was originally thought to be (**484**) ⟨56CI(L)577⟩. The true structure of this product (**485**) was discovered later ⟨63JA3052⟩. Reaction of succinonitrile with hydrazine gives a mixture of pyridazine derivative (**486**) and bicyclic compound

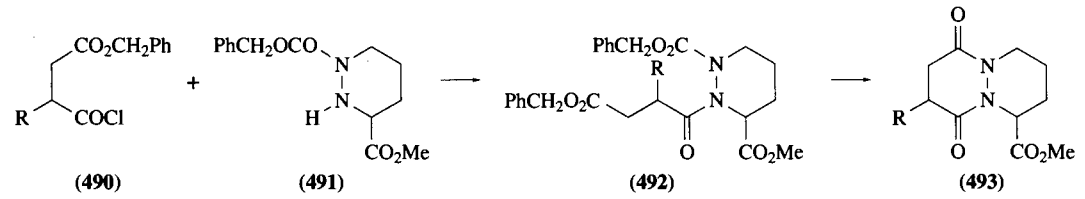
(**487**) ⟨74KGS1420⟩. The cyclization reaction of butadiene dioxide with aqueous hydrazine gives low yields (6%) of (**488**) in the form of its hydrate which is easily acetylated to (**489**) (Scheme 103) ⟨63HCA2685⟩.



Scheme 103

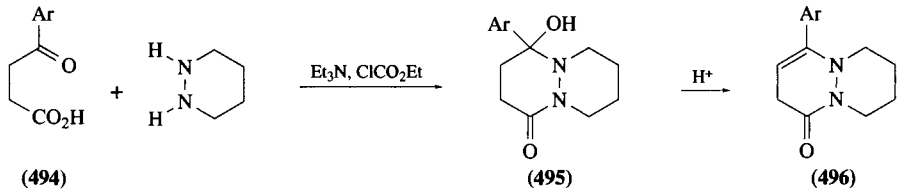
8.31.14.1.2 Ring synthesis by formation of one bond

Piperidazine derivative (**491**) treated with substituted succinic acid ester chloride (**490**) provides (**492**). The intermediate after deprotection with hydrogen bromide in acetic acid is cyclized into (**493**) by a sequential treatment with phosphorus pentachloride and pyridine (Scheme 104) ⟨84JCS(P1)155⟩.



Scheme 104

Reaction of acid (**494**) and piperidazine by the mixed anhydride method provides a product that could be represented by structure (**495**) or its open-chain tautomer. Acidic treatment of this intermediate then provides (**496**) (Scheme 105) ⟨69JOC2720⟩.

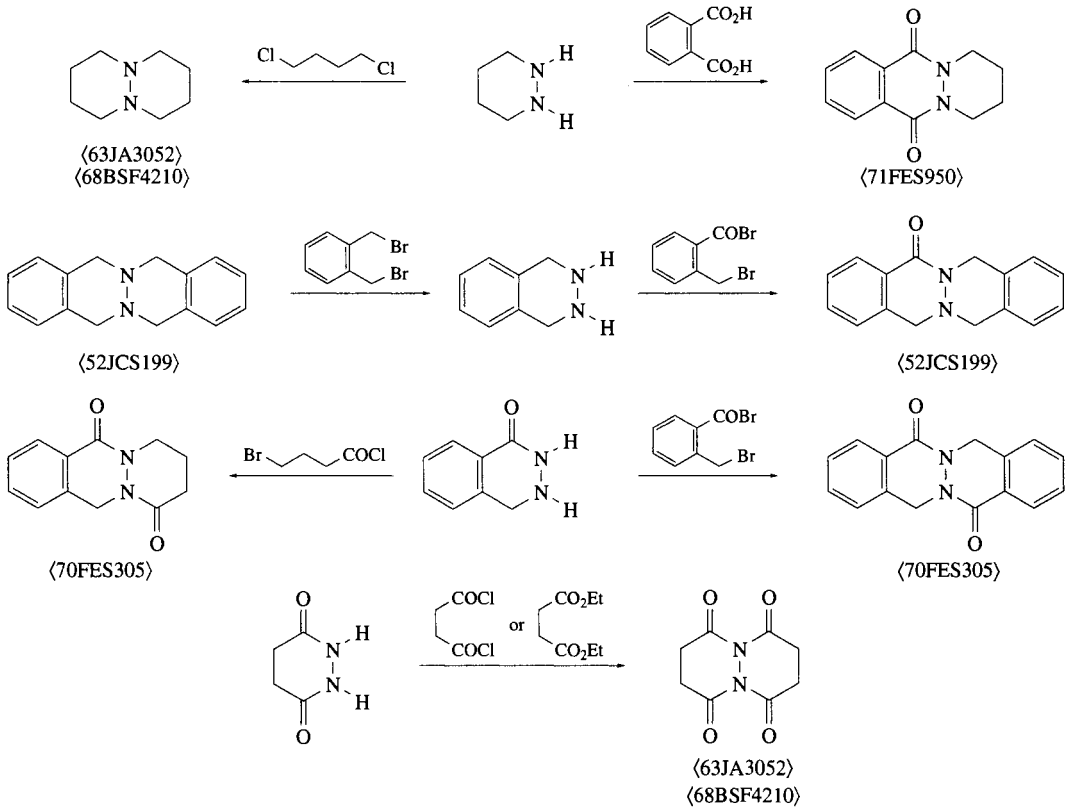


Scheme 105

8.31.14.1.3 Ring synthesis by formation of two bonds

(i) From [4 + 2] atom fragments

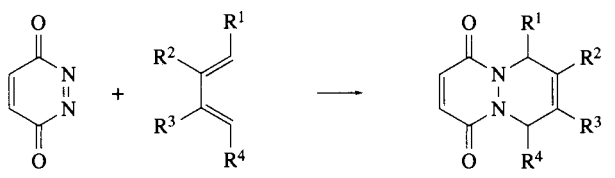
Reaction of bifunctional alkylating and/or acylating agents with piperidazine, its benzo analogs and various similar derivatives provides the corresponding heterocycles. The main reactions of this type are summarized in Scheme 106 ⟨52JCS199, 63JA3052, 68BSF4210, 70FES305, 71FES950⟩.



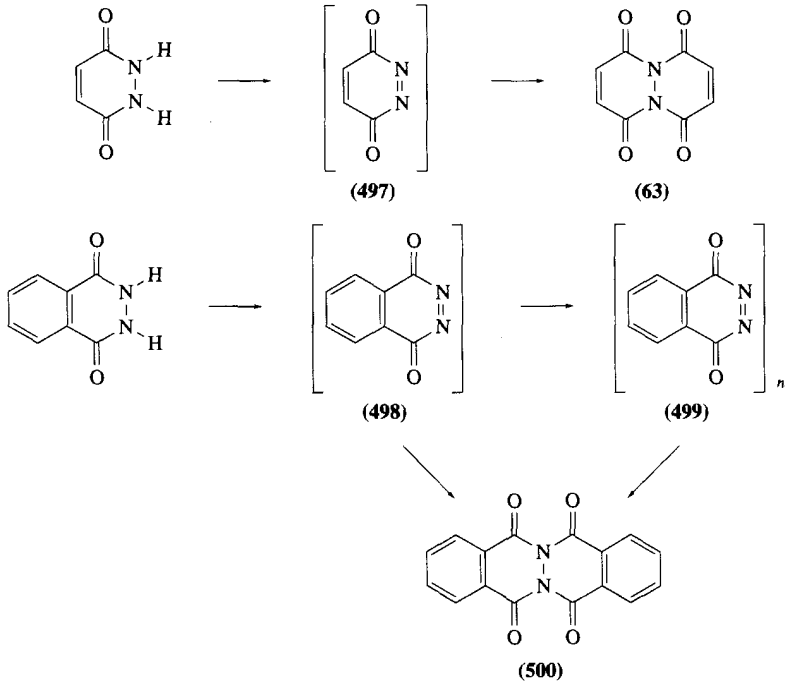
Scheme 106

Pyridazinedione (**497**) can be prepared by oxidation of the corresponding cyclic hydrazide with LTA, usually using acetonitrile as a solvent (Clement's procedure) ⟨60JOC1724⟩ or by oxidation of alkaline salts of the hydrazide with *t*-butyl hypochlorite in acetone (Kealy's procedure) ⟨62JA966⟩. Both procedures are performed at subambient temperatures. In general, the pyridazinedione solutions quickly decompose at room temperature providing bicyclic compound (**63**) in low to medium yields. Phthalazinedione (**498**), generated *in situ* from phthalic hydrazide at 0 °C, gradually decomposes, providing polymeric compound (**499**). Attempts to isolate (**498**) lead to tetracyclic compound (**500**) which is also available by heating of (**499**) (Scheme 107) ⟨94AHC(61)141⟩.

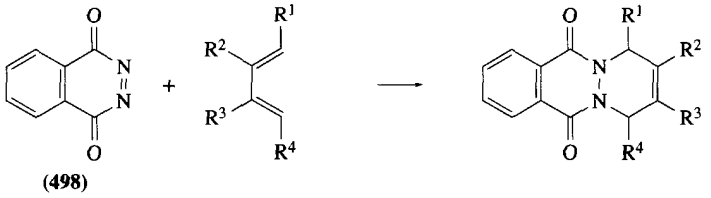
The Diels–Alder reaction is a useful method of synthesis of six-membered rings. Since diaza quinone (**497**) (Equation (78)) and its annelated analogs, for example, (**498**) (Equation (79)), are good dienophiles, this method also provides a versatile way to the corresponding heterocycles containing the pyridazino[1,2-*a*]pyridazine moiety. The diazaquinones are usually generated *in situ* owing to their low stability. Tables 7 and 8 show some examples of the reaction.



(497) (78)



Scheme 107



(79)

Table 7 Reaction of pyridazinedione with dienes (Equation (78)).

R^1	R^2	R^3	R^4	*Ref.*
H	H	H	H	62JA966, 62JOC1115
H	Me	H	H	74AKZ1000
H	Cl	H	H	74AKZ1000
H	Cl	Cl	H	74AKZ1000

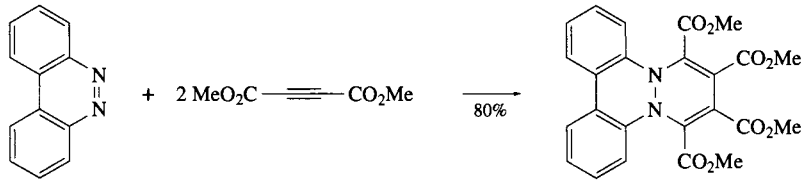
The Diels–Alder reaction with various dienes has been thoroughly studied and used for identification of unstable compounds containing the diene grouping, for protection of steroidal dienes, etc. All these features have been reviewed ⟨94AHC(61)141⟩.

8.31.14.1.4 Ring synthesis by formation of three bonds

Benzo[*c*]cinnoline heated with DMAD in DMF gives 80% yield of (**501**) (Equation (80)) ⟨68MI 831-01⟩.

Table 8 Reaction of phthalazinedione with dienes (Equation (79)).

R^1	R^2	R^3	R^4	*Ref.*
H	H	H	H	85JOC5604
Ph	H	H	Ph	86JOC3123
COOH	H	H	H	71JCS(C)514, 77H119
$-CH_2-C(CF_3)(CO_2H)(NHCOPh)$	H	H	H	91CZ292

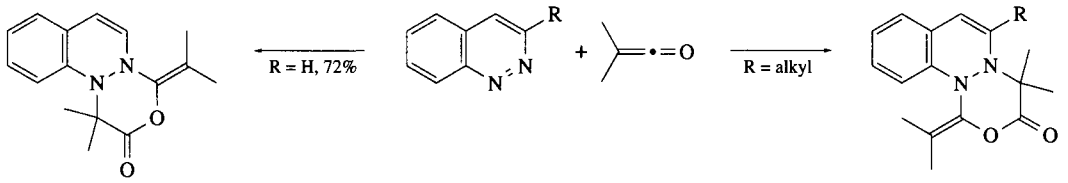


(80)

(501)

8.31.14.2 Pyridazino[1,2-*c*][1,3,4]oxadiazine

Cinnoline reacts regioselectively with dimethylketene in ether to give (**502**). On the other hand, 3-substituted cinnolines form predominantly the opposite regioisomer (**503**) (Scheme 108) ⟨70JCS(C)1642⟩.

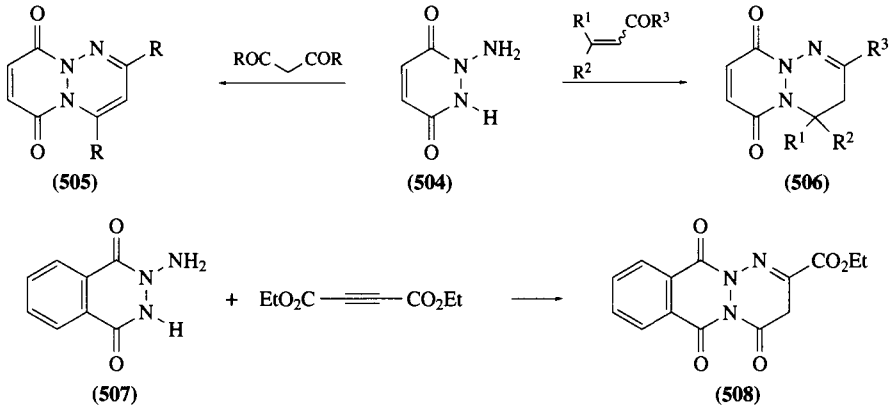


(502) (503)

Scheme 108

8.31.14.3 Pyridazino[1,2-*a*][1,2,3]triazine

Condensation of *N*-amino derivative (**504**) with various α,β-unsaturated carbonyl compounds and β-dicarbonyl compounds leads to the bicyclic derivatives (**505**) and (**506**), respectively ⟨88MI 831-01, 90MI 831-01⟩. Similarly, amino derivative (**507**) treated with diethyl ethynedicarboxylate provides (**508**) (Scheme 109) ⟨85MI 831-01⟩.



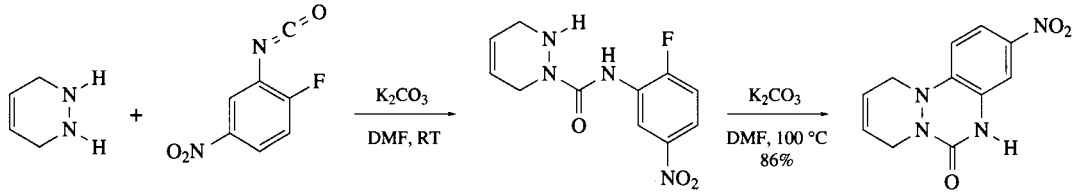
(505) (504) (506)

(507) (508)

Scheme 109

8.31.14.4 Pyridazino[1,2-*a*][1,2,4]triazine

Treatment of tetrahydropyridazine with 2-fluoro-5-nitrophenylisocyanate in DMF at room temperature in the presence of potassium carbonate gives an 86% yield of (**509**) which is then cyclized at 100°C into (**510**) ⟨93JHC45⟩.



(**509**) (**510**)

Scheme 110

8.31.14.5 Pyridazino[1,2-*a*][1,2,4,5]tetrazine

Treatment of piperidazine or tetrahydropyridazine with 1,2-dialkylhydrazines and formaldehyde under alkaline conditions provides low yields of (**511**) and (**512**), respectively (Scheme 111) ⟨74JCS(P2)948, 76JA5748⟩.

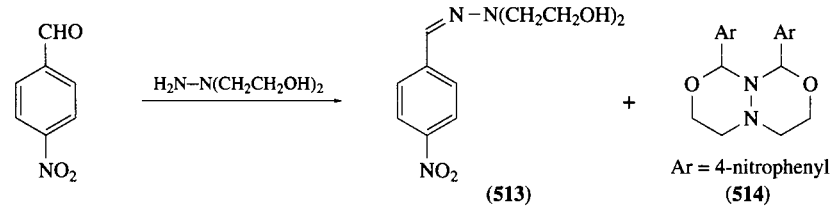


(**511**) (**512**)

Scheme 111

8.31.14.6 1,3,4-Oxadiazino[3,4-*c*][1,3,4]oxadiazine

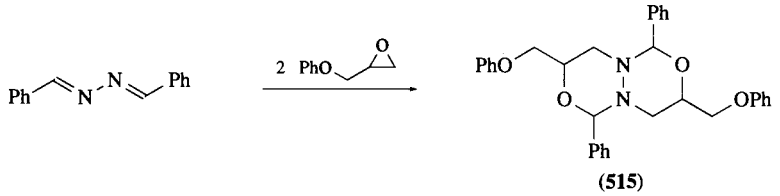
N,*N*-bis(2-Hydroxyethyl)hydrazine treated with 4-nitrobenzaldehyde provides a mixture from which 48% of (**513**) and 6% of (**514**) can be isolated. A greater excess of the aldehyde increases the yield of (**514**) up to 17% (Equation (81)) ⟨85ZOR914⟩.



(**513**) (**514**) (81)

8.31.14.7 1,3,4-Oxadiazino[4,3-*c*][1,3,4]oxadiazine

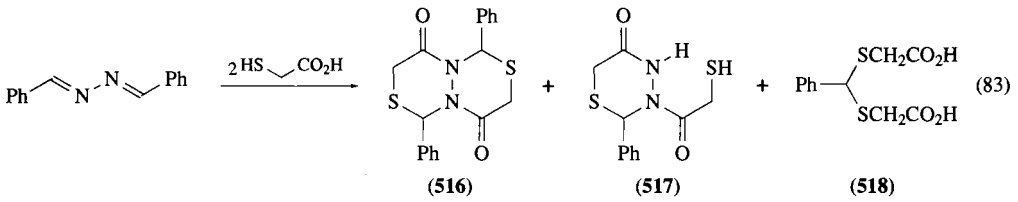
Heating of benzaldazine with 2,3-epoxypropyl phenyl ether catalyzed with stannic chloride provides a low yield (less than 20%) of a product of criss-cross addition (**515**) (Equation (82)) ⟨73CPB2088, 74CPB1468⟩.



(**515**) (82)

8.31.14.8 1,3,4-Thiadiazino[4,3-*c*][1,3,4]thiadiazine

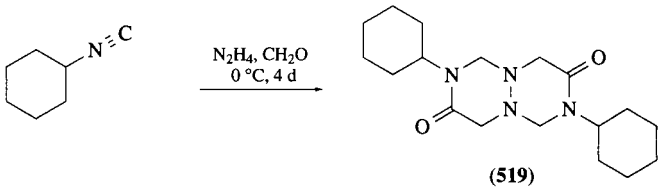
Thioglycolic acid reacts with benzaldazine in concentrated benzene solutions to provide a mixture containing three main products, (**516**), (**517**), and (**518**) (Equation (83)) ⟨65G1258, 66G897⟩.



(83)

8.31.14.9 1,2,4-Triazino[2,1-*a*][1,2,4]triazine

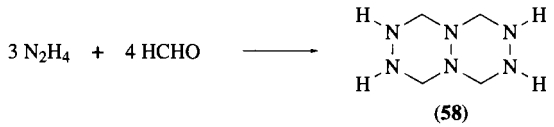
Treatment of hydrazine with aqueous formaldehyde and cyclohexylisocyanide under acidic conditions at 0 °C for several days provides a low yield of (**519**) (Equation (84)) ⟨66AP(299)746⟩.



(84)

8.31.14.10 1,2,4,5-Tetrazino[1,2-*a*][1,2,4,5]tetrazine

Reaction of hydrazine with aqueous formaldehyde provides a white crystalline product called tetraformaltrisazine (**58**) (Equation (85)) ⟨12CB1725, 66BCJ504⟩.



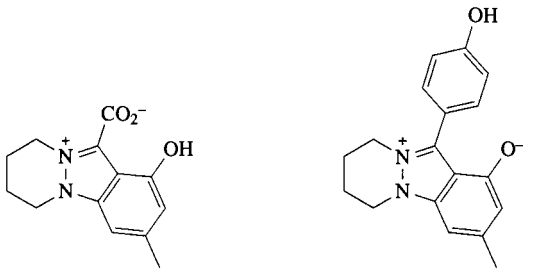
(85)

8.31.15 IMPORTANT COMPOUNDS AND APPLICATIONS

A great deal of the work described earlier has been stimulated by the discovery of several biologically active compounds.

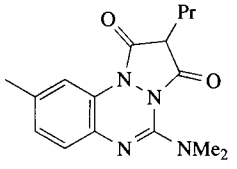
8.31.15.1 Natural Products

Naturally occurring compounds with two ring junction nitrogen atoms are very rare. Nigellicine (**520**) and its derivative nigellidine (**521**) are the only examples in the literature. The alkaloids were isolated from Nigella sativa, which is a plant with a great historical background ⟨85TL2759⟩. Total syntheses of both of these alkaloids has been reported ⟨88DIS(B)3569⟩.

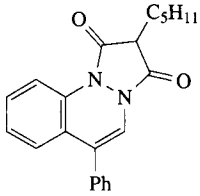


8.31.15.2 Drugs and Pharmaceutical Intermediates

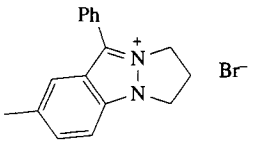
Though it has not become widely used, azapropazone (**522**) has some use in the treatment of rheumatic disease and other muscoskeletal disorders ⟨69AF36⟩. A similar compound, called cinnopentazone (**523**), has antiinflammatory activity but it is also significantly active against some tumors ⟨70AF831⟩. FKK (**524**), a selected compound from a series of pyrazoloindazolium halides, is an active bronchodilator ⟨86YZ1002⟩.



Azapropazone
(**522**)

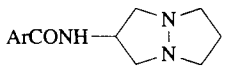


Cinnopentazone
(**523**)

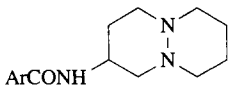


FKK
(**524**)

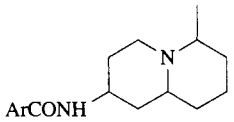
Compounds (**525**) and (**526**) are potent dopamine receptor antagonists active as gastric prokinetic agents. None of the compounds, however, is better than BRL 20627 (**527**), which has only one ring junction nitrogen atom ⟨92BMC1293⟩.



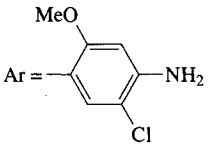
(**525**)

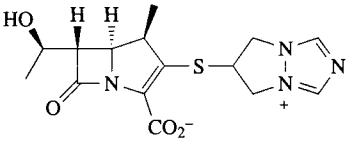


(**526**)

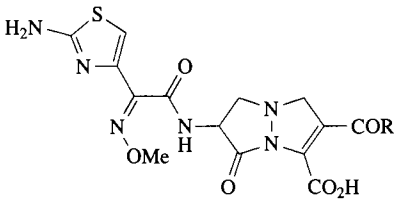


BRL 20627
(**527**)





(**528**)
Biapenem

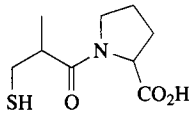


(**529**)
(**a**) R = OMe (LY 173 013)
(**b**) R = Me (LY 186 826)

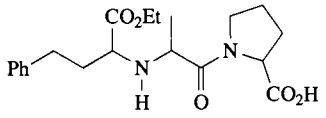
Modulation of the renin/angiotensin system through inhibition of angiotensin-converting enzyme (ACE) has assumed increasing importance in the therapy of hypertension and of congestive heart failure. Captopril (**530**) and enalapril (**531**) are potent ACE inhibitors effective as antihypertensives in man. The postulated binding functions for the active site of ACE has made possible the design of improved inhibitors. An extensive study revealed several highly active bicyclic ACE inhibitors (e.g., (**532**) and (**533**)). These compounds are also highly potent antihypertensives *in vivo* and the 6-7 bicyclic compound Cilazapril (**534**) ⟨87MI 831-01⟩ was introduced into the market in 1990.

8.31.15.3 Agrochemicals

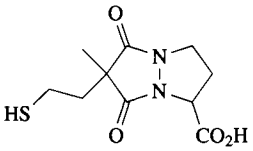
Though some older patents claim useful agrochemical activities of compounds belonging to this chapter, no compound has become used in practice. A publication ⟨92MI 831-01⟩ has revealed a new group of peroxidizing herbicides which seems to be exciting and promising. The general structure of these compounds can be exemplified as (**535**) where X, Y can be O, S, or NCO_2Et.



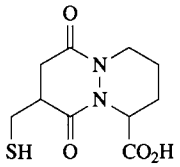
Captopril
(530)



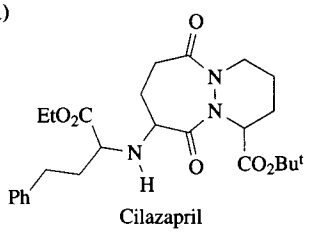
Enalapril
(531)



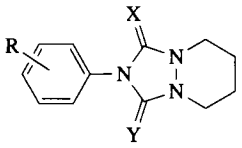
(532)



(533)



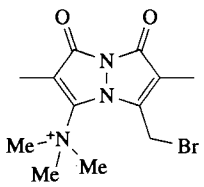
Cilazapril
(534)



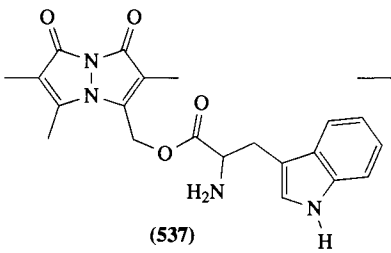
(535)

8.31.15.4 Analytical Reagents

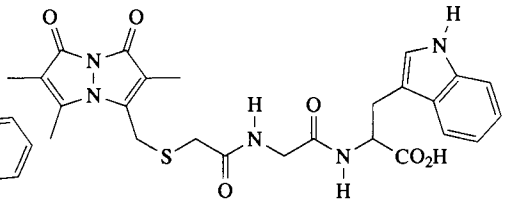
Bromobimane (**12**), which is now commercially available, is used as a fluorescent probe for thiol determination ⟨83BJ(215)159, 83JPP384, 85BBR(127)49, 92JA5509⟩. Monobromotrimethylammoniobimane (**536**) can be used as a conformationally sensitive fluorescent probe for detecting conformational changes in mitochondrial aspartate aminotransferase ⟨84MI 831-01⟩. Tryptophan containing bimane peptide (**537**) is a potent fluorogenic substrate for microdetermination of chymotrypsin and aminopeptidases ⟨88MI 831-02⟩. A similar fluorogenic substrate (**538**) is used for microdetermination of carboxypeptidase A ⟨88CPB4494⟩.



(536)



(537)



(538)

Bromobimane was also used for preparation of a fluorescent lipid analog which is suitable for use in lipid bilayers ⟨85B2203⟩.

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8.32
Bicyclic Systems with Ring Junction Sulfur, Selenium, or Tellurium Atoms

BÜLENT TEREM
Chaminade University, Honolulu, HI, USA

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8.32.1 INTRODUCTION

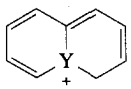
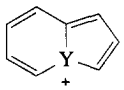
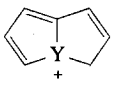
The bicyclic systems discussed in this chapter appear in a number of chapters and volumes of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). This is not surprising since these structurally similar compounds exhibit a broad range of interesting chemistry. The present chapter is organized into three main sections on the basis of the different chemical features of the classes of compounds covered. The first section surveys 6-6, 6-5, and 5-5 fused bicyclic ions with S, Se, and Te heteroatoms in the bridgehead positions. The second section addresses similar systems, but in dicationic form with two heteroatoms in the bridgehead positions. The final section looks at pentalene systems where the bridgehead heteroatom is in its hypervalent state.

The heterocyclic compounds discussed here are named in accordance with the IUPAC rules based on the Hantzch–Widman system also used in *Chemical Abstracts*. However, for fully saturated compounds, the von Baeyer system is preferred in order to avoid the cumbersome *polyhydro* prefixes. The reader is cautioned to the fact that the peripheral numbering is different for the two systems. Whereas according to the Hantzch–Widman system, bicyclic systems discussed here are numbered starting with the atom not engaged in the ring fusion in the most counter-clockwise position of the uppermost ring, the von Baeyer numbering starts with a bridgehead heteroatom ⟨B-79MI 832-01⟩.

8.32.2 BICYCLIC SYSTEMS WITH BRIDGEHEAD HETEROATOM AND NO ADJACENT HETEROATOMS

Fully or near fully conjugated bicyclic systems with bridgehead nitrogen atoms are well known. Quinolizine, indolizine, and pyrrolizine derivatives are all stable compounds because of the participation of nitrogen lone pair electrons in the π-system of the ring. When the nitrogen is replaced with a group 16 atom such as S, Se, or Te on the other hand, the resulting bicyclic structure is very unstable. This is contrary to earlier work using simple Hückel–MO methods which ignored the participation of the sulfur 3*d* orbitals and predicted a high stability for the sulfur analogue of indolizine ⟨65AHC(5)1⟩. However, it is clear that a sulfur atom, when singly bonded to three carbon atoms, undergoes slow inversion which would destroy the coplanarity essential for a fully conjugated system, and thus would be energetically unfavorable ⟨80JCS(P1)1185⟩. For purposes of nomenclature and comparison, the hypothetical structures of S, Se, or Te analogues of quinolizine, indolizine, and pyrrolizine are given in Table 1. Only one of the possible tautomers is shown.

Table 1 S, Se, or Te analogues of quinolizine, indolizine, and pyrrolizine.

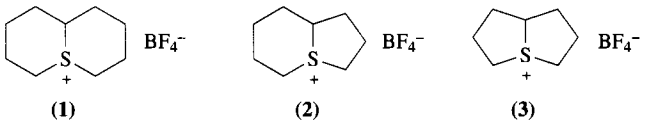
Structures	*Heteroatom*	*Names*
	Y = S	Thiopyrano[1,2-a]thiopyrylium
	Y = Se	Selenino[1,2-a]seleninium
	Y = Te	Tellurino[1,2-a]tellurinium
	Y = S	Thieno[1,2-a]thiopyrylium
	Y = Se	Selenolo[1,2-a]seleninium
	Y = Te	Tellurolo[1,2-a]tellurinium
	Y = S	Thieno[1,2-a]thiolium
	Y = Se	Selenolo[1,2-a]selenolium
	Y = Te	Tellurolo[1,2-a]tellurolium

8.32.2.1 Fused Thiopyrylium and Thiolium Ions

8.32.2.1.1 Structural and stereochemical aspects

The discovery of 1-thioniabicyclo[4.4.0]decane (TBD) tetrafluoroborate (**1**) dates back to Eastman's synthesis in 1959 ⟨59JOC1428⟩. The bicyclic bridgehead sulfonium salt is consequently referred to as Eastman's sulfonium salt ⟨77JA2337⟩. Heathcock and co-workers subsequently developed alternative synthetic strategies allowing the functionalization of each ring ⟨79JA2971⟩. 1-

Thioniabicyclo[4.3.0]nonane (**2**) ⟨82JOC2861⟩ and 1-thioniabicyclo[3.3.0]octane (**3**) salts ⟨82JOC2861⟩ have also been prepared as the transannular cyclization products of the corresponding thiacycloalkenes.



(1) **(2)** **(3)**

The stereostructural aspects of the bicyclic 6-6 and 6-5 systems have been investigated extensively. The energy barriers for the pyramidal inversion of TBD are very similar to those of the monocyclic sulfonium salt (**4**) (Equations (1) and (2)) ⟨79JA2971, 88BCJ707⟩.



(1)

(1) **(1a)**

$\Delta H^{\ddagger} = 28.0 \pm 0.9$ kcal/mol $\Delta S^{\ddagger} = -3.8 \pm 2.5$ e.u.

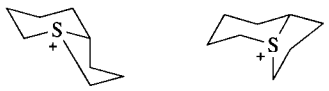


(2)

(4) **(4a)**

$\Delta H^{\ddagger} = \pm 25.7$ kcal/mol $\Delta S^{\ddagger} = -2.2 \pm 0.8$ e.u.

In contrast, *cis*-1-thioniabicyclo[4.3.0] nonane salts do not undergo pyramidal inversion upon heating. The conformation of the salt (**2**) is likely to resemble (**2a**) rather than (**2b**) on the basis of the comparisons between the computed ^{13}C NMR shifts for the two conformations of the model compound *cis*-1,2-dimethylthianium and those measured for (**2**). However, when methyl substitution on the parent system results in diaxial interactions between the substituents and C-7 ring carbon, the conformational preference is altered and can be detected by the change in the ^{13}C NMR shifts of C-7 and C-9 atoms. This semi-quantitative approach is a good predictive tool to identify the more highly populated conformation, although the question of how much of the minor conformation is present, and whether it can be ignored or not remains to be addressed ⟨82JOC2861⟩. The ^{13}C NMR data for the 6-6, 6-5, and 5-5 systems are given in Table 2.



(2a) **(2b)**

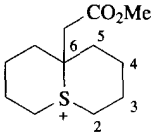
Table 2 ^{13}C NMR chemical shifts of bicyclic sulfonium salts relative to TMS.

Carbon	cis-*thioniabicyclo [4.4.0]decane* ⟨79JA2971⟩	trans-*thioniabicyclo [4.4.0]decane* ⟨79JA2971⟩	cis-*thioniabicyclo [4.3.0]nonane* ⟨82JOC2861⟩	cis-*thioniabicyclo [3.3.0]octane* ⟨80JOC2641⟩
2	30.7	38.3	36.0	45.4
3	20.0	23.9	22.2	29.3
4	19.9	23.5	18.0	35.7
5	29.7	30.7	24.1	66.3
6	42.6	53.3	54.5	
7			31.5	
8			27.6	
9			45.2	

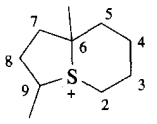
X-ray crystallographic studies on the bromide salt of *trans*-TBD (**1**) show a distinct difference in the two S^+—C bond lengths, 1.806 and 1.872 Å, the ring junction bond being longer ⟨76AX(B)3157⟩. The *cis*- and *trans*-isomers of TBD bromide have different crystal modifications at room temperature

with space groups Cc and $Cmc2_1$ respectively. Upon heating however, the two isomers are transformed into the same crystal modification ⟨81YZ94⟩. The *cis*- and *trans*-isomers of TBD iodide behave similarly at elevated temperatures ⟨82YZ36⟩. A comparison of the bond lengths and bond angles of 6-6 and 6-5 systems based on x-ray crystallographic data is given in Table 3. The trend observed in the data between the two systems is as predicted.

Table 3 X-ray crystallographic data comparison of 6-6 and 6-5 systems.



79JA2971



86JOC825

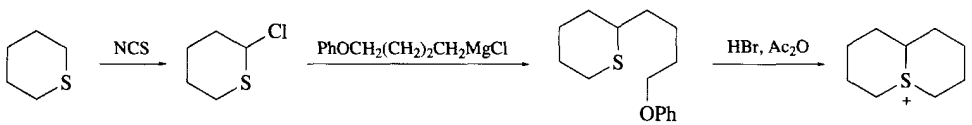
Atoms	*Bond Length* (Å)	*Atoms*	*Bond Length* (Å)
S^+—C(6)	1.85	S^+(1)—C(6)	1.839
S^+—C(2)	1.81	S^+(1)—C(2)	1.798
		S^+(1)—C(9)	1.840
		S(5)—C(4)	1.804
		S(5)—C(6)	1.807
Atoms	*Bond Angle* (°)	*Atoms*	*Bond Angle* (°)
C(2)—S^+(1)—C(6)	100.3	C(1)—S^+(1)—C(6)	103.5
S^+(1)—C(6)—C(5)	106.3	C(1)—S^+(1)—C(9)	103.5
S^+(1)—C(2)—C(3)	107.5	S^+(1)—C(2)—C(3)	111.2
		S^+(1)—C(9)—C(8)	107.1
		S^+(1)—C(6)—C(7)	104.4
		S^+(1)—C(6)—S(5)	108.8

8.32.2.1.2 Syntheses

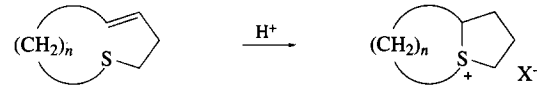
There are a number of synthetic strategies developed over the years in the preparation of bicyclic sulfonium ions. In the original Eastman synthesis (Equation (3)) a symmetrical dihydroxythiol is cyclized to give the bridgehead sulfonium salt ⟨59JOC1428⟩. Heathcock's synthesis, shown in Scheme 1, on the other hand, is shorter with a higher overall yield and gives access to functionalization in either ring, since the two rings are formed consecutively ⟨77JA2337, 79JA2971⟩. Both of the above syntheses give *cis*/*trans* mixtures of the bicyclic sulfonium ion. Exclusively *cis*-products are obtained as a result of the acid-catalyzed transannular cyclizations of (*Z*)- and (*E*)-thiacyclooct-4-enes (**5**) and thiacyclonon-4-enes (**6**) (Equation (4)). The *cis*-fused sulfonium ions are thought to have been formed from a transition state resembling the twist form of the homoallylic sulfide precursor. Since force field calculations indicate that the twist form of the precursors is more stable than the chair form, the *cis*-products are both kinetically and thermodynamically controlled ⟨80JOC2641, 82JOC2861⟩. The 5-5 system can also be constructed starting from thiacyclooctane with an exocyclic methylene group (**7**). Iodocyclization gives 5-(iodomethyl)-1-thioniabicyclo[3.3.0]octane (**8**) the structure of which is confirmed by x-ray studies (Equation (5)). The kinetics of the reaction rule out a mechanism where an iodonium intermediate is involved; instead, a π-complex of iodine with the alkene is attacked by the thioether sulfur in the rate-determining step ⟨85JOC2048⟩.



(3)



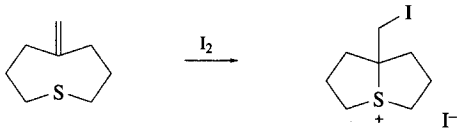
Scheme 1



(4)

(5) $n = 3$
(6) $n = 4$

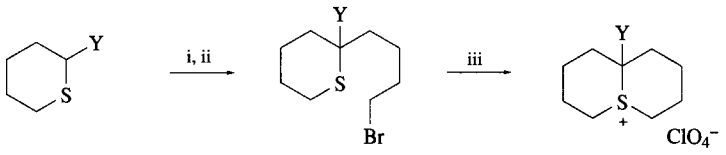
$n = 3,4$



(5)

(7) (8)

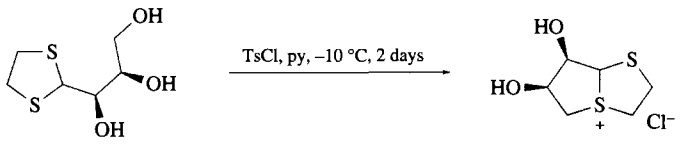
A more general methodology utilizes, as the precursor, a thiacyclohexane with an electron-withdrawing group in the α-position, which can be converted into an anion and subsequently cyclize into the sulfonium ion upon reacting with 1,3-dibromopropane or 1,4-dibromobutane as shown in Scheme 2 ⟨90TL3027⟩.



i, LDA; ii, $BrCH_2(CH_2)_2CH_2Br$; iii, $AgClO_4$
Y = CN, CO_2Me

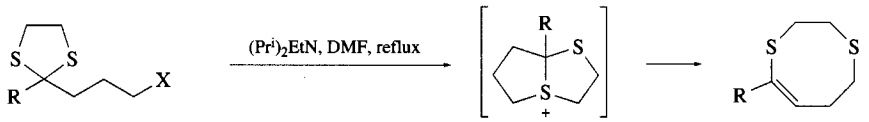
Scheme 2

Intramolecular alkylation reactions of cyclic thioacetals and thioketals have been versatile routes to generate bicyclic 5-5 sulfonium systems containing an additional sulfur atom. This methodology has been used particularly to synthesize sulfur analogues of some biologically active alkaloids for the purpose of carrying out structure-activity correlation studies. The thioniapentalene derivative (**10**), with interesting biological activity is prepared by the cyclization of the thioacetal of erythrose (**9**) (Equation (6)). The structure is identified on the basis of ^{13}C NMR data and the stereochemistry confirmed by an x-ray diffraction study ⟨92CC1531⟩. A similar strategy is applied with a view to synthesize medium-ring dithiacycloalkenes. The bicyclic sulfonium ion intermediate generated from the γ-halo thioketal (Scheme 3) decomposes to the corresponding dithiacycloalkene upon reflux ⟨92JOC6658⟩. The bicyclic sulfonium salt (**11**) was synthesized serendipitously while investigating thioketal formation from a γ,δ-unsaturated ketone. Under Lewis acid catalysis, 5-hexen-2-one and 1,3-propanedithiol react readily to give (**11**) (Equation (7)) ⟨86JOC825⟩.

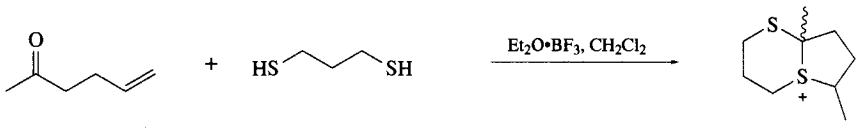


(6)

(9) (10)



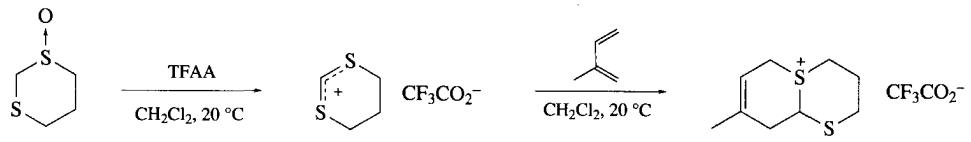
Scheme 3



(7)

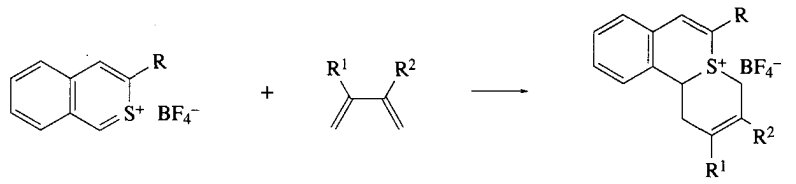
(11)

In the last few years hetero-Diels–Alder reactions have been popular methods particularly in the synthesis of benzo-fused bicyclic sulfonium salts. Although the recognition of the thienium ion (α-thiocarbocation) as a C—S heterodienophile in the [4 + 2$^+$]-type cationic polar cycloadditions dates back to Corey's work ⟨72JA9832⟩, the potential of this reaction has not been explored until the early 1990s. Generally unstable, thienium ions can be trapped as Pummerer reaction intermediates. As shown in Scheme 4, when the monosulfoxide formed by the oxidation of 1,3-dithiane is treated with TFAA, the intermediate thienium ion undergoes a [4 + 2$^+$] cycloaddition upon addition of isoprene. The mechanism of the reaction is confirmed by the detection of the intermediate by ^{1}H NMR. The reaction proceeds with high regioselectivity giving a large excess of the cycloadduct shown ⟨95JCR(S)204⟩.



Scheme 4

The benzo-fused bicyclic sulfonium salts (**13**) can be prepared as the cycloadducts of 2-thianaphthylium ions (**12**) with various butadienes. When the dienophile is 3-benzoyl substituted, as in Equation (8), the reaction goes faster giving higher yields. The cycloadducts undergo retro-Diels–Alder reactions upon heating ⟨91TL5571⟩. The cycloaddition (with isoprene) is regioselective and stereoselective giving only a single *cis*-fused isomer. X-ray studies on 9-benzoyl-6,7-dimethyl-4b,5-dihydro-8H-8a-thioniaphenanthrene tetrafluoroborate (**13a**) confirm the stereochemical assignments ⟨94JCS(P1)3129⟩.



(8)

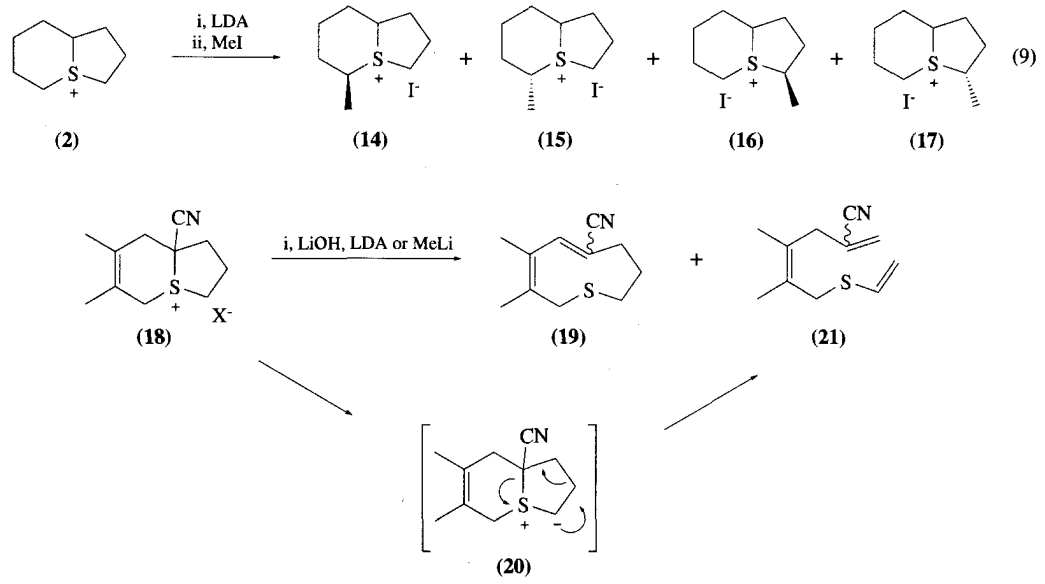
(12)
R = Bz

(13)
a: R = Bz, R^1 = R^2 = Me

8.32.2.1.3 Reactions

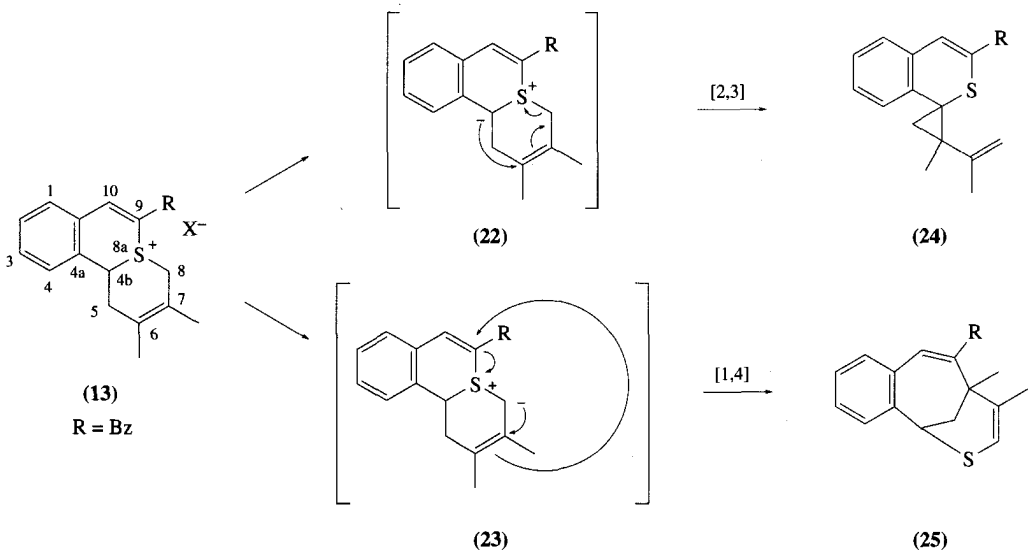
(i) Sulfonium ylides

The extent of overlap between 2*p* and 3*p* orbitals of carbon and sulfur to form a π-bond has been a matter of controversy. As a result of more elaborate *ab initio* calculations, the participation of 3*d* orbitals in π-bond formation is well accepted. This is particularly relevant in the stabilization of sulfur-substituted carbanions. When the sulfur atom bears a positive charge, the 3*d* orbitals contract and are capable of overlapping effectively with 2*p* orbitals of adjacent atoms. Studies on sulfonium ylides demonstrate the above postulates. Comparisons with sulfoxide and sulfilimine ylides where 3*d* participation is more effective show that sulfonium ylides undergo pyramidal inversion much faster ⟨B-91MI 832-01⟩. A study of kinetic versus thermodynamic acidity of α-protons of a bicyclic sulfonium ion shows that when *cis*-1-thioniabicyclo[4.3.0] nonane salt (**2**) is treated with LDA followed by immediate quenching with methyl iodide, the four α-methylated products (**14**) to (**17**) (Equation (9)) are formed with some diastereoselectivity. However, if the ylide is quenched after some time, then methylation favors the larger ring, indicating a thermodynamic preference, and the yields of the methylated products (**16**) and (**17**) are decreased drastically ⟨83TL839⟩. The inclusion of a β,γ double bond in the six-membered ring is expected to increase the stability of the thermodynamically favored ylide. When 6-cyano-2,3-dimethylthioniabicyclo[4.3.0]non-3-ene (**18**) is treated with strong base, two products are obtained as shown in Scheme 5, one of which (**19**) results from the rearrangement of the kinetically favored ylide (**20**), and the second (**21**) from β-elimination to the more conjugated nonadiene ⟨92JCR(S)393⟩.



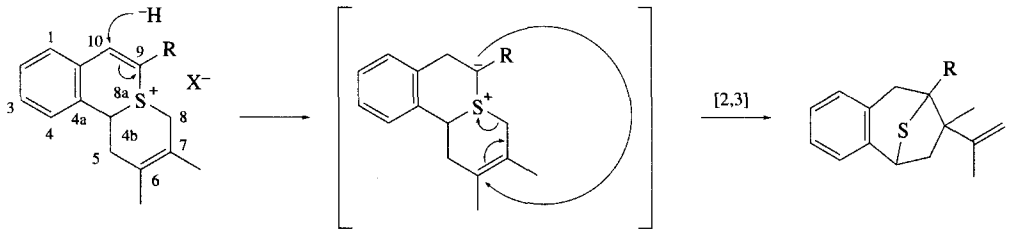
Scheme 5

The benzo-fused bicyclic sulfonium salt (**13**) gives rearrangement products upon treatment with strong non-nucleophilic bases such as LDA, NaH, and K_2CO_3. The mechanism can be rationalized on the basis of possible ylide intermediates shown in Scheme 6. Hydrogen abstraction from the benzylic position C-4b leads to the 2,3-sigmatropic rearrangement of the ylide (**22**) to form the cyclopropane ring and the cleavage of the S^+—C(8) bond in compound (**24**). Hydrogen abstraction from C-8 forms a different ylide intermediate (**23**) which undergoes a 1,4-rearrangement of the vinyl group and the cleavage of the S^+—C(9) bond to form the fused seven-membered ring product (**25**). The ease with which the rearrangement occurs is due to the proximity of the C-6 and C-9 positions brought about by the *cis*-fusion of the two rings ⟨95JCS(P1)1583⟩.



Scheme 6

A rearrangement in the opposite direction (from C-9 to C-6, shown in Scheme 7) is the rational mechanism for the formation of (**27**) when (**13**; R = Bz) is treated with $NaBH_4$. The ylide intermediate (**26**), formed as a result of a Michael-type hydride attack to C-10, undergoes a 2,3-sigmatropic shift to give the product. The justification for the Michael hypothesis comes from the fact that the rearrangement only occurs with the 9-benzoyl sulfonium salt. In the absence of the electron-withdrawing benzoyl substituent, C-10 is no longer activated as a Michael acceptor, and the rearrangement does not take place ⟨95JCS(P1)1583⟩.

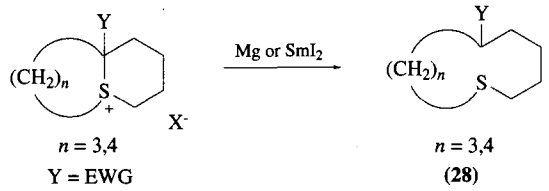


(13) (26) (27)

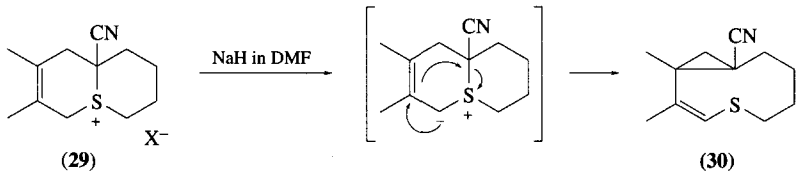
Scheme 7

(ii) Cleavage of S—C bonds

In the synthesis of macrocycles containing heteroatoms the strategy of constructing a rigid polycyclic system of smaller rings has a number of advantages in view of introducing the desired stereogenic centers without the difficulties caused by the conformational mobility of the macrocycle. Sulfonium salts undergo reductive cleavage via a single-electron transfer (SET) mechanism when treated with magnesium metal ⟨89TL981⟩ or samarium diiodide ⟨92PS(67)169⟩. As shown in Equation (10), this methodology is successfully applied to a number of 6-6 and 6-5 fused bicyclic sulfonium salts to cleave the ring junction S^+—C bonds in an attempt to prepare the target macrocyclic compounds (**28**) ⟨90TL3027⟩. The reaction is regioselective when the bridgehead carbon carries an electron-withdrawing substituent. While the desired products can also be obtained using $NaBH_4$ as the reducing agent, NaH treatment of 6-cyano-2,3-dimethylthiabicyclo[4.4.0]dec-3-ene (**29**), on the other hand, gives an ylide rearrangement product (**30**), the mechanism of which is outlined in Scheme 8 ⟨92JCR(S)393⟩.



(10)

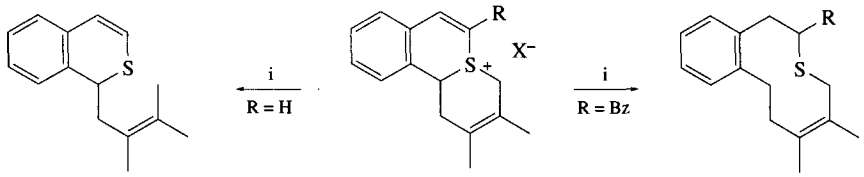


Scheme 8

The reduction of benzo-fused bicyclic sulfonium ions with samarium diiodide also results in the cleavage of the S^+—C bonds. However, as shown in Scheme 9, the regioselectivity here depends on the substitution of C-9. 9-Benzoyl-6,7-dimethyl-4b,5-dihydro-8H-8a-thioniaphenanthrene salt (**13**) undergoes reduction to give the ring-expanded product (**31**) along with a further reduction of the 9,10-double bond. In contrast, the unsubstituted salt undergoes the cleavage of the S^+—C(8) to give the ring-opening product (**32**) ⟨95JCS(P1)1583⟩.

(iii) Reactions with nucleophiles

Sulfonium ions are well-known alkylating agents in view of the electrophilic nature of their α-carbon atoms. Their synthetic and biological applications are extensively studied. Reactions of bicyclic bridgehead sulfonium ions with nucleophiles have been investigated only for the more stable benzo derivative (**13**; R = Bz). As shown in Equation (11), S_N2 and S_N2' attacks by a range of

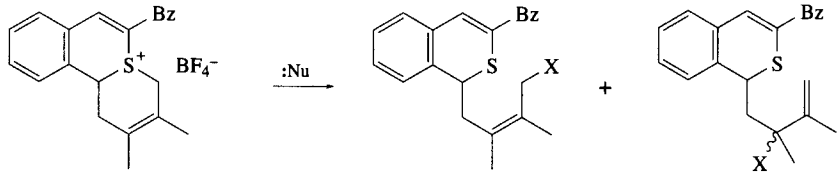


(32) (13) (31)

i, SmI_2, MeOH, THF, RT

Scheme 9

nucleophiles on C-8 and C-6 cleave the S^+—C(8) bond to give rise to two types of ring-opening products ⟨91TL5571⟩.



(11)

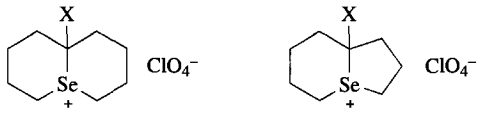
(13) R = Bz

a: X = OH
b: X = OMe
c: X = SePh
d: X = CN

a: X = OH
b: X = OMe

8.32.2.2 Fused Seleninium and Selenolium Ions

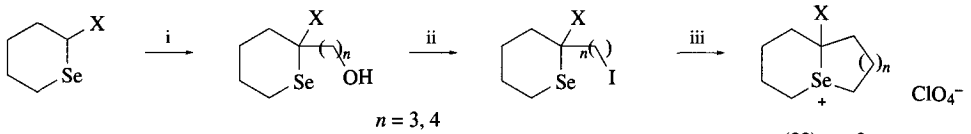
There are very few examples in the literature of fully saturated bicyclic selenonium ions with selenium as the bridgehead atom. The selenonium salts (**33**) and (**34**) are used as precursors for the syntheses of medium sized heterocycles containing a selenium atom.



(33) **a**: X = CN **b**: X = CO_2Me (34)

8.32.2.2.1 Syntheses

The synthetic strategy used for bicyclic sulfonium ions shown earlier in the chapter in Scheme 2 is also utilized for bicyclic selenonium ions. As shown in Scheme 10, both 6-6 and 6-5 bicyclic systems can be constructed in good yields ⟨90TL3027⟩.



n = 3, 4

(**33**) n = 2
(**34**) n = 1

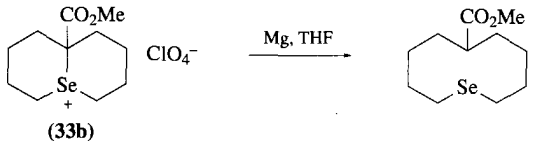
a: X = CN
b: X = CO_2Me

i, LDA or NaH, $Cl(CH_2)_nOTHP$, H^+; ii, MsCl, NaI; iii, $AgClO_4$

Scheme 10

8.32.2.2.2 Reactions

Like their sulfonium analogues, bicyclic selenonium salts (**33**) and (**34**) also undergo a single-electron transfer reduction with magnesium metal ⟨90TL3027⟩ or samarium diiodide ⟨92PS(67)169⟩ where their ring junction Se^+—C bonds are cleaved selectively to give medium-sized cyclic selenides. Higher yields of the ring-enlargement product, shown in Equation (12), are obtained with the selenonium salt (**33b**). This is attributed to its solubility in THF used as solvent.



(33b) (12)

8.32.2.3 Fused Tellurinium and Tellurolium Ions

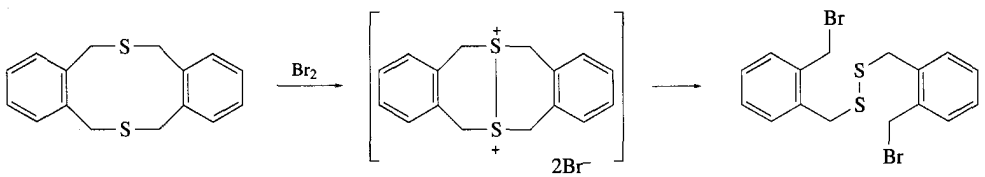
There are no bicyclic systems known with one tellurium atom at a bridgehead position.

8.32.3 BICYCLIC DICATIONS WITH TWO BRIDGEHEAD HETEROATOMS

Cyclic compounds containing two S, Se, or Te atoms may display transannular or intramolecular interactions between the two heteroatoms depending on their positions. If a cation radical is generated on one of the heteroatoms, the second heteroatom can interact to stabilize the cation radical, resulting in the formation of a three-electron-bonded cation radical which further oxidizes to give a dication. Such systems joined by two positively charged heteroatoms have attracted considerable interest. The studies in this field have been hampered by the difficulty of their preparation and further by their instability.

8.32.3.1 Disulfide Cations

The discovery of a disulfide dication dates back to 1903 as the bromine oxidation product of 2,5,7,10-tetrahydrodibenzo[c,h]-1,6-dithiecin ⟨80ACR200⟩. Many years later, the product of the same reaction (Scheme 11) was identified as a disulfide and not the dication ⟨66CHE1⟩. It was subsequently shown that the dication does in fact form but only as an intermediate ⟨80ACR200⟩. Most of the work published on disulfide cations comes from the studies on the dication (**36**) generated from 1,5-dithiacyclooctane (1,5-DTCO) (**35**). Because of the proximity of the two sulfur atoms in 1,5-DTCO, electron transfer from one of the sulfur atoms to the other can occur very readily ⟨78JA6416⟩. There is considerable interest in these reactions, as well as the cation radical and dication products, in view of their importance in both chemical and biological redox reactions.



Scheme 11



(35) (36)

8.32.3.1.1 Structural and spectroscopic aspects

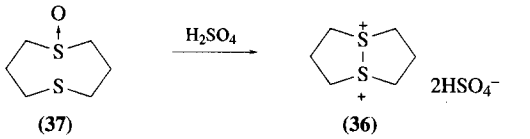
Disulfide cations (**36**)–(**39**) have been prepared from six-, eight-, nine-, and ten-membered cyclic bis-sulfides ⟨B-92MI 832-01⟩. Of these structures x-ray crystallographic data is available only for the triflate salt of the dication, which shows a distorted chair–chair form for the conformation of the eight-membered ring ⟨88BCJ2563⟩. The length of the $S^+(1)$—$S^+(2)$ bond is 2.126 Å, which is only slightly longer than the S—S single bond in disulfides (2.08 Å). The S^+—C lengths are 1.842 and 1.828 Å, which are also slightly longer than the S—C single bond length. On the other hand, the C—C length (1.509 Å) is slightly shorter than the normal C(sp^3)—C(sp^3) bond. The bond angle of C—S^+-C is 104.1°, and that of S^+—S^+—C is 92.7°. A very strong interaction is observed between the S^+ of the dication, and the oxygen atoms of the triflate anions which is thought to contribute to the stabilization of the crystals. Nearly colinear interaction of O···S—S···O is formed with central two-fold symmetry ⟨B-92MI 832-01⟩. According to *ab initio* calculations based on the STO-3G basis set the optimized transannular S—S distance is 3.307 Å for 1,5-DTCO (**35**) and 1.890 Å for 1,5-$DTCO^{+2}$ (**36**) ⟨88JPC1747⟩.

Electrochemical studies show that 1,5-DTCO undergoes oxidation more easily than corresponding sulfide analogues where there are no transannular interactions between the two sulfur atoms. Cyclic voltammetric analysis of 1,5-DTCO gives a peak potential of 0.34 V for a reversible oxidation which can resolve to show two closely spaced one-electron transfer steps, the second step being 20 mV lower than the first ⟨88JPC1747⟩. These results are consistent with the assumption that the removal of the first electron places the odd electron in an antibonding S—S orbital ⟨79ACR436⟩. The removal of the second electron thus creates the energetically more favorable dication compared to the radical cation. Ring size is an important structural factor in disulfide dications. The extent of transannular interaction between the thioether and the radical cation moieties depends largely on structural features which explains the ring sizes of the known disulfide dications.

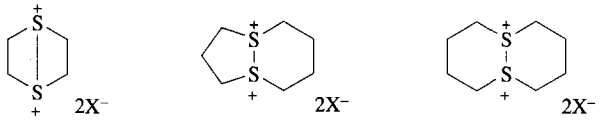
The ^1H NMR spectrum of the dication bistriflate (**36**) shows multiplet peaks at δ3.6–2.9 and 2.7–2.2 ppm with a ratio of 2 : 1. The bis(hydrogen sulfate) salt of (**36**) shows two ^{13}C NMR signals at δ 56.3 and 38.6 ppm ⟨84CC1151⟩. The UV spectrum gives a maximum at λ_{max} 231 nm ⟨93T1605⟩.

8.32.3.1.2 Syntheses

The disulfide cation (**36**) of 1,5-DTCO is formed upon treatment of the monosulfoxide (**37**) with concentrated sulfuric acid as in Equation (13). Similarly with 6-, 9-, and 10-membered cyclic bis-sulfides, the reaction of the corresponding S-oxides with concentrated sulfuric acid affords the dications (**38**)–(**40**).



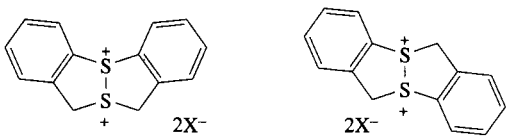
(37) (36) (13)



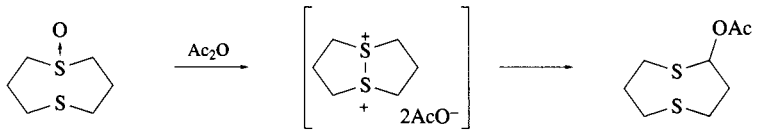
(38) (39) (40)

The benzo derivatives (**41**) and (**42**) of the disulfide dication (**36**) can also be prepared in the reaction of the corresponding *S*-oxides with conc. H_2SO_4. However, since the resulting bis(hydrogen-sulfate) salts are very hygroscopic, the structures are identified only on the basis of elemental analyses. The dication (**36**) is an intermediate in the Pummerer reaction of the *S*-oxide (**37**) with acetic anhydride, shown in Scheme 12, giving the α-acetoxylated product (**43**). However, when trifluoromethanesulfonic anhydride is used instead, the dication (**36**) can be isolated as a triflate

salt. This reaction proceeds via the initial formation of the trifluoromethanesulfonyloxy sulfonium cation (**44**) as shown in Scheme 13 which is then converted into the disulfide cation by an intramolecular nucleophilic displacement of the triflate ion by the second sulfur atom ⟨B-92MI 832-01⟩.

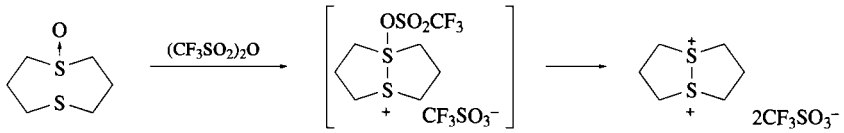


(**41**) (**42**)



(**37**) (**43**)

Scheme 12

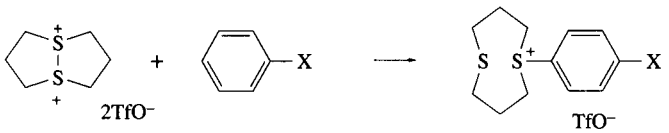


(**37**) (**44**)

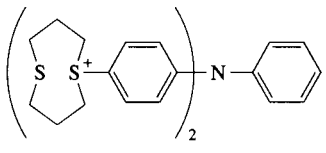
Scheme 13

8.32.3.1.3 Reactions

Nucleophilic attack on disulfide cation (**36**) occurs either on the sulfur atom or on the α-carbons. Treatment of the triflate salt of (**36**) with aniline, triphenylamine, or phenol gives the *para*-substituted monosulfonium salts shown in Equation (14), along with the disubstituted minor product (**45**) in the case of triphenylamine. Surprisingly, anisole does not react with (**36**) which can be attributed to the higher oxidation potential of anisole compared to aniline, triphenylamine, and phenol ⟨B-92MI 832-01⟩. No identifiable products are obtained upon reaction with *para*-substituted anilines such as *p*-methoxyaniline, although a one-electron oxidation product is postulated on the basis that a dramatic bathochromic shift is observed in the UV spectrum of the product mixture (to λ_{max} 530 nm) which becomes purple immediately after mixing the two reactants. The color change does not occur with tris(4-bromophenyl)amine which has a higher oxidation potential than *p*-methoxyaniline.



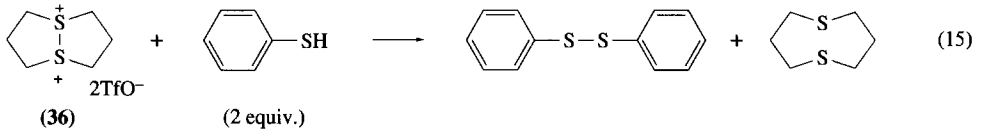
(**36**) X = NH_2, X = $N(C_6H_5)_2$, X = OH (14)



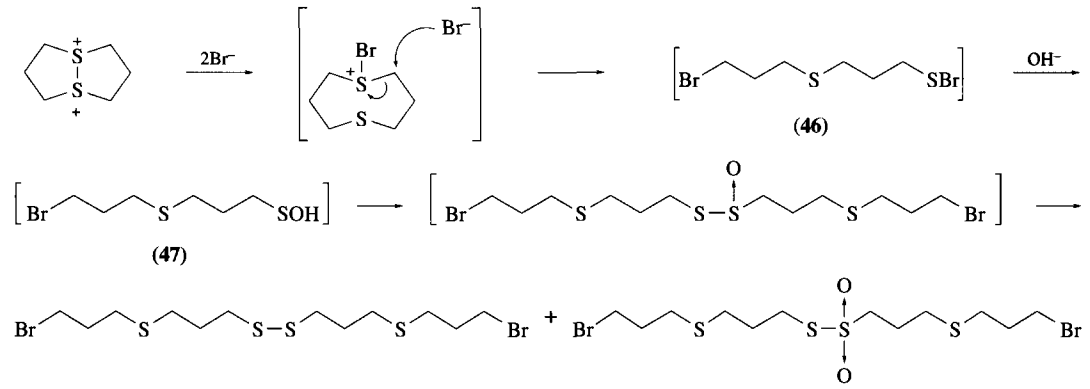
2TfO⁻•H_2O

(**45**)

Electrophilic aromatic substitution is not observed with benzenethiol either. Instead, the treatment of two equivalents of benzene thiol with the S-dication, as shown in Equation (15), gives the oxidation product, diphenyl disulfide, and the monocyclic bis-sulfide as the reduced *S*-dication. The disulfide dication (**36**) similarly oxidizes 1,2-diphenylhydrazine into azobenzene without any accompanying substitution products ⟨93T1605⟩.

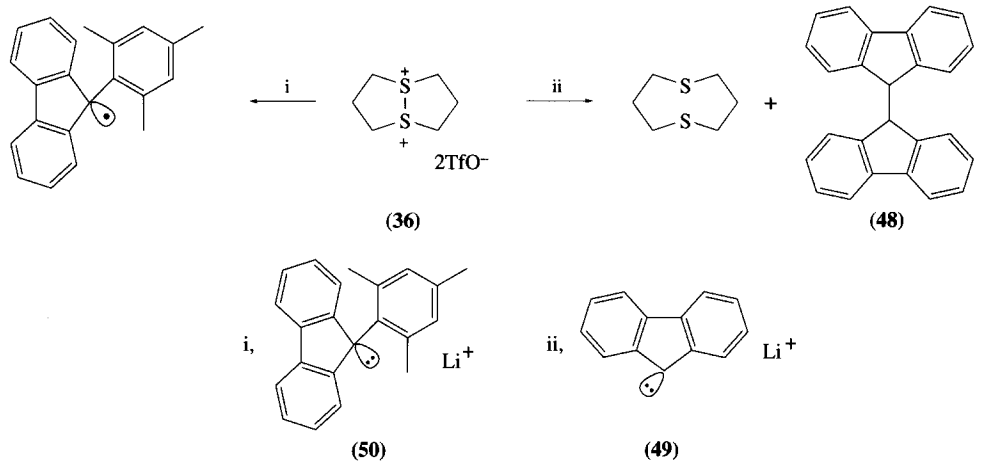


The reduction of the disulfide dication (**36**) to the disulfide can be achieved upon treatment with two equivalents of KI or $Bu^n_4N^+I^-$. However, treatment with KBr followed by aqueous workup gives acyclic dimers. The reaction mechanism outlined in Scheme 14 shows the formation of sulfenyl bromide (**46**) which is hydrolyzed into the sulfenic acid (**47**) which in turn dimerizes into the thiosulfinate intermediate.



Scheme 14

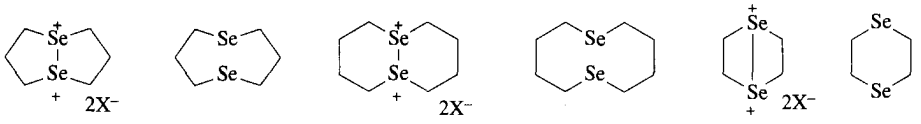
In contrast to most sulfonium ions bearing α-hydrogens, the disulfide dication (**36**) undergoes only redox reactions with organolithium reagents instead of forming sulfur ylides. An oxidative coupling dimer (**48**) is produced upon reaction with fluorenyllithium (**49**). The formation of the radical intermediate is confirmed by using a more sterically hindered organolithium in order to generate a persistent radical by inhibiting dimerisation. Indeed, the free radical from 9-mesityl-fluorenyllithium (**50**) is detected by ESR upon adding the THF solution of the organolithium reagent to the disulfide dication (**36**) ⟨B-92MI 832-01⟩. Both reactions are shown in Scheme 15.



Scheme 15

8.32.3.2 Diselenide Cations

Transannular interactions between the two selenium atoms of cyclic bis-selenides were only demonstrated in 1989 as a result of the formation of the diselenide dication (**51**) from 1,5-diselenacyclooctane (**52**) ⟨89CC1789⟩. This is the first example of an isolable dication salt containing a selenium–selenium σ-bond. Similarly, dications (**53**) and (**55**) are prepared from precursors (**54**) and (**56**).



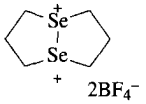
(**51**) (**52**) (**53**) (**54**) (**55**) (**56**)

a: X = PF_6
b: X = BF_4

8.32.3.2.1 Structural and spectroscopic aspects

Diselenide dications (**51**), (**53**), and (**54**) can be isolated as their bis(tetrafluoroborate) or bis(hexafluorophosphate) salts. X-ray studies on 1,5-diselenoniabicyclo[3.3.0]octane bis(tetrafluoroborate) (**51**) confirm the structure as well as elucidating further features ⟨91AX(C)1463⟩. In contrast to 1,5-dithioniabicyclo[3.3.0]octane bis(tetrafluoroborate) (**36**), the conformation of the eight-membered ring of the diselenide dication (**51**) is in a chair–boat form. The Se—Se bond length is 2.382 Å, which is only slightly longer than the normal Se—Se bond (2.34 Å). Strong interactions are observed between the Se atoms and the fluoride atoms of the tetrafluoroborate anions. The crystal has one acetonitrile molecule as a crystal solvent in an asymmetric unit. The coordination around the Se atoms is a distorted octahedron with two C and F and N (or F) atoms in a plane and an apical Se—Se bond and Se···F contact. The bond lengths and angles of the bis(tetrafluoroborate) salt of the dication (**51**) is shown in Table 4.

Table 4 X-ray crystallographic structure data for 1,5-diselenoniabicyclo[3.3.0]octane bis(tetrafluoroborate) (**51**) ⟨91AX(C)1463⟩.



(**51**)

Bond	*Bond length* (Å)	*Bond*	*Bond length* (Å)
Se(1)—Se(5)	2.382	C(2)—C(3)	1.534
Se(1)—C(2)	1.963	C(3)—C(4)	1.483
Se(1)—C(8)	1.967	C(6)—C(7)	1.499
Se(5)—C(4)	1.952	C(7)—C(8)	1.519
Se(5)—C(6)	1.981		
Bond	*Bond angle* (°)	*Bond*	*Bond angle* (°)
Se(5)—Se(1)—C(2)	92.6	Se(1)—C(2)—C(3)	109.0
Se(5)—Se(1)—C(8)	91.9	C(2)—C(3)—C(4)	111.7
C(2)—Se(1)—C(8)	101.7	Se(5)—C(4)—C(3)	111.1
Se(1)—Se(5)—C(4)	90.7	Se(5)—C(6)—C(7)	108.0
Se(1)—Se(5)—C(6)	91.9	C(6)—C(7)—C(8)	112.7
C(4)—Se(5)—C(6)	102.2	Se(1)—C(2)—C(3)	108.9

Diselenide dication bis(hexafluorophosphate) salt (**51**) exhibits a UV maximum at λ_{max}248 nm. Downfield shifts are observed both in the ^1H and ^{13}C NMR spectra of the dication (**50**) compared

to its precursor 1,5-diselenacyclooctane (**52**). A drastic downfield shift to δ806.5 in the ^{77}Se NMR spectrum (from δ141.3 for 1,5-diselenacyclooctane) is the strongest indication for the dicationic structure. Table 5 shows the NMR data for the diselenide dications and their precursors.

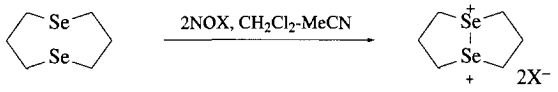
Table 5 NMR data for compounds (**51**)–(**56**) ⟨93TL1605⟩.

Compound	*Chemical shift* (δ ppm)		
	^1H	^{13}C	^{77}Se
(**51**)	4.39–3.91 (m, 8H), 3.85–2.92 (m, 4H)	52.6, 35.3	806.5
(**52**)	3.02–2.71 (m, 8H), 2.42–2.05 (m, 4H)	30.9, 23.4	141.3
(**53**)	4.02–3.61 (m, 8H), 2.45–2.05 (m, 4H)	37.8, 21.1	439.1
(**54**)	3.25–2.88 (m, 8H), 2.28–1.89 (m, 4H)	30.2, 28.1	165.7
(**55**)	4.25 (br, s)	47.0	1202.0
(**56**)	3.08 (s)	20.4	206.9

Solvents for ^{1}H and ^{13}C NMR, $CDCl_3$ for (**52**), (**54**), and (**56**); CD_3CN (relative to TMS) for (**51**), (**53**), and (**55**). Solvents for ^{77}Se NMR, $CHCl_3$ for (**52**), (**54**), and (**56**); CH_3CN (relative to Me_2Se) for (**51**), (**53**), and (**55**).

8.32.3.2.2 Syntheses

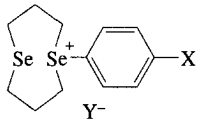
Diselenide dication (**51**) is formed via a two-electron oxidation of 1,5-diselenacyclooctane (**52**) with two equivalents of a one-electron oxidizing agent, nitrosyl hexafluorophosphate or nitrosyl tetrafluoroborate as shown in Equation (16). Six- and ten-membered ring bis-selenides (**56**) and (**54**) are oxidized similarly to the dications (**55**) and (**53**) respectively ⟨93T1605⟩. The ease with which 1,4-diselenoniabicyclo[2.2.0] salt (**55**) is obtained from 1,4-diselenacyclohexane (**56**) is somewhat surprising since the transannular interaction between the two selenium atoms at 1,4-positions is not expected to be extensive.



(**52**) **a**: X = PF_6; **b**: X = BF_4 (**51**) (16)

8.32.3.2.3 Reactions

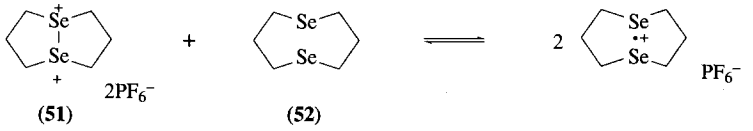
The reactivity of the diselenide dication (**51**) towards various nucleophiles and in redox reactions is investigated. The diselenide dication undergoes electrophilic substitution reactions with activated aromatic compounds to give *para*-substituted selenonium salts (**57**), but oxidizes benzenethiol into diphenyl disulfide ⟨90CL393⟩, both of which are analogous chemical behaviors to those of the disulfide dication (**36**). Thus, the Se-dication can both function as an electrophile and as an oxidant. The oxidation potential of the aromatic compound it reacts with determines the mode of reaction. Indeed, the reaction with phenothiazine, whose oxidation potential is known to be lower than that of the Se-dication (**51**), generates a cation radical detected by the color of the reaction mixture and the UV-visible absorptions at λ_{max} 436 and 515 nm.



(**57a**) X = NH_2, Y = PF_6
(**57b**) X = NMe_2, Y = BF_4

Unlike the S-dication, the Se-dication (**51**) does not undergo hydrolysis with water and still retains its oxidant capability. The reaction of the Se-dication (**51**) with its precursor, the cyclic bis-selenide (**52**), follows the expected one-electron-transfer mechanism, shown in Equation (17), to generate the cation radical which can be detected by its UV absorption characteristics and, more importantly,

by its ESR signal. The cation radical can in fact be isolated as an orange crystalline product ⟨90TL6375⟩. The one-electron-transfer mechanism is further confirmed upon reaction with ferrocene whose electrochemical behavior is well documented. Cyclic voltammetry studies done on the Se-dication show a reversible reduction peak at a very low potential (+0.11 V), which provide evidence for the comparatively long life-time of the cation radical as well as confirming the strength of the dication as an oxidant. On the whole, the preliminary electrochemical studies reported are consistent with the chemical reactions of the Se-dication (**51**).



(17)

8.32.3.3 Ditelluride Cations

There is only one example of a ditelluride dication with bridgehead Te atoms reported in literature. In parallel to the disulfide and diselenide dications discussed earlier, hexafluorophosphate and tetrafluoroborate salts of 1,5-ditelluroniabicyclo[3.3.0] octane (**58**) are prepared from 1,5-ditellurocyclooctane (**59**) ⟨91TL4537⟩ thus demonstrating the presence of strong transannular interactions between the two Te atoms in the cyclic bis-telluride (Equation (18)).

8.32.3.3.1 Structural and spectroscopic aspects

Although the PF_6^- and BF_4^- salts of the Te-dication (**58**) are stable solids, there is as yet no crystallographic data available. In addition to the NMR data given in Table 6 for the dication (**58**) and the precursor cyclic bis-telluride (**59**), a phosphorus absorption at δ −143.0 (sept, $J_{PF} = 712$ Hz; relative to H_3PO_4) is observed in the ^{31}P NMR of the hexafluorophosphate salt of the dication (**58**). The drastic downfield shift observed in the ^{125}Te NMR spectrum (δ 1303.7) is consistent with the dication structure ⟨91TL4537⟩.

Table 6 NMR data for compounds (**58**) and (**59**) ⟨91TL4537⟩.

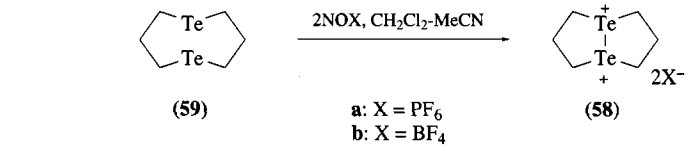
Compound	*Chemical shift* (δ ppm)		
	^1H	^{13}C	^{125}Te
(**58**)	3.03–2.89 (m, 8H), 2.10–1.74 (m, 4H)	36.1, 17.8	1303.7
(**59**)	2.78–2.69 (m, 8H), 2.16–2.10 (m, 4H)	34.1, 4.88	163.5

Solvents for ^1H and ^{13}C NMR, $(CD_3)_2SO$ for (**58**); $CDCl_3$ for (**59**). Solvents for ^{125}Te NMR, $(CH_3)_2SO$ for (**58**); $CHCl_3$ for (**59**) (relative to Me_2Te).

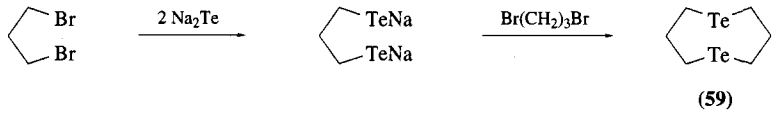
8.32.3.3.2 Syntheses

The Te-dication (**58**) is prepared from 1,5-ditellurocyclooctane (**59**) using a similar synthetic strategy to those utilized for the syntheses of S- and Se-dications. Two equivalents of nitrosyl hexafluorophosphate or tetrafluoroborate gives the PF_6^- or BF_4^- salt of the Te-dication (**58**) as shown in Equation (18). The cyclic bis-telluride (**59**) is prepared using standard methods (Scheme 16). The Te-dication (**58**) can also be prepared by the ddq oxidation of the cyclic bis-telluride (**59**).

This is in contrast with the reactions of analogous cyclic bis-sulfides and bis-selenides where no corresponding dications are obtained upon treatment with ddq ⟨91TL4537⟩.



(59) **a**: X = PF_6; **b**: X = BF_4 (58) (18)



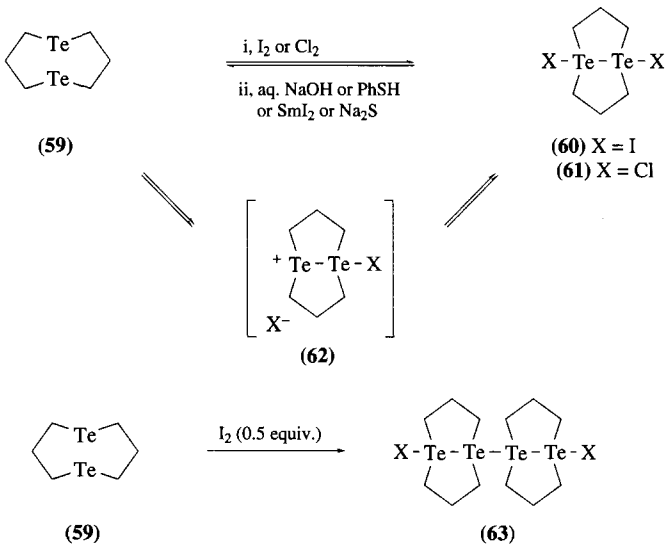
(59)

Scheme 16

8.32.3.3.3 Reactions

There are no electrophilic aromatic substitution reactions, analogous to those of S-dications or Se-dications, reported in the literature involving the Te-dication (**58**). As expected, the oxidant properties of the Te-dication are observed in reactions with 1,2-diphenylhydrazine and with benzene thiol where oxidation products, azobenzene and diphenyl disulfide, are obtained respectively. Unlike its S-dication counterpart, the Te-dication does not undergo hydrolysis with water and retains its oxidant properties. $NaBH_4$ reduction converts the Te-dication (**58**) into the cyclic bis-telluride (**59**) ⟨91TL4537⟩.

Treatment of the cyclic bis-telluride (**59**) with iodine does not yield the Te-dication, but gives an interesting bicyclic diiodo ditellurane (**60**), shown in Scheme 17, containing a Te^{IV}—Te^{IV} bond. Reaction with chlorine similarly affords the dichloro ditellurane (**61**) ⟨92JCS(P1)2583⟩. On the other hand, when excess bis-telluride (2 equiv.) (**59**) is treated with iodine, the ditellurane dimer (**63**) is obtained. The mechanism of the formation of the ditellurane (**60**) is somewhat ambiguous; however, it is likely that the the ditelluride monocation (**62**) is involved as an intermediate. Consequently, it seems appropriate to discuss the chemistry related to the ditellurane (**60**) in the present section. Both the dichloro and the diiododitelluranes (**60**) and (**61**) undergo reduction with NaOH or with thiols back to the bis-telluride (**59**). Not surprisingly, benzene thiol is oxidized into diphenyl disulfide in the reaction. The ^{125}Te NMR spectra of the telluranes (**60**), (**61**), and (**63**) all show the expected downfield shifts ⟨92JCS(P1)2583⟩.

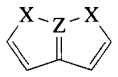


(59) (60) X = I; (61) X = Cl (62) (59) (63)

Scheme 17

8.32.4 1,6,6aλ^4-TRIHETERAPENTALENES

Triheterapentalenes have long been regarded as heterocyclic analogues of the hydrocarbon, pentalene dianion, with a four-electron, three-center bonding heteroatom unit as their distinguishing feature. In the general formula (**66**) the central atom Y can be regarded as having a singly occupied p_z orbital and X and Z as having a doubly occupied p_z orbital available for p_π-p_π conjugative interaction with neighboring ring atoms ⟨82JCS(P1)499⟩. The precise nature of bonding in these systems is still being investigated. Early theoretical considerations and a broad background on these systems are surveyed by Lozac'h with particular emphasis to trithiapentalenes where the nature of the bonds between the heteroatoms has been addressed ⟨84CHEC-I(4)1049⟩. The trithiapentalene structure represented by the general formula (**64**) assumes a C_{2v} geometry, which implies a no-bond-single-bond resonance concept as in Equation (19), as opposed to a C_s geometry, which assumes the compound to be a mixture of the two valence tautomers shown in Equation (20). Alternatively, the C_{2v} geometry might represent a transition state between the two valence tautomers where the energy barrier is too low to be measured.



(**64**)



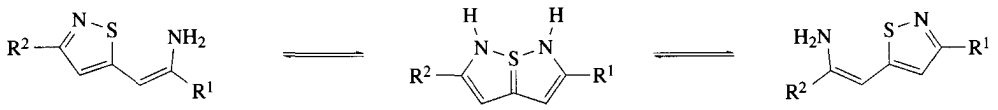
(19)



(20)

8.32.4.1 Theoretical Considerations

Developments in *ab initio* MO theory led several groups to reinvestigate 1,6,6aλ^4-trithiapentalene systems as well as 1,6-diaza and 1,6-dioxa analogues ⟨91JA6449, 92JPC9268⟩. Complete geometry optimization performed on the symmetric and asymmetric forms employing the 3-21G(*) and 6-31G* basis sets show the C_s form to be more stable. However, when the correlation energy is considered, the C_{2v} structures of the trithia, dioxathia, and 1,6-disubstituted diazathia molecules are more favorable. For the 1,6-unsubstituted diazathia molecule (**65**), shown in Scheme 18, the presence of the aromatic isothiazole ring changes the situation to favor the valence tautomer. Earlier experimental data, confirming ring transformation from one isothiazole form to another, postulates the C_{2v} structure as an intermediate in the equilibrium ⟨85JA2721⟩.



(**65**)

Scheme 18

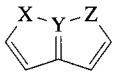
Annulation of a phenyl ring to 1,6aλ^4-dithia-6-azapentalene is thought to perturb the trihetera system sufficiently to favor a C_2 geometry, since the resulting product can also be envisioned as a (pyridinylmethylidene)dithiole, where the nitrogen atom is part of a separate aromatic nucleus, and possibly have different electronic properties compared to the parent azadithiapentalene system. However, theoretical calculations using MNDO are inconclusive, whereas experimental results indicate an azadithiapentalene character ⟨92JOC3895⟩.

Excited electronic states of 1,6,6aλ^4-trithiapentalenes were calculated in order to explain the orange color of the compound which is not observed with carbocyclic 10π-electron systems. Quantum chemical configuration interaction calculations using the AM1 model and *ab initio* Hartree–

Fock theory predicts the transition giving rise to the color by identifying a strong interaction between the HOMO-LUMO (π-π^*) and the SHOMO-SLUMO (σ-σ^*) configurations ⟨94JA11433⟩. The $a_2(\pi)$ and $b_1(\pi^*)$ orbitals are similar to the MOs of naphthalene, but the $a_1(\sigma)$ and $b_2(\sigma^*)$ are unique for the system, being highly localized on the sulfur atoms and largely composed of $3p_y$ atomic orbitals.

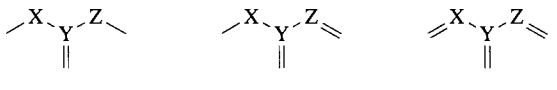
8.32.4.2 Structural Aspects

The number of possible structural variations on triheterapentalene systems gives an indication of the broad scope of the research in this field. Based on the generic structure (**66**), the molecule can possess S, Se, or Te as its central hypervalent atom Y. The number of permutations increases dramatically since each of the atoms X and Z can be replaced by S, Se, O, or NR. Furthermore, one or more of the remaining ring carbons can also undergo "aza" replacements. Tautomeric variations (**a**), (**b**), and (**c**) on the triatomic sequence of the generic structure (**66**) ⟨93JCS(P1)1753⟩ suggests new synthetic challenges, with a view to gain a better understanding of this intriguing ring system. Structures where X and/or Z are nitrogen atoms without any alkyl substitution such as (**67**) and (**68**) are known to be unstable compounds.

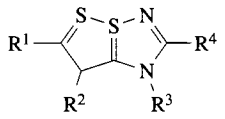


(**66**)

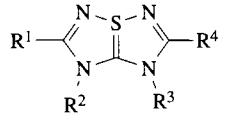
Y = S, Se or Te; X and Z = S, Se, O or NR



(**a**) (**b**) (**c**)



(**67**)



(**68**)

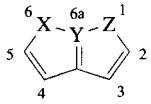
The x-ray crystallography of triheterapentalenes has been studied extensively, for the purposes of gathering information about the nature of bonding as well as for structure identification. Some of the later results given in Table 7 are in agreement with earlier data ⟨84CHEC-I(4)1049⟩ that the bond lengths between the three heteroatoms are significantly shorter than their corresponding van der Waals distances. Substituents generally have pronounced effects on bond distances, and the extent of perturbation to the three heteroatoms increases with the size of the substituents. This is in line with earlier x-ray studies carried out by Hordvik and co-workers on phenyl-substituted trithiapentalenes ⟨66ACS2001, 71ACS1822⟩.

The structural features of pyridoazadithiapentalenes (**69**) are of considerable interest in addressing the question whether the nitrogen atom is part of the aromatic pyridine system or part of the triheteroatomic sequence as demonstrated in Equation (21). The results of the x-ray crystallographic analyses show that the pyridine and the dithiole rings are coplanar ⟨92JOC3895⟩. The S—S bond length is shorter than comparable analogues (2.124 versus an average of 2.466 Å) ⟨72CJC324⟩. While the S—N bond length of 2.502 Å is well within the van der Waal radii for sulfur and nitrogen, and therefore indicative of an interaction between the pyridine nitrogen and the dithiole sulfur, it is significantly longer than for other compounds some of which are shown in Table 7. The most likely conclusion on the basis of crystallographic data is that both the azadithiapentalene and the dithiole forms contribute to the overall structure but neither form predominates. It is also worth noting that the azadithiapentalene canonical form leads to the loss of aromaticity in the pyridine ring, which explains the lack of more bonding character between the sulfur and nitrogen atoms.



(69) (21)

Table 7 Selected bond lengths and angles in 1,6,6aλ^4-triheterapentalenes.



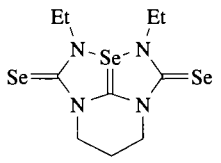
(66)

Triatomic sequence			*Substituents and "aza" replacements*	*Bond angles* (°)	*Bond lengths* (Å)		*Ref.*
1	*6a*	*6*		*1-6a-6*	*1-6a*	*6a-6*	
S	S	S	2-β-naphthyl-4-cyano-5-methylthio-3-aza	175.5	2.23	2.49	85CC1704
N	S	N	1-(*p*-bromo)phenyl-4-t-butyl-6-methyl-2,3,5-triaza	164.0	2.06	1.76	94JCS(P1)2895
N	S	N	1-(*p*-bromo)phenyl-5-phenyl-6-benzyl-2,3,5-triaza	164.0	1.98	1.85	93JHC349
S	Se	S	2,4-dimethyl-3-aza	170.0	2.47	2.37	87CC967
S	Se	Se	2,4-dimethyl-3-aza	171.3	2.51	2.47	87CC967
Se	Se	O	3,4-dimethyl-5-aza	171.0	2.44	2.04	87CC967
Se	Se	Se	2-benzoylamino-5-diethylamino-3,4-diaza	169.9	2.51	2.64	90T7735

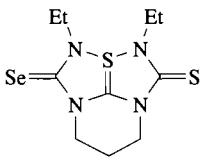
The triheterapentalenes (**70**)–(**72**), shown in Table 8, are examples of a 12π-electron system which is expected to display somewhat different chemical characteristics compared to the 10π-electron pentalenes discussed earlier. Although the tetraazapentalenes (**70**) and (**71**) have four nitrogen atoms within the ring system, x-ray crystallographic analyses show a remarkably planar framework for both systems. This is attributed to significant contribution from polar resonance forms ⟨88BCJ2419⟩ and sp^2 geometry for the nitrogen atoms. The exocyclic double bond distances in all three molecules are between single and double bond distances which is an indication of conjugation with the ring and further evidence of a delocalized 12π-electron system.

Coordination compounds of triheterapentalenes also provide structural information about the bicyclic ring system. Some trithiapentalene (ttp) complexes are described. In [Au(ttp)Cl] the ligand is monocoordinated to the gold atom through a terminal sulfur atom. The complex coalesces in the NMR time scale ⟨88CC22⟩. Qualitative molecular orbital studies predict a coplanar conformation of AuCl with the ring system in the terminal coordination mode of the unsubstituted ttp ⟨93NJC147⟩. Trithiopentalene can also act as a chelating ligand through the central and one terminal sulfur atoms in [Ni(ttp)(allyl)]. A cyclometallated complex of ttp with Pd is also known ⟨79AG(E)683⟩.

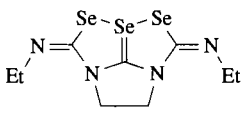
Table 8 Selected bond lengths and angles in 12π-1,6,6aλ^4-triheterapentalenes.



(70)



(71)



(72)

Compound	*Triatomic sequence*			*Bond Angles* (°)	*Bond lengths* (Å)		*Ref.*
	1	*6a*	*6*	*1-6a-6*	*1-6a*	*6a-6*	
(**70**)	N	Se	N	159.4	2.05	2.04	93AX(C)917
(**71**)	N	S	N	165.5	1.93	1.89	88BCJ2419
(**72**)	Se	Se	Se	167.5	2.60	2.66	93AX(C)917

8.32.4.3 NMR Spectroscopy

Both ^{13}C and ^{1}H NMR have been used extensively to determine the structures of triheterapentalene derivatives. The strong deshielding of the ring protons observed, compared to monocyclic heteroaromatic analogues, is indicative of aromatic pentalene systems ⟨83JCS(P1)777, 92JOC3895⟩. Developments in NMR techniques and multinuclear capabilities now enable studies to be carried out with very small quantities of samples where intermediates with short life times can be observed for mechanistic studies. Bond switch rearrangements of 3-oxo-Δ^4-1,2,4-thiadiazolin-5-yl ureas were detected largely based on ^{13}C evidence including nuclear Overhauser effect (NOE) studies ⟨91JHC1619⟩ which led to the correction of earlier erroneous results.

In a ^{13}C NMR study of bis(dialkylamine) substituted 1,6,6aλ^4-trithia-3,4-diazapentalenes, three signals are detected for the bridgehead carbon, and three signals for the equivalent C-2 and C-5 atoms bearing substituents. This is attributed to the presence of three different conformations due to the restricted rotation of the C—N bonds of the dialkylamine substituents with C-2 and C-5. The possibility that the signal splitting might be as a result of valence isomers is ruled out on the basis of high temperature studies where each of the three signals coalesce into singlets ⟨94CB2209⟩. The restricted rotation observed has further implications about the extent of conjugation between the dialkylamino substituents and the pentalene ring system.

It has been found that in ^{15}N NMR of 1,2,3-thiadiazoles, the substituents on C-5 have a marked influence on the N-2 resonances. Conjugative interactions of C-5 side chains result in the shielding of the N-2 atom. However, nitroso or azo side chains fail to cause any significant shielding of N-2. This can be attributed to the thiapentalene character of the molecules characterized with high electron density at the terminal heteroatoms, which in turn decreases the shielding effect of the substituent on N-2 ⟨93JHC301⟩.

Critical information about the hypervalent nature of the central Se atom comes from a ^{77}Se NMR study of a 1,6,6aλ^4-triselena-3,4-diazapentalene system ⟨90T7735⟩. The large difference in the chemical shifts (δ 352.2, 514.9, and 742.6 ppm) is attributed to the different substituents in the 2- and 5-positions. A coupling constant of $J_{Se\text{-}Se}$ 360 Hz is indicative of the linear triselena arrangement.

8.32.4.4 Visible and UV Spectroscopy

The visible absorbance maxima for triheterapentalenes appear at higher wavelengths (up to 560 nm) when Se is part of the triheteroatom sequence. 1,6,6aλ^4-Trithiapentalenes display stronger absorbance at slightly lower wavelengths, around 500 nm. Aza- or oxa-substitution in the triheteroatom sequence lowers the absorbance maxima by 20–80 nm. Similar trends are observed for the UV region ⟨82JCS(P1)499, 83JCS(P1)777⟩.

With the exception of substituents on the aza positions, the effect of substituents on the absorption spectra seems to be minor. With 5-aryl-1-aza-6,6aλ^4-dithiapentalenes, methyl and methoxy substitution on the 5-phenyl ring does not result in the expected bathochromic shifts. This is attributed to the non-coplanarity of the parent ring system with the 5-aryl substituents, and consequently, to the absence of π-orbital overlap ⟨92JOC3895⟩.

8.32.4.5 Miscellaneous Physical Measurements

X-ray irradiation (ESCA) studies on 2,5-disubstituted 1,6,6aλ^4-triselena-3,4-diazapentalene give two signals for Se atoms at 54.0 eV and 55.3 eV. The difference in the intensities of the signals is comparable with analogous studies of trithiapentalene systems ⟨90T7735⟩.

Electrochemical studies on pyridodithiapentalene (**69**) using cyclic voltammetry show scan rate-independent irreversible oxidation peaks. Oxidation potentials vary between +0.70 and +0.93 V depending on the substituents. However, no correlation is found between Hammet σ constants and oxidation potentials, which can be rationalized in terms of the lack of π-orbital overlap between the substituents and the parent ring ⟨92JOC3895⟩.

8.32.4.6 Syntheses

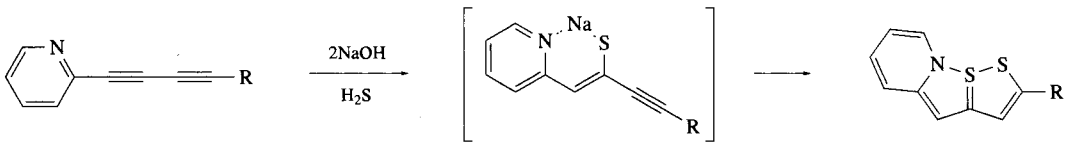
During the early years of synthetic work in this area, β-dicarbonyl or β,δ-tricarbonyl functionalities, or their synthetic equivalents were the most common precursors used to build the

triheteroatomic framework of heterapentalenes. The heteroatom source for these preparations are chlorides of sulfur, and chlorides or oxides of selenium or tellurium ⟨79BSF(2)199, 79BSF(2)205, 84CHEC-I(4)1049⟩. Out of the large number of triheterapentalenes synthesized since the mid-1960s, those reported since the mid-1980s are included here. New synthetic strategies using fewer numbers of steps and giving higher yields are also discussed. It is noteworthy that there have been very few reports published on telluropentalenes since the mid-1980s. The classification followed is based on the number of fragments necessary to build the bicyclic ring sytem.

8.32.4.6.1 Formation of two rings

(i) From [6 + 2] atom fragments

Carbonylbutadiynes are versatile precursors in the syntheses of oxadithiapentalenes ⟨84CHEC-I(4)1049⟩. Reaction of hydrogen sulfide with unsymmetrically substituted butadiynylpyridines furnish the pyridoazadithiapentalenes (**69**). The double addition of hydrogen sulfide is facilitated by the intermediacy of the complex shown in Scheme 19.



a: R = *n*-C_4H_9
b: R = $CH_2(CH_2CH_3)OH$
c: R = C_5H_5
d: R = *p*-MeC_6H_4
e: R = *p*-$MeOC_6H_4$
f: R = 2-C_5H_4N

(69)

Scheme 19

(ii) From [4 + 2 + 2] atom fragments

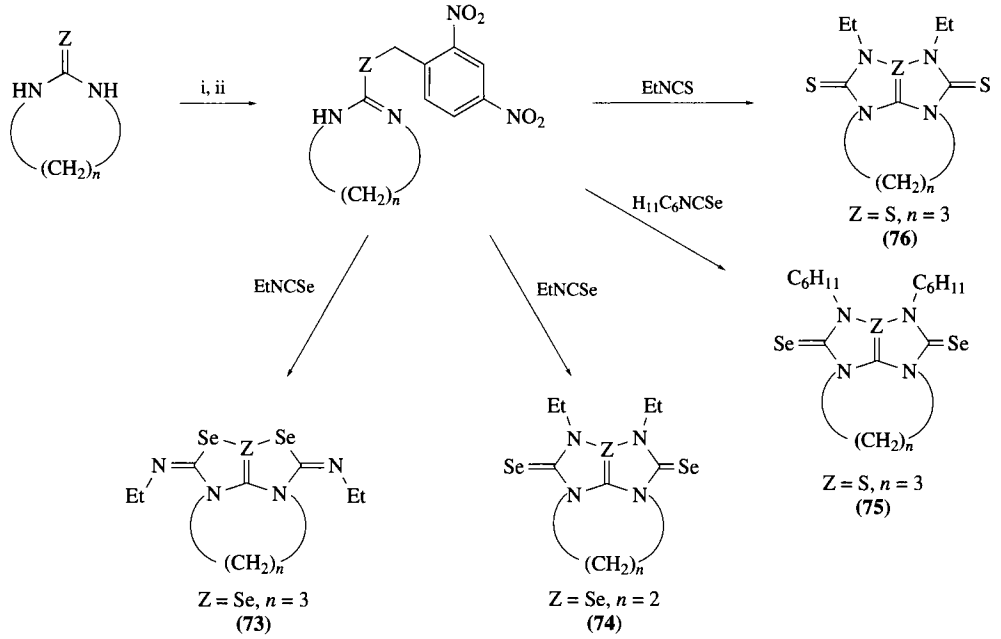
In a general synthetic method for the preparation of 12π-triheterapentalenes (**73**)–(**76**), cyclic thioureas or selenoureas are alkylated with 2,4-dinitrobenzyl chloride followed by neutralization with sodium carbonate. The resulting bases when treated with alkyl isothiocyanate or isoselenocyanate, undergo elimination of 2,4-dinitrotoluene and concomitant addition of two molecules of the heterocumulenes to give the products shown in Scheme 20 ⟨93AX(C)917⟩.

Alkylation of the cyclic thiourea with phenacyl chloride followed by treatment with isothiocyanate also yields the product (**76**) and other symmetrical *N*-alkyl derivatives in a convenient one-pot reaction ⟨88BCJ2419⟩. Unsymmetrical tetraazapentalene derivatives can be prepared from the periodate oxidation products of their symmetrical analogues as described in the following section.

Acylation of 5-amino-1,2,3,4-thiatriazole with two equivalents of chlorothioformates yields 2,5-disubstituted 1,6,6aλ^4-trithia-3,4-diazapentalenes where a zwitterionic dithioazole ring forms following the opening of the thiatriazole ring and the subsequent loss of nitrogen. As shown in Scheme 21, the second equivalent of the chlorothioformate adds to the imino side chain to form the pentalene. The zwitterionic intermediate, isolated from the reaction mixture, displays mass spectral characteristics consistent with the structure proposed ⟨89M997⟩.

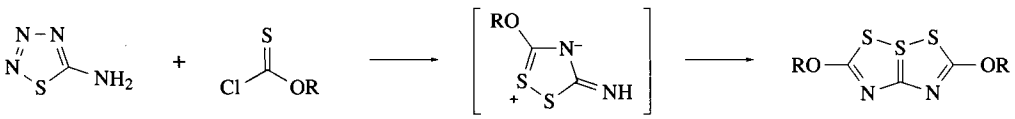
(iii) From [3 + 3 + 2] atom fragments

2-Benzoylamino-5-diethylamino-1,6,6aλ^4-triselena-3,4-diazapentalene (**77**) shown in Equation (22) is prepared from benzoyl chloride and selenocyanate in a one-pot reaction analogous to an



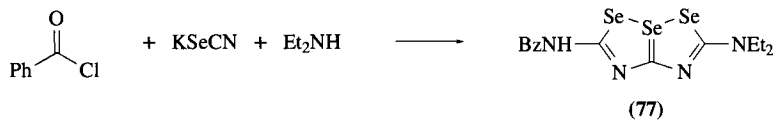
i, 2,4-dinitrobenzyl chloride; ii, Na_2CO_3

Scheme 20



Scheme 21

earlier method ⟨37JA740⟩ used for the preparation of benzoylthiourea derivatives. Although the yields are poor, the mild reaction conditions and fast rates are definite advantages ⟨90T7735⟩.



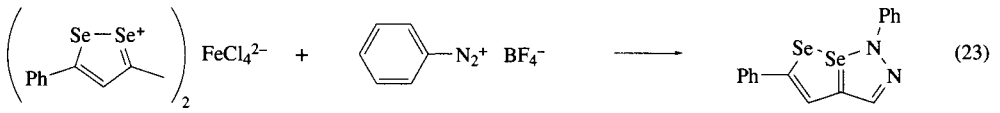
(22)

(77)

8.32.4.6.2 Formation of one ring

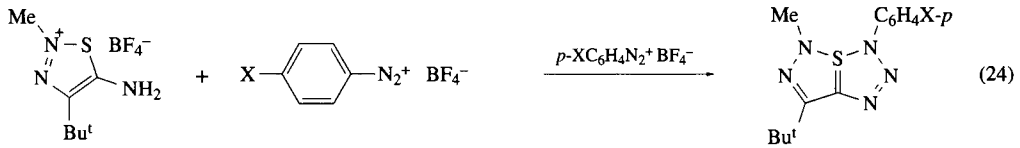
(i) From [3 + 2] atom fragments

Utilization of the conjugate bases of 3-alkyl-1,2-dithiolylium and 3-alkyl-1,2-diselenolylium salts as precursors for sulfur or selenium containing 6,6aλ^4-triheterapentalenes is a widely used synthetic method. In a slight variation bis-(1λ^4,2-diselenol-1-ylium) salts have been used as precursors. 3-Alkyl-substituted diselenolylium tetrachloroferrates (**78**) give 6,6aλ^4-diselena-1,2-diazapentalenes (**79**) upon treatment with benzenediazonium tetrafluoroborate (Equation (23)). The mechanism involves the deprotonation of the 3-methyl substituent followed by rapid electrophilic substitution ⟨93HAC337⟩.



(78) (79) (23)

The amino substituent of 5-aminothiadiazolium salt (**80**) functions as the nucleophile in reactions with various substituted benzenediazonium salts to give 6aλ^4-thia-1,2,3,5,6-pentaazapentalenes (**81**) shown in Equation (24). The preparation of (**80**) involves *N*-methylation using Meerwein's reagent. The directing effect of the *t*-butyl group safeguards the formation of the desired *N*-methylated regioisomer (**80**) ⟨94JCS(P1)2895⟩. Use of 5-imino-1,2,4-thiadiazolines instead of the 1,2,3-thiadiazolium salt precursor (**80**) leads to the 6aλ^4-thia-1,2,3,4,6-pentaazapentalenes shown in Table 9 ⟨93JHC349⟩.



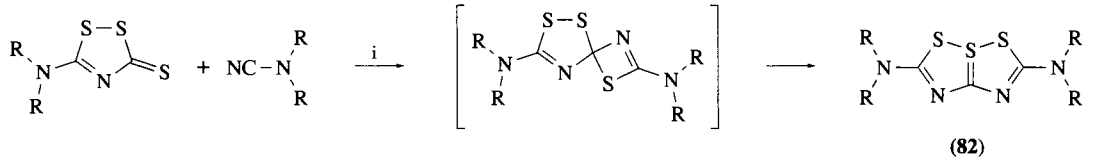
(80) X = OMe, Br or NO_2 (81) (24)

Table 9 6aλ^4-Thia-1,2,3,4,6-pentaazapentalene derivatives.



R^1	R^2	R^3
Ph	Ph	*p*-$NO_2C_6H_4$
p-MeC_6H_4	Pr^i	*p*-$NO_2C_6H_4$
Me	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$
Me	Ph	*p*-$NO_2C_6H_4$
Br	Ph	*p*-$NO_2C_6H_4$
Me	Ph	*p*-BrC_6H_4
Br	Ph	*p*-BrC_6H_4

Cycloaddition of 1,2,4-dithiazoles with dialkylcyanamides under high pressure at elevated temperatures gives the trithiapentalene derivatives (**82**) as [2 + 2] adducts as shown in Scheme 22 ⟨89CL1357⟩.



(82)

i, 800 MPa, 160 °C

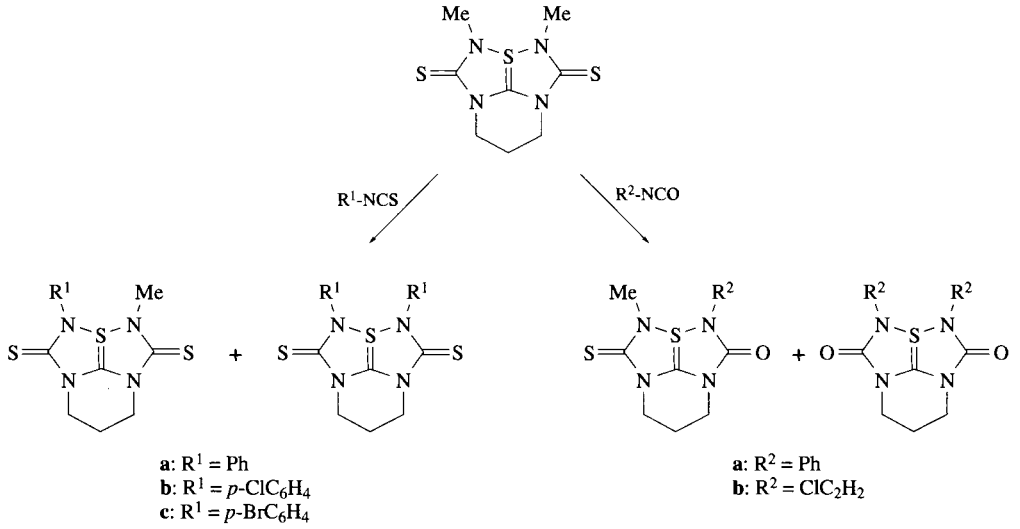
Scheme 22

Unsymmetrical tetraazathiapentalenes (**84**) can be prepared in 1,3-dipolar cycloadditions of 1,2,4-thiadiazolo[4,5-a]pyrimidine-3-thione (**83**) with various isothiocyanates as shown in Equation (25). The precursor (**83**) is the thermolysis or periodate oxidation product of the symmetrical tetraazapentalene (**76**) ⟨88BCJ2419⟩.



(83) (84) (25)

Heating the symmetrical tetraazathiapentalenes under reflux in the presence of phenylisothiocyanate or isocyanate results in a postulated retro-cycloaddition followed by a subsequent cycloaddition to give the unsymmetrical products as well as new symmetrical products shown in Scheme 23. It is noteworthy that in contrast to substituted phenyl isothiocyanates, alkyl isothiocyanates fail to give any new products in this reaction. Similarly, reactions with isocyanates give asymmetric tetraazathiapentalenes which cannot be synthesized easily by other methods ⟨91JHC221⟩.

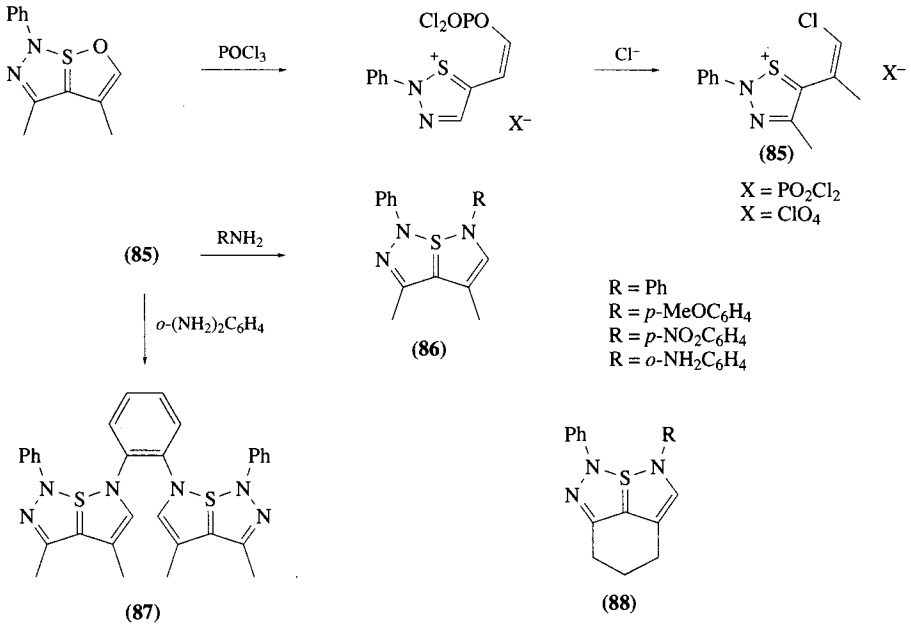


Scheme 23

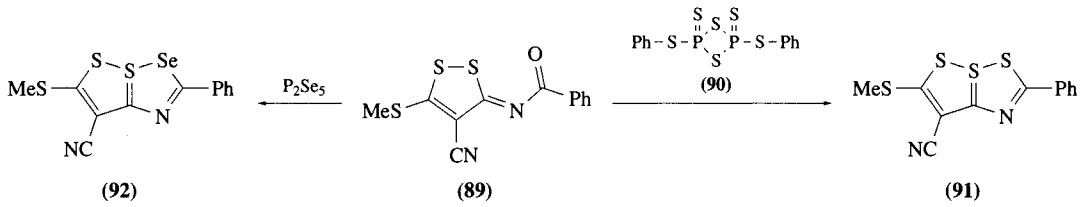
(ii) From [4 + 1] atom fragments

Perchlorate or phosphorodichloridate salts of 5-(2-chlorovinyl)-2-phenyl-1,2,3-thiadiazolylium ions (**85**) have been versatile precursors in the synthesis of 6aλ^4-thia-6-hetera-1,2-diazapentalenes, with a choice of S, Se or an aza functionality for the 6-position. Particularly high yields of 6aλ^4-thia-1,2,6-triazapentalenes (**86**) are reported upon treatment of 1,2,3-thiadiazolylium salts with a number of amines including benzene diamine which gives the bis(pentalene) (**87**). Tricyclic pentalenes (**88**) are prepared using the same methods ⟨83JCS(P1)777⟩. The 1,2,3-thiadiazolylium salts (**85**) are prepared immediately before the reactions by the addition of phosphoryl chloride to 6aλ^4-thia-6-oxa-1,2-diazapentalenes which in turn can be prepared by partial desulfuration of the corresponding dithiadiazapentalenes with mercury(II) acetate ⟨78JCS(P1)195⟩. Similarly, the dithiadiazapentalene and the thiaselenadiazapentalene analogues are prepared by the addition of aqueous sodium hydrogen sulfide or potassium selenosulfate respectively to the 1,2,3-thiadiazolylium salts. The reactions of the 1,2,3-thiadiazolylium salts are shown in Scheme 24.

The exchange of carbonyl oxygens with heteroatoms has provided useful routes for the introduction of S and Se atoms into pentalene systems. A mixture of (4-cyano-5-methylthio-1,2-dithiole-3-ylidine)benzamide (**89**) and 2,4-bis(phenylthio)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (**90**) upon reflux, give 1,6,6aλ^4-trithia-3-azapentalene derivative (**91**) shown in Scheme 25. If the benzamide (**89**) is refluxed with P_2Se_5 instead, the 1-selena-6,6aλ^4-dithia analogue (**92**) is formed as a result ⟨85CC1704⟩.



Scheme 24



Scheme 25

8.32.4.6.3 *By ring transformation*

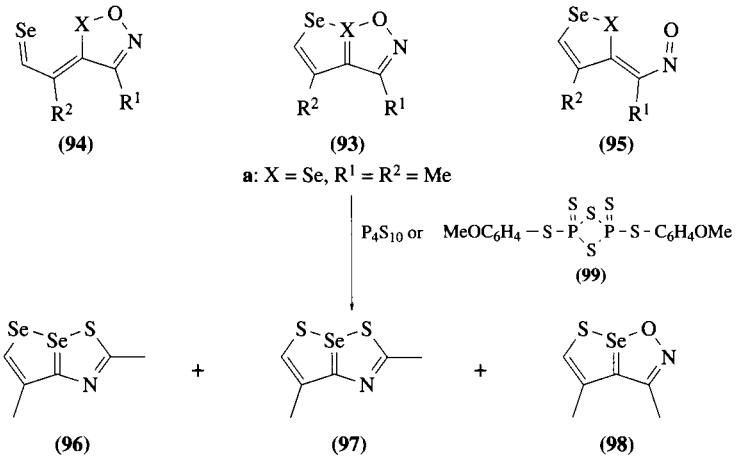
In view of the general structural characteristics of the trihetarapentalene systems discussed earlier, the general structure of 1-oxa-6-selena-6aλ^4-hetera-2-azapentalenes (**93**) can be regarded as a masked form of a selenoaldehyde (**94**) and a nitroso compound (**95**). Consequently, the ring transformation can also be considered as a ring formation from [4 + 1] atom fragments by the well established C=O to C=S conversion. However, the reaction of 3,4-dimethyl-1-oxa-6,6aλ^4-selena-2-azapentalene (**93a**) with P_4S_{10} gives the rearranged ring transformation products (**96**)–(**98**) shown in Scheme 26 ⟨87CC967⟩. Using Lawesson's reagent (**99**) as the thionating agent gives the 1-oxa compound (**98**) as the major product with only traces of others.

Scheme 27 shows the mechanism postulated for the interesting molecular rearrangement for the transformation of (**93**) to (**96**) or (**97**) when P_4S_{10} is used as the sulfurylating agent.

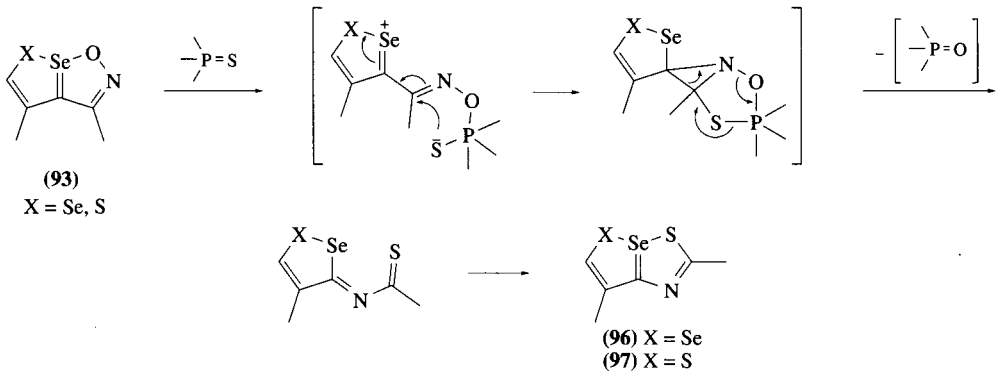
8.32.4.6.4 *Formation of extended structures*

Treatment of the azadithiapentalene derivative of (**69**) with TCNQ generates a radical cation which gives the dimer (**100**).

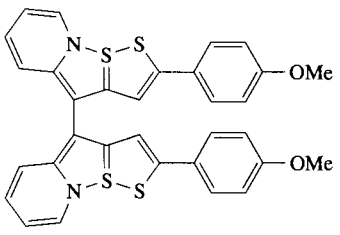
Reaction of two equivalents of 2,5-bis(aryloxy)-1,6,6aλ^4-3,4-diazapentalenes (**101**) with diamines links the two heterapentalene systems together; the product (**102**) still possesses aryloxy groups and can thus be functionalized further. The length of the linkage can be varied, the shortest having four methylene units between the amino groups as shown in Scheme 28. Reaction with another diamine forms a macrocycle (**103**) containing two pentalene units. When polyether groups are included in the linkage, the macrocycle bears the characteristics of an azacrown ether ⟨94CB2209⟩.



Scheme 26



Scheme 27

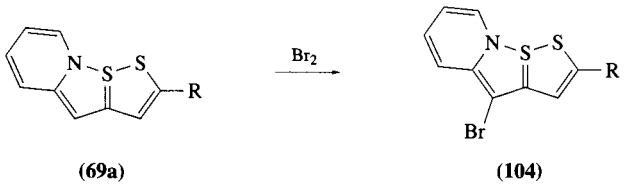


(100)

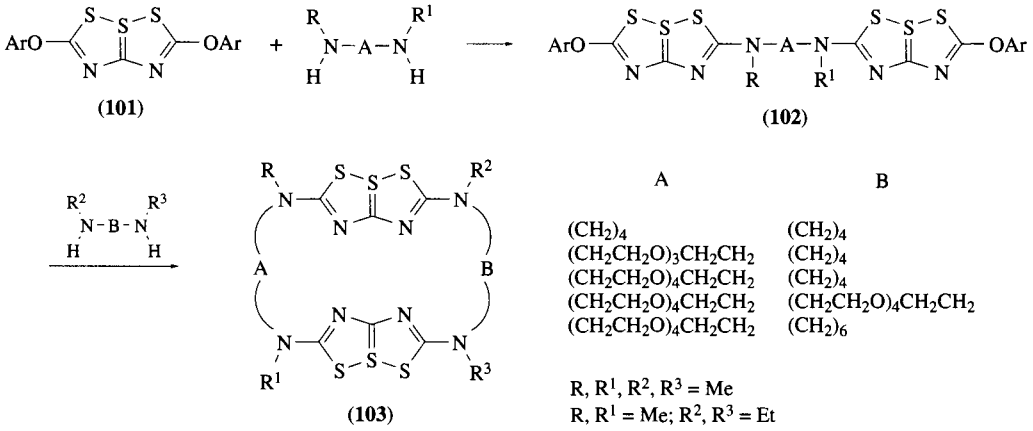
8.32.4.7 Reactions

8.32.4.7.1 Halogenation

Bromination of (pyridinylmethylidene)dithiole (**69a**) gives the 4-bromo product (**104**) (Equation (26)) ⟨92JOC3895⟩.



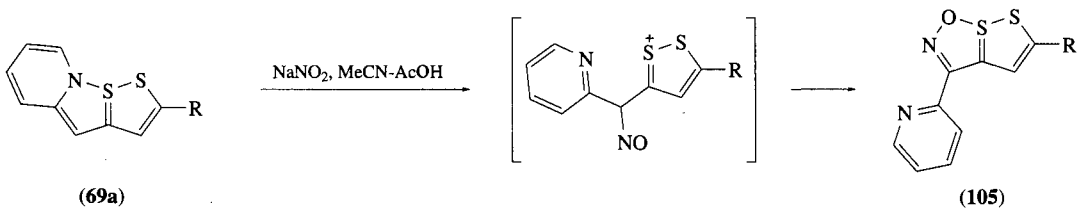
(26)



Scheme 28

8.32.4.7.2 Nitrosation

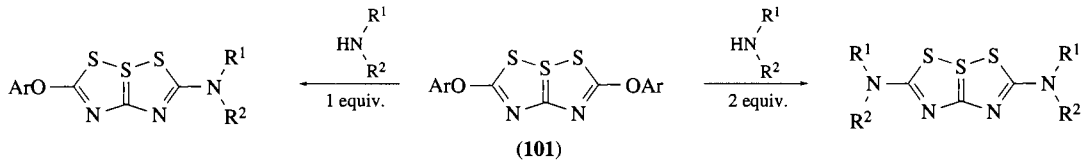
Nitrosation of 1,6,6aλ^4-heterapentalenes give the 3- or 4-nitroso substituted product followed by rearrangement whereby oxygen becomes a part of the triheteroatomic sequence. Nitrosation of (pyridinylmethylidene)dithiole (**69a**) follows the same mechanism to give the pyridine substituted 5-aza-1,6aλ^4-dithia-6-oxapentalene (**105**) (Scheme 29) ⟨92JOC3895⟩.



Scheme 29

8.32.4.7.3 Replacement of a substituent

2,5-Aryloxy substituents of 2,5-bis(aryloxy)-1,6,6aλ^4-3,4-diazapentalenes (**101**) are replaced by secondary amines yielding 2-monoamino and 2,5-diaminoheterapentalenes shown in Scheme 30 ⟨94CB2209⟩.

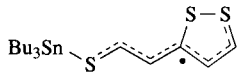


Scheme 30

8.32.4.7.4 Radical addition

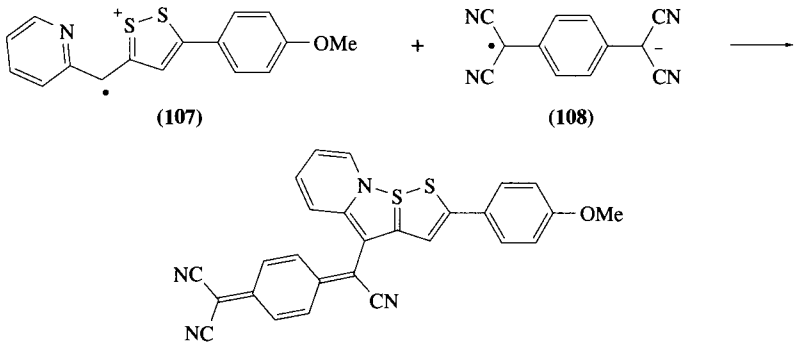
In a comprehensive study, adduct radicals formed as a result of the addition of tri-*n*-butylstannyl radical to triheterapentalenes are investigated. With 1,6,6aλ^4-trithiapentalenes, the addition cleaves the S(1)—S(6a) (or S(6)—S(6a)) bonds forming persistent radicals which are detected by ESR and whose g values and hyperfine splitting constants are determined. Whereas selena analogues behave similarly, radical attack on oxygen is not observed for 1,6-dioxa-6aλ^4-thiapentalenes, or on nitrogen

for 1,6-diaza-6aλ^4-thiapentalenes. The conformation (**106**) is postulated for the adduct radicals derived from the trimethylene-3,4-bridged trithiapentalenes where the degrees of freedom are restricted. On the basis of the similarities in their ESR parameters, adduct radicals from a number of other trithiapentalenes are also assigned conformations of the type (**106**) ⟨82JCS(P2)431⟩.



(**106**)

In an attempt to prepare the charge-transfer complex of a substituted azadithiapentalene (**69**), reaction with TCNQ resulted in a coupling product (**109**). The mechanism outlined in Equation (27) postulates the formation of a radical cation (**107**) from the azadithiapentalene which reacts with the radical anion of TCNQ (**108**) followed by a loss of HCN ⟨92JOC3895⟩.



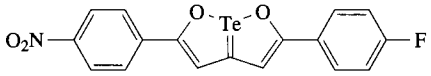
(**107**) (**108**)

(**109**)

(27)

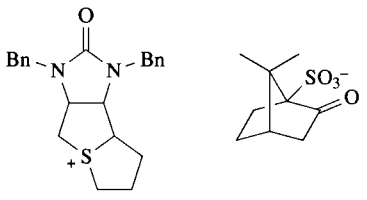
8.32.5 INDUSTRIAL AND BIOLOGICAL APPLICATIONS

The antifogging activity of a number of triheterapentalenes in color photography has been studied. The RN-S-NR triatomic sequence is found to be the most effective structural requirement ⟨92MI 832-02⟩. Dioxatellurapentalene (**110**), along with the 6aλ^4-selena analogues, is used as a sensitizer in electrophotography. However, the sensitizer activity is limited to those pentalenes containing only Se and Te as their hypervalent atoms ⟨84USP4450217⟩.



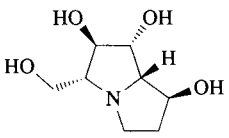
(**110**)

The camphorsulfonate (camsylate) salt of trimethaphan (**111**) is a well known antihypertensive drug. Its pharmacological properties are well documented ⟨B-74MI 832-01⟩. The bicyclic unit with a bridgehead sulfur atom is a characteristic structural feature of trimethaphan. Another apparent feature is its structural similarity to biotin, which in fact is a logical precursor. Seleno analogues of biotin and trimethaphan have also been synthesized ⟨76TL2033⟩. Presynaptic anticholinergic activity of trimethaphan makes it a good candidate as a prophylactic against organo-phosphate poisoning, particularly, in the event of exposure to organo-phosphate based nerve-gas intoxication ⟨94LS69⟩.

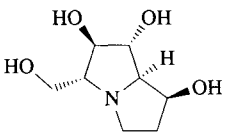


(**111**)

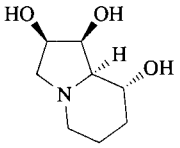
The bicyclic sulfonium salt (**10**) whose synthesis is described in Section 8.32.2.1.2 was designed on the basis of its structural similarity to polyhydroxylated pyrrolizidine alkaloids (**112**)–(**114**) which are known for their glycosidase inhibitor activities. Swainsonine (**114**), in particular, a potent α-mannosidase inhibitor, by the protonation of its bridgehead nitrogen, is thought to mimic the charged mannosyl intermediate during the enzyme hydrolysis of mannosides. For the same purpose, the sulfur analogue (**10**) is tailored to incorporate the bridgehead sulfur as its cationic center. The activity tests show that the chloride salt of the bicyclic sulfonium ion (**10**) inhibits 12 different human liver glycosidases with good selectivity towards α-mannosidase and α-fucosidase, while its α-mannosidase inhibitory activity is pH dependent and slightly lower than that of swainsonine ⟨92CC1531⟩.



(**112**)



(**113**)



(**114**)

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8.33
Bicyclic Systems with Ring Junction Phosphorus, Arsenic, Antimony, or Bismuth Atoms

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Staffordshire University, Stoke-on-Trent, UK

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8.33.1 INTRODUCTION

This series of bicyclic compounds was not covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). The compounds have usually been studied as part of the general development of the organic chemistry of the group 5 elements which has occurred since the 1950s and centers mainly on the chemistry of phosphorus. Virtually all the compounds are alicyclic and very few fall into the aromatic class. Most involve more than one heteroatom in the ring system, the additional atoms usually being oxygen and nitrogen.

These heterocycles rarely have trivial names and thus, apart from compounds such as phospholes and phosphorins and their saturated derivatives phospholan and phosphorinan, they are usually named by identifying the heteroatoms as substituents of carbon: phospha, arsa, stiba, and bisma. Whilst lower group 5 equivalents to quinolizine and indolizine are not known, several hydro derivatives have been characterized and some authors have adapted these names; thus 1-phosphabicyclo[4,4,0]decane (**16**) has also been named as 2*H*-octahydrophosphinolizine as well as 5-phosphadecalin. One group which has been given a trivial name is the bicyclic phosphabicyclo-[3,3,3]undecanes (**152**)–(**154**), that is, the phosphatranes. There was a move to rename phosphines as phosphanes, mainly by German chemists, but this did not receive wide acceptance. Two-coordinate compounds, for example, phosphaalkenes RP=Y, have also been named as phosphenes, arsenes, etc.

The heterocycles covered in this chapter have a very wide range of ring sizes, from very small fused-ring systems (e.g., [1,1,0]) to quite large nonfused-ring systems, (e.g. [6,6,6]). Only one nonsubstituted fused-ring parent heterobicycle possessing one heteroatom has been prepared. In the vast majority of examples there are other heteroatoms in the ring and/or additional rings present. Because of the very wide variety of ring systems, the range of bicyclic compounds covered here has been widened. The bicyclic systems [4,4,0], [4,3,0], and [3,3,0] are covered first in this order, followed by other fused heterobicyclic systems: [3,2,0], etc. The other ring systems [*n*,*m*,1], [*n*,*m*,2], [*n*,*m*,3], etc. are covered briefly in order of decreasing ring size, beginning with [4,4,1], proceeding to [4,3,1], etc. and then to [*n*,*m*,2], [*n*,*m*,3], etc. Note that these basic ring systems are often part of a wider ring system but are not tricyclic with respect to the key heteroatom. Within each section covering a specific ring system any nonsubstituted parent ring systems are covered first, and thereafter compounds are covered in order of heteroatoms included in the heterocyclic ring system (e.g., $P > P_2 > P_n > PN > PNO > PN_2 > PO > PS$, etc.) and then in order of increasing saturation.

In most cases the bicyclic compounds are end products and whilst their spectral properties are usually reported, studies of their reactivities are fewer. Frequently the heteroatom acts as a focus for reactions with many reagents and as a consequence leads to a destruction of the ring system.

8.33.2 THEORETICAL METHODS

The incorporation of P, As, Sb, and Bi heteroatoms in a ring system has not played a large part in the theoretical studies of these classes of compound. Relativistic effects, which contract the size of the *s* orbitals and to a lesser extent the *p* orbitals, become more important for the heavier elements, and this can cause irregular effects on the periodic trends ⟨B-94MI 833-01⟩. The effect leads to the inert electron pair concept. Thus the three-coordinate five-membered heterocycles such as phosphole show considerable decrease in the involvement of the lone pair in stabilizing the ring system, and for As, Sb, and Bi there appears to be no net stabilization, which follows the same trend as their ability to participate in conjugation as substituents. Studies of the two-coordinate heterosubstituted benzene analogues, such as phosphabenzene, indicate a significant but decreasing amount of aromatic stabilization with atomic number of the heteroatom ⟨88JA4204⟩. However, two-coordinate heteroatoms are unable to occupy bridgehead positions. In the higher valence state the involvement

of *d* orbitals as opposed to sigma antibonding orbitals in the stabilization of compounds such as the ylides and pentacoordinate phosphoranes has aroused considerable theoretical interest ⟨B-90MI 833-01⟩. In the case of molecular mechanics there has been development of force field data for phosphoranes ⟨78T627⟩ and phosphazenes ⟨70JA1995⟩ in addition to the well-established force fields for phosphates and phosphines.

8.33.3 EXPERIMENTAL STRUCTURAL METHODS

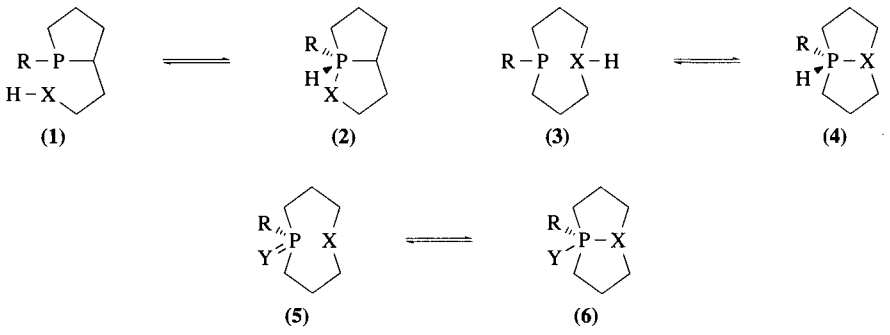
X-ray diffraction has shown that the bond angles to three-coordinate P, As, Sb, and Bi atoms tend towards 90°, the ultimate angle depending on other steric factors. Whilst four-coordinate heteroatoms are tetrahedral, the five-coordinate atoms are generally trigonal bipyramidal for phosphorus and arsenic (with steric factors producing distortion of this stereochemistry towards a square pyramidal conformation), but they are square pyramidal for the antimony and bismuth compounds. Thus the involvement of the lower group 5 heteroatoms in small rings can be used to favour the formation of five-coordinate heterocyclic compounds.

Phosphorus-31 NMR spectroscopy has played a central role in the development of organophosphorus chemistry, the chemical shifts being dependent on valency, coordination, bond angles and directly bound atoms, and the coupling constants being used to identify adjacent NMR active nuclei and indicate stereochemistry ⟨B-87MI 833-01⟩.

8.33.4 THERMODYNAMIC ASPECTS

The physical properties vary widely, primarily because of the very wide range of other heteroatoms and substituents involved either in the ring system or as substituents. Thus there have been few systematic studies of solubilities and chromatographic properties, although the latter are used frequently for the purification of the compounds. Aromatic properties are restricted to those with low-coordinate heteroatoms, which consequently are not then able to act as ring junction heteroatoms. They are generally somewhat unstable unless they bear very large substituents. On the other hand, such compounds have been found to be useful as starting materials for the synthesis of bicyclic heterocycles via cycloaddition reactions.

Tautomerism with valence expansion of the heteroatom has been studied in some detail for three ring systems: **(1)**⇌**(2)**, **(3)**⇌**(4)** and **(5)**⇌**(6)**. The five-coordinate compounds (phosphoranes) are favoured by the generation of small rings and the presence of electronegative atoms bound to the heteroatom.



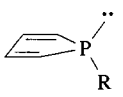
The barriers to inversion at the three-coordinate heteroatom increases markedly with atomic number (ca. 35, 40, 45, and 60 kcal mol^{-1} for P, As, Sb, and Bi respectively) and is generally sufficiently slow to allow the synthesis of optically active compounds ⟨B-94MI 833-01⟩. The barrier is enhanced further by incorporation of the heteroatom at a bridgehead.

The Lewis basicity also decreases with atomic number, and incorporation at a bridgehead can decrease the basicity to such an extent that compounds may become resistant to complexation, oxidation, and alkylation.

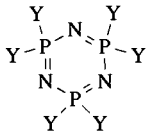
8.33.5 REACTIVITY OF FULLY CONJUGATED RINGS CONTAINING PHOSPHORUS

8.33.5.1 Fused-ring Systems

Conjugation in phosphorus and the heavier group 5 elements takes on a new perspective in comparison with nitrogen. Thus the high *s*-character of the lone pair of electrons in phosphines reduces its tendency to become involved in ground state delocalization. Thus whilst phospholes (**7**) are believed to have some aromatic stability, the phosphorus substituent remains out of the plane of the ring and the phospholes readily undergo cycloaddition reactions: e.g., dimerization. Five-valent $\sigma^4\Lambda^5$ phosphorus stabilizes anions quite effectively but does not transmit through-conjugation, acting to isolate substituents which have potential to conjugate. Likewise, in cyclophosphazenes (**8**) the P=N groups behave more like isolated islands than as a delocalized ring system.

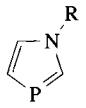


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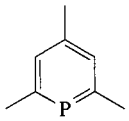


(8)

In contrast, two-coordinate derivatives are able to become involved in aromatic properties, and there are many examples of phosphazoles (**9**) and phosphabenzenes (**10**).



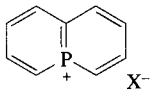
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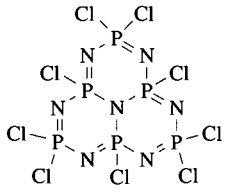
(10)

8.33.5.1.1 [4,4,0] Ring systems

Neither the fully unsaturated 10-phosphanaphthalene cation (**11**) nor any of its derivatives have been described. The only fully "unsaturated" example incorporating a [4,4,0] ring system is the phosphazene (**12**) which is formed in the reaction of phosphorus pentachloride with ammonium chloride ⟨73CJC520⟩.



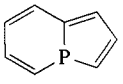
(11)



(12)

8.33.5.1.2 [4,3,0]Ring systems

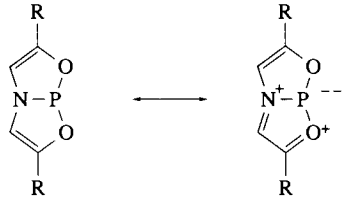
Neither the phosphorus equivalent to indole, such as 8-phosphaindene (**13**), nor any of its derivatives have been reported. When such compounds are synthesized it will be interesting to see whether the enforced planarity about the phosphorus atom enables the phosphorus to improve its participation in conjugation so as to impart additional aromatic character to the heterocycle.



(13)

8.33.5.1.3 [3,3,0]Ring systems

The bicyclic compound (**14**) formed by the reaction of phosphorus trichloride with an aminodiketone ⟨84JA1164⟩ has been shown to be planar, which has been interpreted as evidence for the delocalized dipolar canonical structure (**15**) rather than the neutral form (**14**). It forms a silver complex with trigonal bipyramidal stereochemistry at phosphorus ⟨91JA1071⟩.



(**14**) (**15**)

8.33.6 REACTIVITY OF NON- AND PARTLY CONJUGATED RINGS CONTAINING PHOSPHORUS

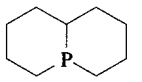
8.33.6.1 Fused-ring Systems

8.33.6.1.1 [4,4,0]Ring systems

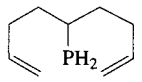
The synthesis of 1-phosphabicyclo[4,4,0]decane (**16**) by the radically initiated cyclization of the primary dibutenylphosphine (**17**) was achieved by Cremer's group in the USA ⟨87PS(30)369⟩ and by Issleib's group in Germany ⟨87ZAAC(553)136⟩. It is the only example of a parent monoheterobicycle. Both *trans* and *cis* fused ring systems (**18**) and (**19**) were isolated separately and are equilibrated by UV light. Unlike the *trans* isomer, $\delta P = -45.2$ ppm, the *cis* isomer, $\delta P = -30.4$ ppm, is conformationally mobile as shown by the broadening of the latter signal with decreasing temperature. The conformational energy barrier for the *cis* isomer was estimated to be about 3.1 kJ mol^{-1}, and its ring inversion barrier was estimated to be 41.9 kJ mol^{-1}. The phosphine was converted to its oxide, sulfide, methoxy, methyl, and benzyl salts, and some other complexes. The stereochemistry of the hydrolysis of the methoxide salt was studied and compared with that of monocyclic heterocycles. The triarylphosphine (**20**) was produced by the ppa cyclization of a tertiary benzyl alcohol ⟨85JOC2914⟩. Electrophilic cyclization of a dipropene precursor produced a similar ring system ⟨90AGE689⟩. Reaction of a phosphabenzene with sulfur gave a highly reactive intermediate (**21**; R = Me) which reacted with a diene to give the sulfide (**22**; X = S). The sulfide may be converted to the corresponding oxide (**22**; X = O) by reaction with an epoxide ⟨84CC508, 84TL4659⟩. A similar intermediate (**21**; R = Ph) was formed by heating the sulfide (**23**) in toluene ⟨86BCJ2047, 87BCJ1558⟩. A related structure (**24**) was prepared by the reaction of the phosphonic diamide (**25**) with carbon disulfide in the presence of a base ⟨89S618, 90S137⟩. The tetrasilylphosphonium ylide (**26**) was made from a trimethyl(disilylmethylene)phosphonium ylide and $Me_2SiClCH_2SiClMe_2$ ⟨76AGE367⟩. The triazo compound (**27**; X = NMe) was prepared from 2,6,10-triazaundecane $MeNH(CH_2)_3NH(CH_2)_3NHMe$ and trisdimethylaminophosphine ⟨80JA7072⟩ as was the corresponding dioxazaphosphine (**27**; X = O) ⟨83PS(15)281⟩. Their potential for the formation of pentacoordinate phosphoranes with interesting steric restraints (e.g. (**28**)), was studied.

8.33.6.1.2 [4,3,0] Ring systems

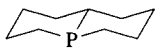
The parent saturated ring system (**30**) was synthesized by the free radical cyclization of the octadienylphosphine (**29**) (Equation (1)) and converted to the corresponding oxide, sulfide, and methiodide ⟨91ZAAC(600)195⟩. Phospholes react readily with two molecules of DMAD to give bicyclic adducts. Thus the 1,2,5-triphenylphosphole (**31**; R^1 = Ph, R^2 = H) gave the stabilized bicyclic ylide (**32**) ⟨69JCS(C)1542⟩ (a structure confirmed by x-ray diffraction in 1993 ⟨93CJC1873⟩) whereas 1-phenylphosphole (**31**; $R^1 = R^2$ = H) and its 3,4-dimethyl analogue (**31**; R^1 = H, R^2 = Me) produced the ylide (**33**; R = Me, H) ⟨78JHC1319⟩. It has been shown that deprotonation and reprotonation of 1*H*-phospholes produces 2*H*-phospholes which readily dimerize to give [2,2,1] adducts (**34**). These



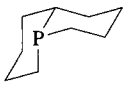
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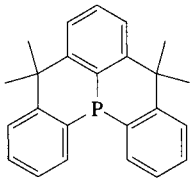
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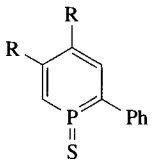
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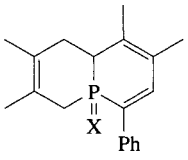
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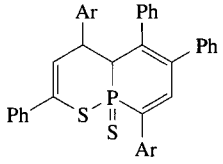
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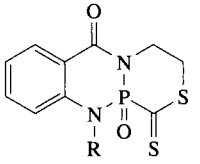
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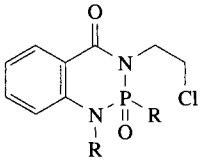
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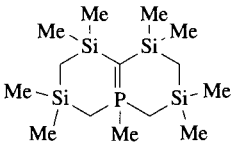
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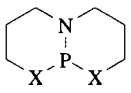
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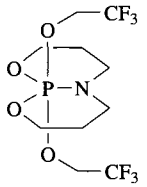
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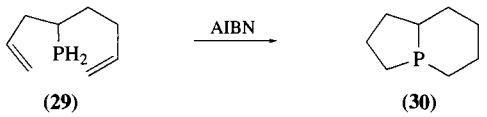


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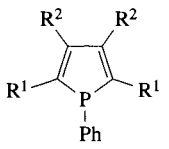
(28)

adducts at 130 °C give monomeric 2*H*-phospholes which react with dienes to give the dihydrophospholizine (8*P*-tetrahydroindene) (**35**) (Scheme 1) ⟨82CC1272⟩.

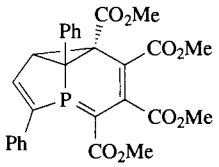


(29) (30)

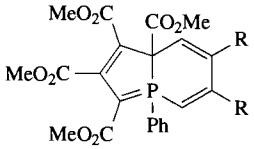
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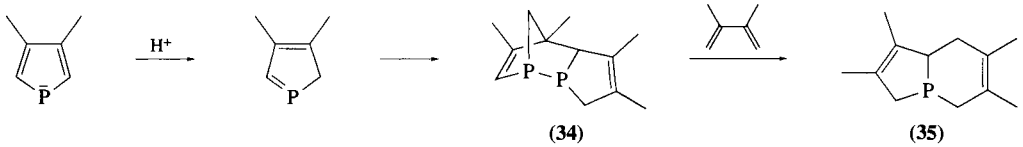
(31)



(32)



(33)

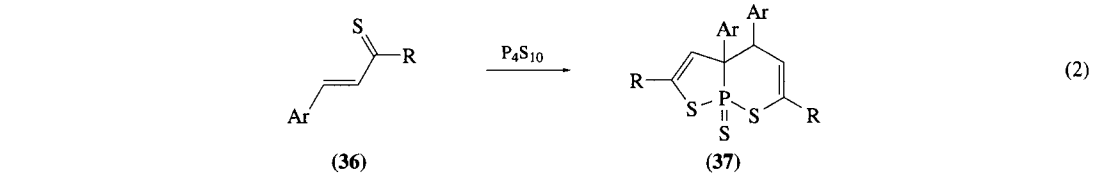


(34) (35)

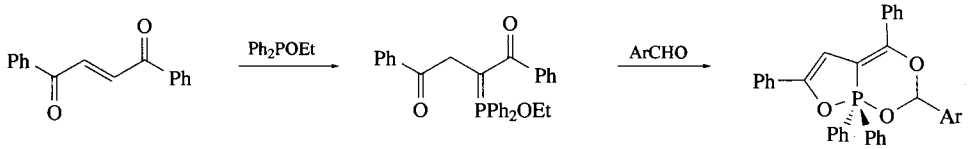
Scheme 1

The unsaturated thioketone (**36**) reacts with P_4S_{10} in the presence of triethylamine to give the unexpected product (**37**) (Equation (2)). X-ray crystallography showed that the phenyl analogue (**37**; Ar = Ph) adopts a boat conformation ⟨84BCJ1990⟩. Whilst 1,2-diketones lead directly to dioxaphosphoranes, the 1,4-unsaturated diketone took an unusual pathway before yielding the bicyclic oxaphosphorane (**38**) shown in Scheme 2 ⟨71JA5236⟩. Another unusual reaction involves two molecules of the diynol (**39**) reacting with two molecules of trihydroxymethylphosphine to give the diphospha heterocycle (**40**) (Equation (3)) ⟨74PS(4)279⟩. Depending on the substituents R^1 and

R^2, the reaction of 2-aminobenzamides (**41**; R^1 = H, $(CH_2)_nCl$; R^2 = $(CH_2)_nCl$, H) with PCl_3 followed by sodium hydride can be used to prepare either amide (**42**) or (**43**) ⟨79JHC897⟩. The dibenzobicyclic phosphonate structure (**44**) was attributed to the product from the reaction of an *o*-aminomethylphenol with tris(diethylamino)phosphine ⟨74IZV2079⟩, and the mechanism of this unusual transformation was investigated ⟨67DOK(174)846⟩. Conversion of phosphabenzenes to the reactive $\Lambda^5\sigma^3$ sulfide (**21**) led to the formation of the bicyclic dimer (**45**) ⟨90HAC37⟩. Electrophilic cyclization of a butenyl phosphorus substituent has been used to prepare the benzo analogue (**46**) ⟨81JOC361⟩. Hexafluoroacetone, diphenylchlorophosphine, and mercurous cyanide in the presence of triethylamine gives the dioxaphosphorane (**47**) ⟨86CB2687⟩. Finally the intermediacy of the bicyclic oxide (**48**) during the hydrolysis of cyclophosphamide was established by its isolation as a solid ⟨77JA5785⟩.

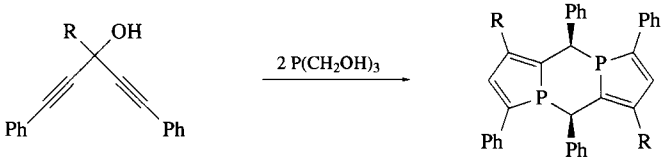


(36) (37) (2)

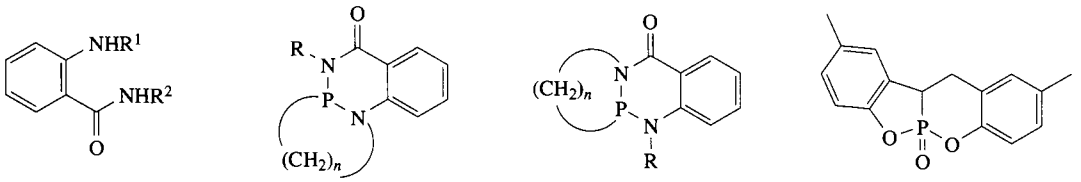


(38)

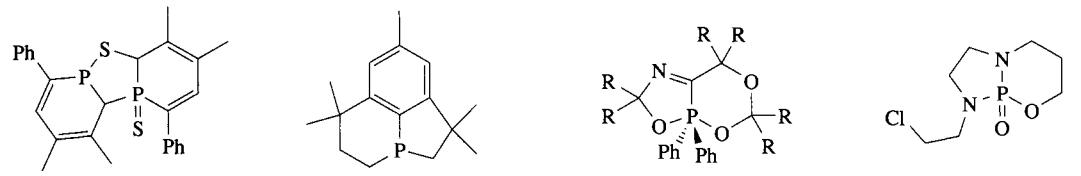
Scheme 2



(39) (40) (3)



(41) (42) (43) (44)

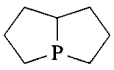


(45) (46) (47) (48)

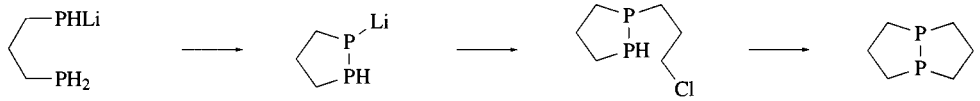
8.33.6.1.3 [3,3,0] Ring systems

Neither the parent heterocycle (**49**) nor any of its derivatives have been reported, nor have any of its dehydro forms. However many di-, tri- and multiheteroatom [3,3,0] ring systems have been characterized, most of them quite highly substituted. The simplest nonsubstituted are two perhydro compounds: the bicyclic diphosphine (**50**) and the corresponding silylphosphine (**51**). The former was synthesized by cyclization of a chloropentyldiphosphacyclopentane which was formed via the

unexpected spontaneous cyclization with loss of hydrogen as shown in Scheme 3. The diphosphine may be converted to the mono- and dioxides, sufides, and methiodides ⟨78PS(4)137⟩; their NMR ⟨77OMR(10)172⟩ and disulfide crystal structures ⟨78T1993⟩ have been reported. The bicyclic silylphosphines (**51**; R = Me, Ph) were synthesized by a more conventional route: the free radical initiated cyclization of the diallylsilylphosphines (**52**) (Equation (4)) ⟨85PS(21)367⟩.

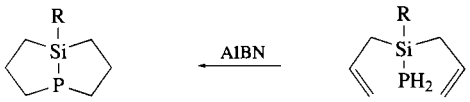


(**49**)



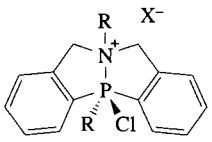
(**50**)

Scheme 3

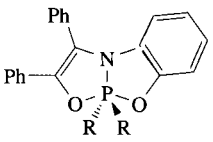


(**51**) R = Me, Ph (**52**) (4)

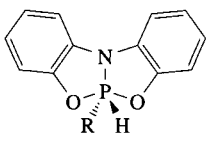
The dibenzo salts (**53**; R = Me, Ph) were formed by formation of the PN bond by the action of thionyl chloride on the aminophosphine oxides ⟨86TL5221⟩. A number of PNO_2 bicyclic compounds have been made: the pentacoordinate phosphoranes (**54**) by the reaction of iminoketones with chlorophosphines ⟨78CB2086⟩ and more recently from 2,2′-dihydroxydiphenylamine ⟨90PS(53)87⟩. Related alicyclic analogues have also been studied ⟨75PS(5)229⟩. Most interest in their chemistry lies in the structures of their pentacoordinate phosphoranes, for example, (**55**) ⟨90PS(47)215⟩ and (**54**; R = Ph) ⟨80AX(B)2316⟩, the latter also being studied by MM modeling ⟨89CC1103⟩. Two-coordinate azaphospholes react with nitrile ylides ⟨83CJC1105⟩ and with phenylcyanates ⟨81CC1131⟩ to give triaza bicyclic compounds (**56**; Z = CR_2, O). The P_2S_2 heterocycle (**57**; Z = P) obtained from the reaction of thioanisole with $PCl_3/AlCl_3$, can be converted to the PS_2 system (**57**; Z = CHR) by Friedel–Craft acylation ⟨90JCS(P1)19⟩. A variety of routes are available for the conversion of the 1,2-diphosphinobenzenes (**58**; X = H, Cl) to the dibenzotetraphosphines (**59**; R = TMS, Cl, I) (Equation (5)) ⟨87JOM(330)17⟩. The crystal structure of the diiodide (**59**; R = I) has been determined ⟨84ZN(B)139⟩. Two routes to the dioxaphosphoranes (**60**; Z = CO, CH_2) have been developed: one involving dehydration of the 2,2′-dicarboxyphenylphosphine oxide ⟨78JA5130⟩, the other from a 2,2′-di(hydroxymethyl)phenylphosphorane ⟨78CB13⟩.



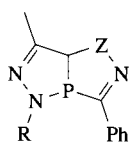
(**53**) R = Me, Ph



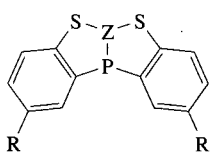
(**54**)



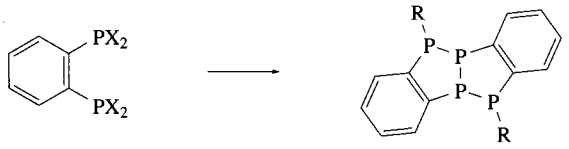
(**55**) R = OMe, NMe_2, H, Ph



(**56**) Z = CR_2, O



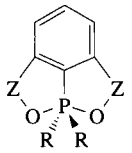
(**57**) Z = CHR, P



(58) X = H, Cl

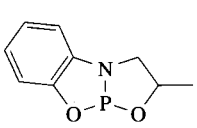
(59) R = H, Et, TMS, Bu^t, Cl, I

(5)

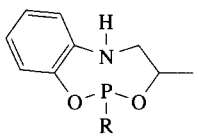


(60) Z = CO, CH_2

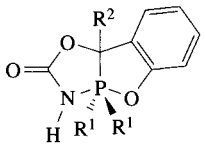
A number of monobenzo PNO_2 derivatives (**61**) have been made by cyclization of 2-aminophenol derivatives ⟨84ZOB2448⟩. Alcohols and amines convert the three-coordinate compounds into the phosphoranes ⟨82IZV1408⟩ which can undergo slow ring-chain tautomerism to give the nonbridged compound (**62**) ⟨84ZOB2448⟩. Isocyanatophosphines with salicylaldehyde or 2-trifluoroacetylphenol give the urethanes (**63**; R^1 = Ph, R^2 = H) ⟨84JGU1489⟩ and (**63**; R^1 = RO, R^2 = CF_3) ⟨92PS(66)301⟩, whereas with various 1,1,1-trifluoro-2,4-pentadiones the dehydrobicyclic compounds (**64**) are obtained ⟨89CB301, 84JGU2445⟩. An interesting reaction of a two-coordinate diazaphosphole with diazo-2-propane (Scheme 4) involves the formation of a C—C bond to give a product which upon hydrolysis gives the diazadiphosphabicyclic compound (**65**) ⟨84IZV2023⟩. The dioxaphosphorane (**66**) formed in the reaction of 2-hydroxycinnamic acid with methyl diphenylphosphonite is one of the few compounds without nitrogen in the heterocycle ⟨77CC156⟩.



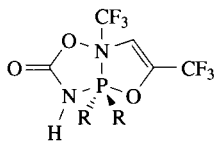
(61)



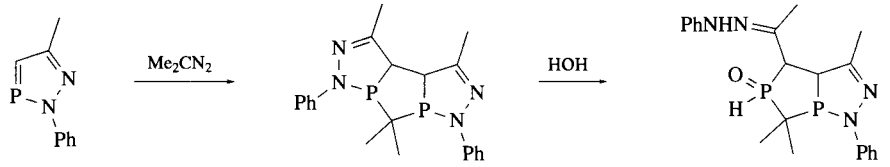
(62)



(63)

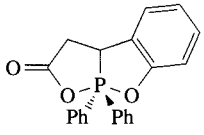


(64) R = Ph, OR



(65)

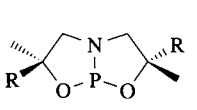
Scheme 4



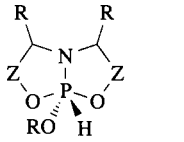
(66)

Perhydro bicyclic PNO_2 heterocycles, such as compound (**67**), have been made from diethanolamines and various phosphorus reagents: for example, $(Me_2N)_3P$ ⟨77TL3041⟩, $PhOPCl_2/Et_3N$ ⟨77AG(E)549⟩, or PCl_3/Et_3N ⟨81JCS(P2)19⟩. The compounds will oligomerize at 140 °C forming [8,3,0] ring systems ⟨83JCS(P2)773⟩ and react with alcohols to form pentacoordinate phosphoranes (**68**) ⟨92PS(69)43⟩ which are more ready to undergo ring–chain tautomerism than the corresponding benzo compounds. Bis(neopentoxy)phosphine, $(RO)_2PH$, undergoes ester exchange with diethanolamine to give the monocyclic compound (**69**) which undergoes a transannular interaction with valence expansion of phosphorus to produce the rare bicyclic phosphorane (**70**) (Equation (6)) ⟨81JCR(S)348⟩. The formation and stereochemistry of a variety of other phosphorane derivatives have also been

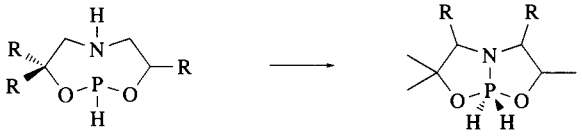
studied ⟨76OMR(8)558, 80JA5073⟩. The bicyclic phosphortriamidite (**71**) was prepared from the appropriate triamine and $(Me_2N)_3P$. It was unstable, polymerizing spontaneously, but it could be converted to a tricyclic phosphorane ⟨80JA7072⟩. The P-monooxides of the diphosphinoimides (**72**) which are formed in the reaction of silyl derivatives of *N,N*-dialkyl or *N,N*-alkylarylureas with PCl_3 ⟨83ZN(B)460⟩ form disulfides and disalts ⟨85AG(E)975⟩ but on permanganate oxidation can produce oxygen-bridged [3,3,1] bicyclic trioxides ⟨81CB2132⟩. The dithiadiphosphabicyclooctane (**73**; M = P) was prepared as shown in Equation (7). Use of $(Me_2N)_3As$ produces the arsaphosphine (**73**; M = As) ⟨82TL1345⟩. For both compounds the carbon-bound phosphorus is the more reactive nucleophilic centre. The tetrathio compound (**74**; X = Y = S) was formed in 24% yield from diphosphorustetraiodide and methanedithiol ⟨72PS(2)161⟩ and the corresponding tetraphosphine (**74**; X = P, Y = CH_2) was obtained in 55% yield from methyldichlorophosphine and 1,2-diphosphinoethane ⟨78CB3838⟩.



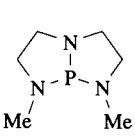
(**67**)



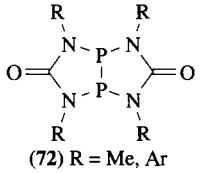
(**68**) R = Me, H; Z = CO, R



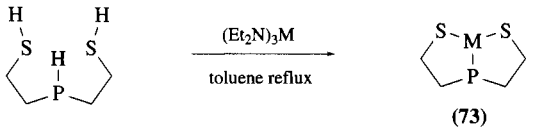
(**69**) (**70**) (6)



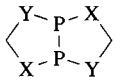
(**71**)



(**72**) R = Me, Ar



(**73**) (7)



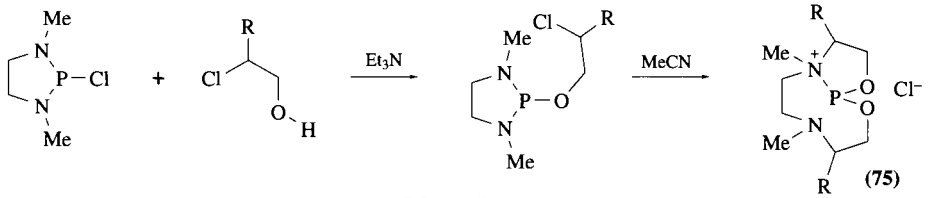
(**74**) X = Y = S
X = P, Y = CH_2

8.33.6.2 [*n*,2,0] and [*n*,1,0] Fused-ring Systems

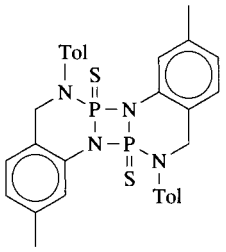
8.33.6.2.1 [6,2,0] and [4,2,0] Ring systems

The product from the reaction of chloro-1,3,2-diazaphospholan with a chlorohydrin cyclizes in acetonitrile to give a bicyclic salt (**75**) which is in a tautomeric equilibrium (see Scheme 5) ⟨77TL1583⟩. This represents another example of the transannular interactions exhibited by the phosphatranes.

The disulfide (**76**), was formed by the action of thiophosphoryl chloride on 2-amino-*N*-tolyl-benzylamine ⟨79JCS(P1)2896⟩.



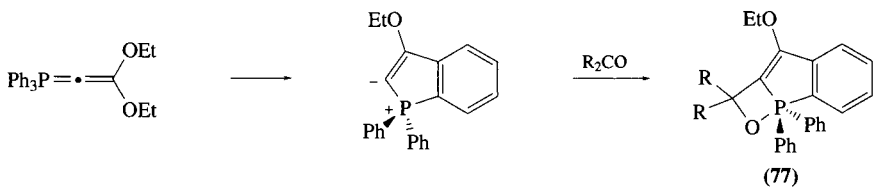
Scheme 5



(**76**)

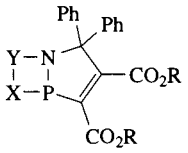
8.33.6.2.2 [3,2,0] Ring systems

The benzophosphole (**77**) has been reported as the product of the reaction shown in Scheme 6 ⟨77AG(E)877⟩. A wide range of dehydro P—N fused heterobicycles have been made, some by dimerization of, or addition to, cyclic phosphazenes formed by condensation and elimination routes. Compounds (**78**; X = O, S, NR; Y = CS, C=CPh$_2$, PXNTMS, CMeTMS) are formed in addition reactions to a five-membered phosphazene ⟨79CB3472, 80CB55⟩. P—N Bridged compounds (**79**), (**80**; Y = OR), (**81**), and (**82**) have also been formed in one step from semicarbazides ⟨76CB3581⟩, 2-azidophenols ⟨78ZOB44⟩, oxalic acid diamide ⟨70ZAAC(373)245, 72JGU520⟩, and acetohydrazide ⟨69AG(E)674⟩. Elimination of HX from phosphorane precursors has given phosphazenes which combine to produce dimers (**80**; Y = Ph) ⟨84JCS(P1)1449⟩. Three-coordinate starting material (**83**) was converted by a diaminomethane, Et$_2$NCH$_2$NEt$_2$, to bicyclic phosphorane (**80**; Y = X, CH$_2$NEt$_2$) ⟨87JGU496⟩ and two-coordinate phosphole (**84**) dimerized upon reaction with MeO$_2$CNNCO$_2$Me, to give phosphorane (**85**) ⟨81CB825⟩. Carbonyl additions to alkynic phosphines (RC≡CPX$_2$) gave oxaphosphoranes (**86**; X = MeO, Y = Z = CF$_3$) ⟨89JGU1773⟩ and (**86**; X = OCH$_2$ CH$_2$ CH$_2$O, Y = Ph, Z = CO$_2$Me/Et) ⟨90JA7451⟩ have been extended to other isocyanates. A variety of saturated [3,2,0] compounds have also been reported. The reactions of hexafluoroacetone with a vinylphosphine or isocyanates ⟨73JCS(P1)972, 86CB2687⟩ produce oxyphosphoranes (**87**) and (**88**), respectively; and a diisocyanate with an α-ketophosphonate, RCOP(O)(OEt)$_2$, gave phosphoramidate (**89**; R = CHCl$_2$) ⟨78ZOB1700⟩. Two-coordinate phospholidene (**90**), from the reaction of an amidoacetal with EtPHNHMe, dimerized to bicyclic phosphine (**91**) (Equation (8)) ⟨88JOM(355)71⟩. A series of P=N dimers (**92**) have been made from the reactions of phosphines (X$_2$P—N=C=Y), for example, isocyanates, with carbonyl compounds ⟨79JGU641, 88JGU1148⟩.

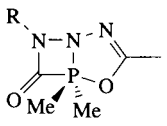


(**77**)

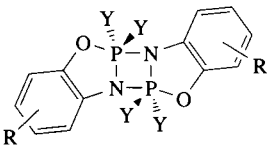
Scheme 6



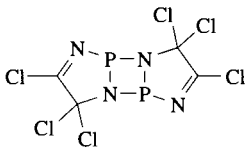
(78)



(79)



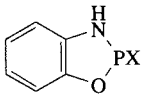
(80) Y = OR, Ph



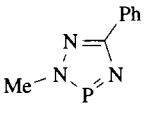
(81)



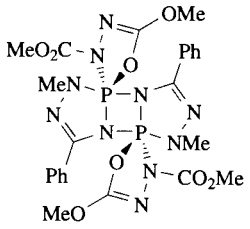
(82) X = Cl, NMe_2, Me



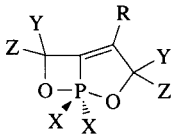
(83)



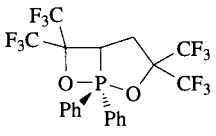
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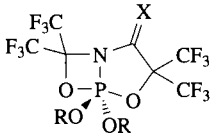
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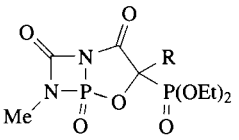
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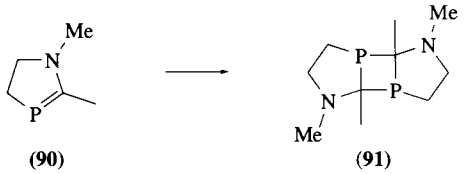
(87)



(88) X = O, S

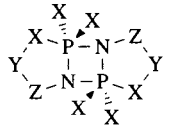


(89)



(8)

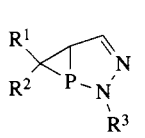
(90) (91)



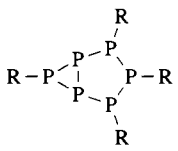
(92)

8.33.6.2.3 [3,1,0] Ring systems

The bicyclic compounds (**93**) which were prepared from various diazomethanes $R^1R^2CN_2$ and two-coordinate diazaphospholes, react with alcohols to give diazadehydrophosphorins ⟨83IZV2275⟩. The ring system is favoured by the hexaphosphines (**94**) being formed directly from Bu^tPCl_2, PCl_3, and Mg ⟨81AG(E)967⟩. Air oxidizes one of the five-membered-ring phosphorus atoms, in contrast to the [3,2,0] heptaphosphine where a bridged phosphorus atom or one of the four-membered-ring atoms is oxidized ⟨86AG(E)471⟩.



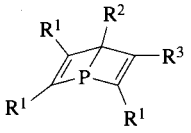
(93)



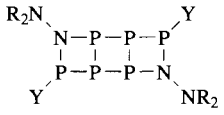
(94) R = Bu^t

8.33.6.2.4 [2,2,0] Ring systems

Low-melting bicyclic phosphine (**95**; $R^1 = R^2 = Bu^t$, $R^3 = CO_2Me$) and the sulfide of isomer (**95**; $R^1 = R^3 = Bu^t$, $R^2 = CO_2Me$) were formed in thermal rearrangements involving phosphabenzenes ⟨87AG(E)85⟩. Dimerization of a dihydrazido derivative of triphosphine, YP=P—PClY, gave the unexpected heterocyclic compound (**96**) ⟨87AG(E)1256⟩.



(**95**)



(**96**) Y = $NRNR_2$

8.33.6.2.5 [1,1,0] Ring systems

All four examples with this system possess P—P fused rings (**97**). A Wurtz-type reaction on two-coordinate halophosphine YZC=P—Hal ⟨90CB67⟩ gave YZC=P—P=CYZ which cyclized to give the diphosphine (**97**; Y = Z = CPh-TMS), whereas the disiladiphosphine (**97**; Y = Z = $SiAr_2$) was produced by the reaction of white phosphorus with a disilene. Dichlorosupermesitylphosphine, Sms-PCl_2 (Sms = supermesityl = 2,4,6-triBu^tphenyl), and dicoordinate phosphine TMS_2P—P=C-TMS gave the triphosphine (**97**; Y = C-TMS_2; Z = PSms) ⟨88AG(E)957, 88CC945⟩ and the reaction of tri-*t*-butylphenyllithium with white phosphorus gave the tetraphosphine (**97**; Y = Z = P-Sms) ⟨85AG(E)1056⟩.



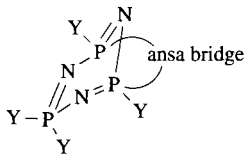
(**97**)

8.33.6.3 Non-fused Bicyclic Ring Systems

There are many examples of heterobicyclic compounds with phosphorus at the bridgehead which have one or more atoms linking the two bridges. Those compounds which have one linking atom (e.g., [3,3,1] systems) are reviewed first, followed by those with two or more.

8.33.6.3.1 [n,3,1] Ring systems where n > 3

This group of compounds consists mainly of ansa-bridged cyclophosphatriazenes (**98**). The bridging group may be as simple as aminoethanol ⟨84IC1495, 84ICAL61⟩, propanediol ⟨84CC675⟩, highly complex diphenols or diols ⟨91PS(56)133⟩, or diamines ⟨90JST(221)239⟩. An additional phosphazene bridge has been achieved using a diamino derivative of cyclophosphatriazene as a starting material ⟨76AG(E)39⟩.



(**98**)

8.33.6.3.2 [3,3,1] Ring systems

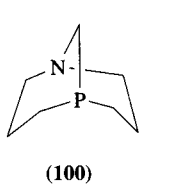
The parent 1-phosphabicyclo[3,3,1]nonane (**99**) was synthesized by Issleib's group by the AIBN-catalyzed cyclization of the phosphinodiene as shown in Equation (9). The CH deformation band (1480 cm^{-1}) in the IR spectrum indicated that the phosphine and its oxide and sulfide adopt a twin chair conformation ⟨76ZAAC(425)209⟩. An XRD study of the corresponding sulfide confirmed this conclusion and showed that the chairs were flattened to some extent, apparently by repulsions between the *endo* methylenes $r_{(CC)} = 3.2$ Å ⟨88AX(C)1435⟩.



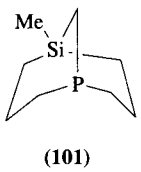
(9)

(**99**)

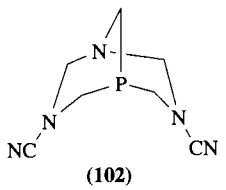
Diallylaminomethylphosphine cyclized during its preparation to give a mixture of monocyclic azaphospholan and azaphosphorin. Further cyclization of the mixture gave a mixture of [3,3,1] and [3,2,1] compounds, the former, (**100**), being characterized as its CS_2 adduct ⟨83PS(17)73⟩. The corresponding silyl analogue (**101**) was prepared by the same method ⟨82PS(13)153⟩ and was converted to its oxide either directly or via a salt ⟨87ZC295⟩. The dinitrile derivative of the corresponding triaza heterocycle (**102**) was prepared by the reaction of cyanamide with trishydroxymethylphosphine in the presence of formaldehyde ⟨73USP374584⟩. Issleib's group has synthesized the parent diphosphine (**103**) via the bis(allylphosphino)methane and converted it into a range of derivatives ⟨91ZAAC(594)66⟩. Whilst 1,5 ansa bridging of cyclophosphatetrazenes can lead to this ring system (e.g., methylamine gives phosphazene (**104**; R = Me) ⟨81PS(9)323⟩) the related heterobicycle (**105**) was prepared by the action of chlorophosphines on RC(N-TMS_2)=N-TMS ⟨88CB1681, 90PS(47)145⟩. The hexazaphosphabicyclononane (**106**) was made in two steps from $PSCl_3$ and phenylhydrazine followed by reaction with formalin at 0 °C ⟨76JCS(P1)2093⟩, and several urea-based heterocycles (**107**; Y = CH_2) were made from bis(dichlorophosphino)methane and silyl derivatives of urea ⟨85ZN(B)1532⟩. Related oxygen-bridged compounds (**107**; Y = O) were produced from four-membered diazaphosphetans ⟨80CB1847⟩ or from *spiro* analogues ⟨86ZN(B)207⟩. In contrast to aliphatic aldehydes, aromatic aldehydes reacted with dihydroxyalkylphosphine (**108**) to give the dioxabicyclophosphine (**109**) (Equation (10)) ⟨80ZAAC(471)155⟩. Simply heating phosphorus trichloride and ethylamine in tetrachloroethane gave a 40% yield of the crystalline pentaazatetraphosphabicyclo[3,3,1]nonane (**110**) ⟨83JCS(D)425⟩.



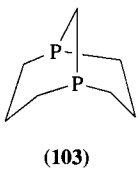
(**100**)



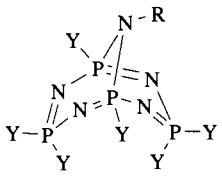
(**101**)



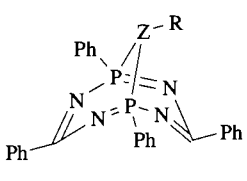
(**102**)



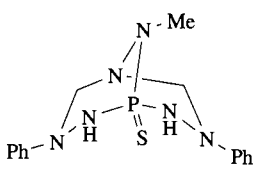
(**103**)



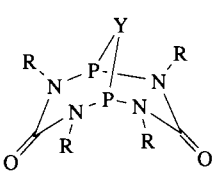
(**104**)



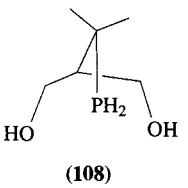
(**105**)



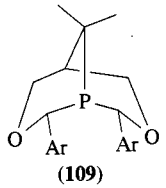
(**106**)



(**107**) Y = CH_2, O

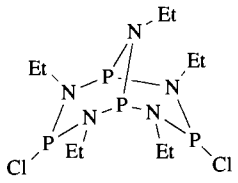


(**108**)



(**109**)

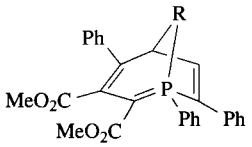
(10)



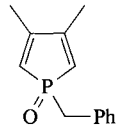
(110)

8.33.6.3.3 [3,2,1] Ring systems

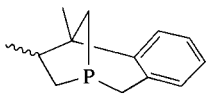
Ring expansion of an ylidic phosphole followed by cycloaddition of an alkynic ester to the resultant phosphine gave heterocyclic ylide (**111**) ⟨85TL531⟩. Dihydrophosphole (**112**) underwent electrophilic cyclization with aluminum chloride to give one isomer of an oxide which was reduced to the corresponding phosphine (**113**), which in turn could be alkylated to give phosphonium salts ⟨82TL2529⟩. Issleib's group has also synthesized the parent 1-aza-5-phospha[3,2,1]bicyclooctane (**114**) as shown in Scheme 7. Whilst sulfur attacked the phosphorus atom as expected, methylation occurred at nitrogen ⟨85ZAAC(523)7⟩.



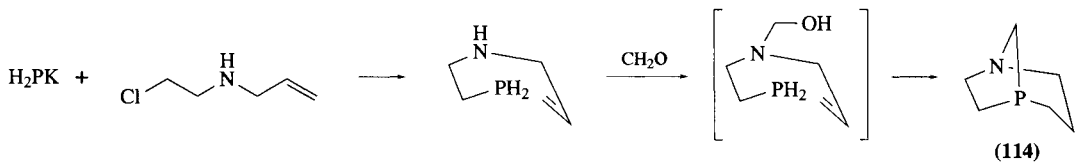
(111) R = fluorenyl



(112)



(113)



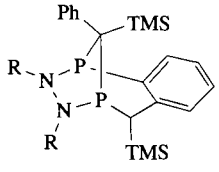
(114)

Scheme 7

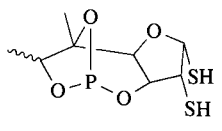
Two equivalents of two-coordinate phosphorus in the form of ClP=CPh-TMS reacted with 1,2-dialkylhydrazines to produce the bicyclic compound (**115**) wherein one of the phenyl rings has become involved in an intramolecular cyclization ⟨82CB3610⟩. Bicyclic phosphite (**116**) was prepared from the reaction of a furanose derivative with HEPT [$(Et_2N)_3P$] ⟨77TL4125⟩.

8.33.6.3.4 [2,2,1] Ring systems

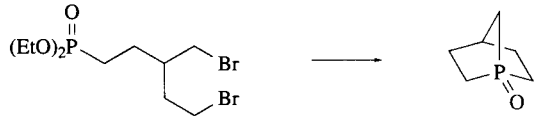
Cyclization of the dibromophosphonate (**117**) by magnesium in THF gave the P-oxide (**118**), which showed large NMR couplings from phosphorus to the bridge CH group: $J_{PH} = 28$ Hz and $J_{PC} = 35$ Hz ⟨72JA9230⟩.



(115)

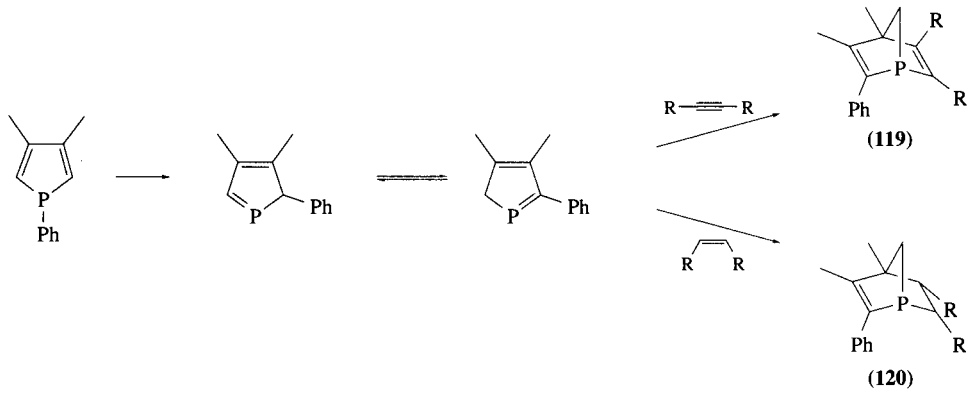


(116)



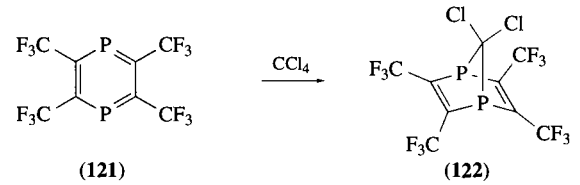
(117) (118) (11)

Cycloadditions of alkynes and alkenes to phospholes have led to bicyclic phosphines (**119**; R = Ph, CO_2R) and (**120**; Y = Ph, CO_2R), respectively, with this ring system. The reaction appears to proceed via phenyl migration to give a 2*H*-phosphole which tautomerizes to the isomeric 2*H*-phosphole and then undergoes 1,4-cycloaddition reactions with alkynes and arynes as shown in Scheme 8 ⟨81JA4595⟩. Tetrachloromethane reacts in an interesting way with diphosphabenzene (**121**) to give the diphosphanorbornadiene (**122**) (Equation (12)) ⟨77JA8511⟩. Another intriguing rearrangement involving loss of hydrogen is the thermal conversion of the diphosphaspiran (**123**) to the dibenzo compound (**124**) (Equation (13)) ⟨92AG(E)625⟩. Another example of initial conversion of a 1*H*-phosphole to a 2*H*-phosphole occurs when the phospholyl anion is protonated, which leads to spontaneous dimerization to the diphosphanorbornene (**125**) ⟨82TL511⟩. An equimolar mixture of the corresponding diphosphatri-*t*-butyl and triphosphadi-*t*-butyl phosphole anions reacts similarly upon protonation, giving dimer (**126**) ⟨90CC1307⟩. The heptaphosphanorbornane (**127**) was formed directly from methyldichlorophosphine, phosphorus trichloride and magnesium in 11% yield ⟨81ZAAC(473)20⟩. The reaction of bis(dichlorophosphino)methane with two equivalents of 1,2-dimethylhydrazine is reported to give the tetraaza compound (**128**) ⟨86CB2767⟩.

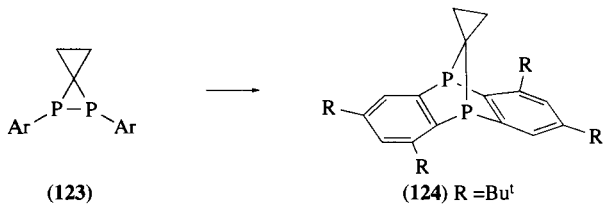


(119) (120)

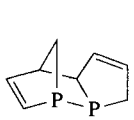
Scheme 8



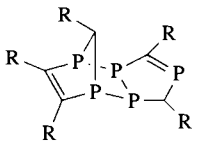
(121) (122) (12)



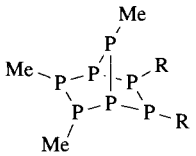
(123) (124) R =Bu^t (13)



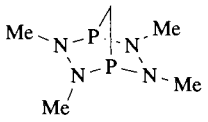
(125)



(126) R = Bu^t

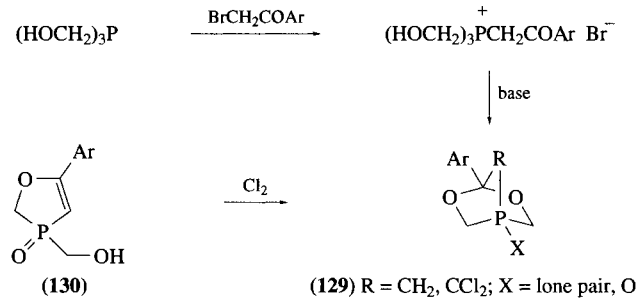


(127)



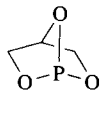
(128)

A number of oxygen heterocycles have been prepared. Scheme 9 shows an Arbuzov reaction between tris(hydroxymethyl)phosphine and α-bromoacetophenone followed by base-catalyzed cyclization to give the phosphine (**129**; R = CH_2, X = O) in 65% yield ⟨68ZOB1881⟩. Oxidation of the phosphine by hydrogen peroxide caused ring opening to give phospholene (**130**), which upon chlorination recyclizes to the bicyclic phosphine oxide (**129**; R = CCl_2) ⟨72ZOB519⟩. The phosphite (**131**) was prepared from the appropriate triol and trimethyl phosphite ⟨66TL4935⟩. Its spectroscopic properties have been studied ⟨70JMR(3)111⟩, and it was converted to its oxide by the action of N_2O_4 ⟨62JA610⟩. The trithiaphospha[4,3,0]bicyclononane (**37**) is converted to the [2,2,1] compound (**132**) upon thermolysis in the presence of acrylonitrile ⟨82TL1263⟩. The corresponding diphosphathiobicycloheptane (**133**) was made via the pyrolysis of a diphospha[2,2,2]bicyclooctadiene and trapping of the diphosphabenzene with sulfur as shown in Scheme 10 (see below) ⟨81JA2465⟩. The trithiocompound (**134**) was prepared by reduction of the corresponding diphosphine sulfide which was synthesized by heating P_4S_{10} and alkylamines at 162 °C for 10 h ⟨85ZAAC(521)153⟩. The diphosphapentaselenobicycloheptane (**135**) was isolated from an annealed amorphous glass of P_2Se_5 by extraction with carbon disulfide ⟨91AG(E)605⟩.

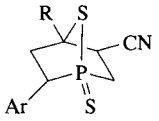


(130) (129) R = CH_2, CCl_2; X = lone pair, O

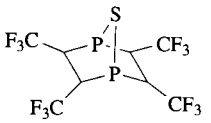
Scheme 9



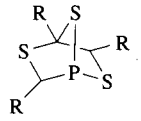
(131)



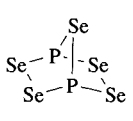
(132)



(133)



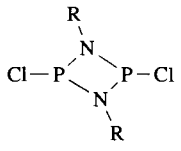
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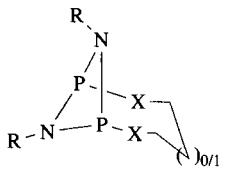
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8.33.6.3.5 [n,1,1] Ring systems

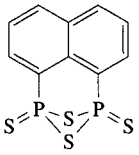
The diazadiphosphetans (**136**) react with diols and diamines to give bicyclic compounds (**137**) ⟨77AG(E)797⟩. α-Bromonaphthalene and P_4S_{10} at 240 °C give the tetrasulfide (**138**) in 25% yield ⟨87CC1741⟩ which is converted to monocyclic phosphonates by the action of methanol ⟨91CC116⟩. There is one example of a [1,1,1] ring system: the triboradiphosphabicyclopentane (**139**) ⟨87CC496⟩.



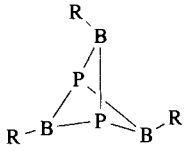
(136)



(137)



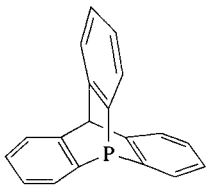
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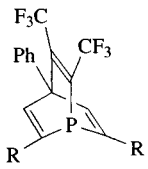
(139)

8.33.6.3.6 [2,2,2] Ring systems

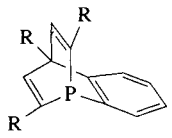
Phosphatriptycene (**140**) has been prepared by the action of LDA on 9-(2-chlorophenyl)-9-phospha-9,10-dihydroanthracene ⟨74T3465⟩. Its crystal structure has been determined ⟨80AX(B)1247⟩, and it has been converted to its oxide and the usual phosphonium salts. Phosphabenzene reacts with alkynes to give barrelene derivatives (**141**) ⟨68AG(E)733⟩ and with benzyne to give the benzo compound (**142**) ⟨71TL1249⟩. An alternative approach to this type of compound, (**143**), involved the reaction of phosphanaphthalene with an alkyne ⟨74TL4369⟩. Reaction of phosphabenzene with sulfur gives the $\sigma^3\Lambda^5$ sulfide (**21**) which reacts as a dienophile with butylvinyl ether to give the sulfide (**144**) ⟨86BCJ2047⟩. Note that the sufide (**21**) is also capable of reacting as a dienophile.



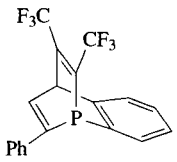
(**140**)



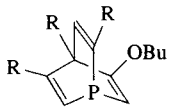
(**141**)



(**142**)

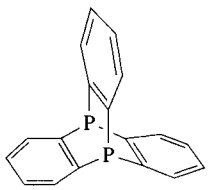


(**143**)



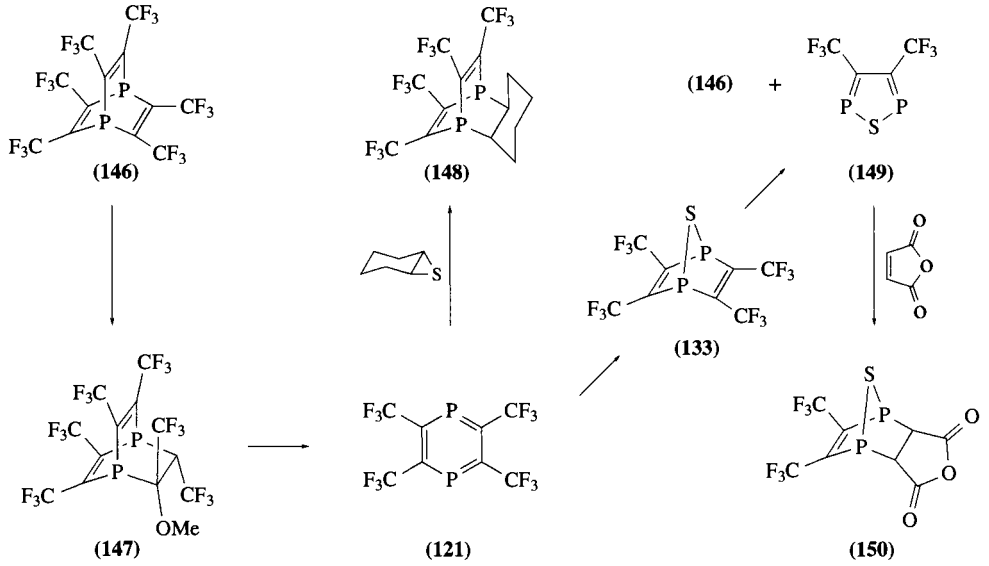
(**144**)

Diphosphatriptycene (**145**) was formed in the reaction of white phosphorus and 1,2-dichlorobenzene at 280°C with ferric chloride as a catalyst. Peracetic acid converted it to the dioxide, but benzyl chloride gave the monobenzyl salt ⟨71JA1801⟩. Hexafluorobutyne and red phosphorus heated at 200°C for 8 h with iodine as catalyst gives 43% of the diphosphabarrelene (**146**) ⟨61JA3432⟩. Treatment of this compound with rhodium trichloride in methanol gives the adduct (**147**) which, when heated at 100°C, is cleaved to the diphosphabenzene (**121**) as shown in Scheme 10. The diphosphabenzene reacts (a) with cyclohexene sulfide to give the bicyclic diphosphine (**148**), and (b) with sulfur to give the sulfur-bridged bicyclic[2,2,1]diphosphine (**133**) as described above. If excess diphosphabenzene (**121**) is present it reacts with diphosphine (**133**) to give an adduct which dissociates to diphosphabarrelene (**146**) and diphosphene (**149**), the latter undergoing a cycloaddition reaction with maleic anhydride to give adduct (**150**) (see Scheme 10) ⟨81JA2465⟩. The high-melting parent diphosphabicyclo[2,2,2]octane (**151**) was synthesized in 1959 by Hinton *et al.* and converted to its dioxide, disulfide, and dimethiodide ⟨59JCS2835⟩. Its benzo analogue (**152**) was synthesized by Issleib *et al.* by the reaction of the disodium salt of 1,2-diphosphinobenzene with 1,2-dihaloethanes ⟨86SRI446⟩.

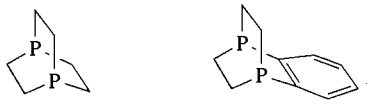


(**145**)

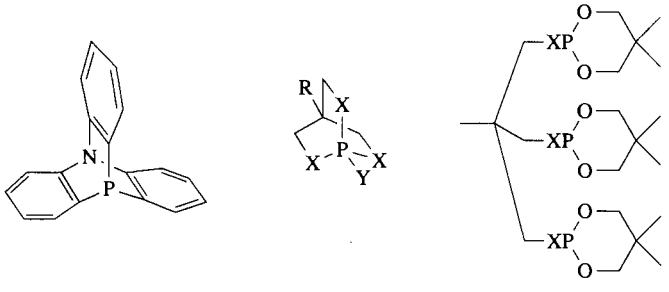
There are a number of bicyclo[2,2,2]octanes which include other heteroatoms in the ring system, notably the 9-aza-10-phosphatriptycene (**153**) which was synthesized by Hellwinkel and Schenk via the reaction of triphenyl phosphite with the 2,2′,2″-trilithium derivative of triphenylamine ⟨69AG(E)987⟩. The triaza- and trioxa-bicyclo[2,2,2]octane ring systems (**154**; X = NR, O) have been extensively studied, especially by Verkade and his coworkers. Whilst this series of compounds is available directly from the reactions of triols and triamines with various phosphorus compounds such as triethyl phosphite ⟨81PS(10)27⟩, high yields of the bicyclic compounds have been reported using the trisamidite and trisphosphite (**155**; X = NMe, O) as intermediates ⟨84PS(21)111⟩. The mass spectra of the phosphites, for example (**154**; X = O, Y = lone pair), was characterized by loss of CH_2O whereas the corresponding phosphates (**154**; X = Y = O) fragmented with loss of C_2H_4 ⟨79OMS(14)459⟩. The tristhiophosphite and its thiophosphate (**154**; X = S) have been investigated ⟨68IC1469⟩ and there is one example of an azadioxaphosphabicyclo[2,2,2]octane, (**156**), which was prepared by the cyclization of a 5-chloromethyl-1,3,2-dioxaphosphorin (**157**) (Equation (14)) ⟨83S445⟩. The phosphites form stable ozone adducts ⟨70CC956⟩ as well as phosphazenes ⟨74AG(E)543⟩, and phosphite (**154**; R = Bu^t, X = O, Y = lone pair) was converted to the corresponding phosphate by sulfuryl chloride ⟨80PS(8)315⟩. The mass spectra ⟨80PS(8)315, 83IJM459⟩ and the vibrational spectra

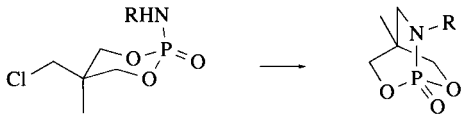


Scheme 10

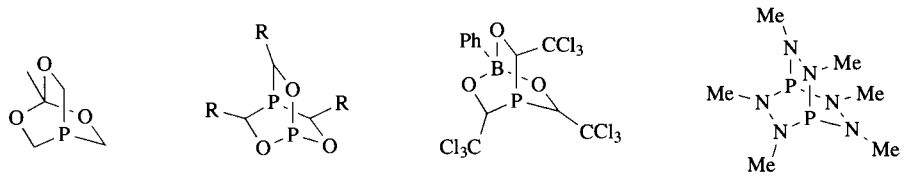


⟨69CR(C)236⟩ of the phosphites and corresponding phosphates ⟨70BSF876⟩ have been studied. The phosphates have been studied by XRD, and the hydrolysis of the phosphate and thiophosphate have been investigated ⟨86JA6311⟩; the formation of pentacoordinate derivatives required the use of pentaethoxyphosphorane ⟨84JA7825⟩. The synthesis of similar [3,2,2] ring systems with potential for phosphorane formation has also been investigated ⟨91IC1330⟩. The silyl derivatives of triols and trimethyl orthoacetate have been used to synthesize the isomeric phosphines (**158**) ⟨80ZOB1499⟩. The PE spectra of the phosphite (**154**; X = O, Y = lone pair) and isomeric phosphines (**158**) have been compared and the first band found to have more phosphorus character than oxygen character ⟨78CC161⟩. The corresponding diphosphorus ring systems (**159**; R = H) were made (35%) by the reaction of tris(hydroxymethyl)phosphine with trimethyl phosphite, converted to the dioxide ⟨65IC1655⟩ and their NMR spectra studied ⟨70JA71⟩. Trishydroxyalkylphosphines produced by the reaction of PH_3 with aldehydes have been converted to the diphospha ring system (**159**) using PCl_3 and Et_3N ⟨85ZOB2218⟩ and to the phenylborane compound (**160**) ⟨89MI 833-01⟩. When the second bridge atom is an electron donor and the phosphorus is four-coordinate the possibility of a trans-annular interaction is possible. There was XRD evidence for this interaction when an amino group is the donor ⟨92JA3129⟩. The synthesis and reactions of the hydrazino compound (**161**) were studied ⟨72CB2637⟩, and XRD gave evidence of π-bonding ⟨71IC2591⟩. The corresponding hexastannyl compound is formed in the reaction of white phosphorus and $Me_2SnSnMe_2$ ⟨81AG(E)1029⟩.





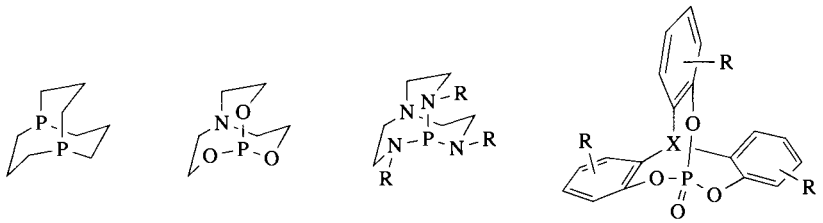
(157) (156) (14)



(158) (159) (160) (161)

8.33.6.3.7 *[3,3,3] Ring systems*

Whilst the parent system with one phosphorus atom has not been made, the diphosphabicyclo-[3,3,3]undecane (**162**) was synthesized by Hinton and Mann from tribenzylphosphine via a sequence of alkylation reactions with 1,2-dibromoethane followed by LAH debenzylation ⟨59JCS2835⟩. The diphosphine (**162**) was isolated (26%) from the product obtained by the action of AIBN on mono-allylphosphine ⟨82PS(12)227⟩. Verkade and Milbrath prepared the phosphatrane (**163**) and a very wide range of phosphorus derivatives, in low yield, from tris(hydroxyethyl)phosphine and HMTP ⟨77JA6607, 85JA7084⟩. The potential of the phosphorus atom of this ring system to support trans-annular interactions between donor and acceptor atoms at the bridgehead positions was highlighted by Buck *et al.* in 1979 ⟨79RTC12, 81MI 833-01⟩. Conversion of the phosphine oxide to alkoxy salts produced a leaving group on phosphorus which then allowed transannular bond formation to take place ⟨86JA4918⟩. The corresponding tetraazaphosphatranes (**164**) have been similarly investigated and the phosphonium salts found to be unusually stable ⟨89JA3478, 89PS(41)21⟩. The neighbouring group effects on the reactivities and spectra have been thoroughly investigated ⟨90PS(49)163⟩ and XRD comparisons made between the phosphite and triamide ring systems ⟨90IC2214⟩. The benzo analogues (**165**; X = P, N) have also been made ⟨87HCA1063⟩. They may be prepared via triols made by the reaction of phosphine (PH_3) with aldehydes ⟨85ZOB2218⟩. The NMR vicinal PP coupling constant for the parent dioxide was exceptionally large (139.1 Hz) ⟨70JA71⟩.



(162) (163) (164) (165)

8.33.7 REACTIVITY OF CONJUGATED AND NONCONJUGATED RINGS CONTAINING ARSENIC, ANTIMONY, AND BISMUTH

8.33.7.1 Fused-ring Systems

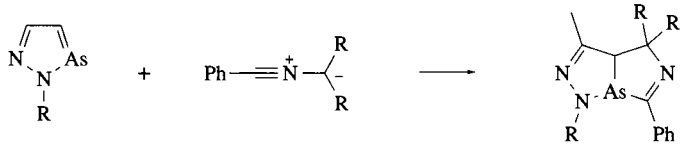
All the fused-ring compounds have additional heteroatoms in the ring system. Diels–Alder reactions of two-coordinate intermediates have been utilized to good effect. Thus the arsine (**166**), used as a dienophile with 2,3-dimethylbutadiene, gave 93% of the arsoxabicyclo[4,3,0]nonane (**167**) (Equation (15)) ⟨83TL5481⟩. On the other hand, the diazaarsine (**168**) was used as a diene in its reaction with a nitrile ylide (**169**) to give the [3,3,0] heterocycle (**170**) (Equation (16)) ⟨83CJC1105⟩. The potential for transannular interactions between an electron donor and all three elements in [3,3,0] ring systems was noted from studies of the heterocyclic octanes (**171**; X = O, S; Y = O, N;

M = As, Sb, Bi) ⟨80ZC49⟩, and the use of a secondary amine as the donor atom was shown to lead to a bicyclic ring system. Thus the diketoamine (**172**) reacted with arsenic or antimony trichloride in the presence of triethylamine at −78 °C (in a similar manner to phosphorus trichloride) to give the bicyclic products (**173**; M = As, Sb) as shown in Scheme 11. The planarity of the ring system has been interpreted in terms of the delocalized structure (**174**) shown. In contrast, bismuth trichloride gave a nine-coordinate structure in which the bismuth atom was surrounded by three bicyclic ring systems. The arsenic and antimony compounds reacted with 1,1,1,4,4,4-hexafluoro-2-butyne to give the adducts (**175**; M = As, Sb) ⟨87JA627⟩. XRD studies of dihydrothiostiboles showed that the compounds have the dimeric structure (**176**) in the solid phase ⟨91JA165⟩. Dithioethanolphosphine reacts with $(Et_2N)_3As$ to give the saturated heterocycle (**73**; M = As) as shown in Equation (7) ⟨82TL1345⟩. Several [1,1,0] di-*t*-butyl compounds (**177**; M = As, Sb; Y = As, P) were prepared from the reactions of arsenic ⟨84AG(E)379⟩ or antimony trichloride ⟨90OM1459⟩ with *t*-butyldichloroarsine or *t*-butyldichlorophosphine.



(15)

(166) (167)

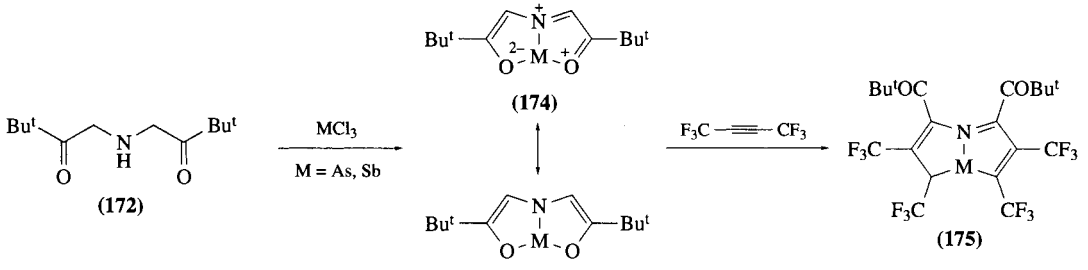


(16)

(168) (169) (170)

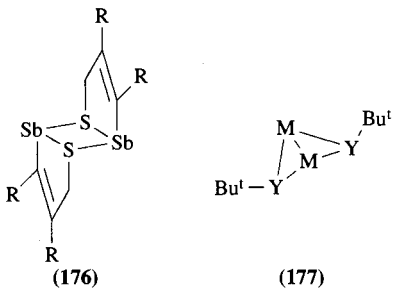


(171)



(172) (173) (174) (175)

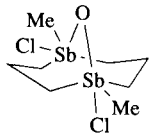
Scheme 11



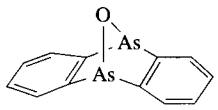
(176) (177)

8.33.7.2 Nonfused ring Systems

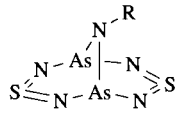
The structure of oxadistibabicyclo[3,3,1]nonane (**178**), which was prepared by the reaction of the Grignard reagent from 2,2-dimethyl-1,3-dibromopentane with methyldichlorostibine, was confirmed by XRD ⟨91RTC290⟩. The product from the reaction of partially oxidized arsenic powder and diiodotetrafluorobenzene was shown by XRD to be diarsabis(perfluorobenzo)bicyclo[2,2,1]heptane (**179**) ⟨80JFC(16)483⟩. Four-membered diazadiarsacyclobutane reacts with K_2SN_2 in hexane to produce the unusual [3,3,1] bicyclic compound (**180**) ⟨92PS(73)249⟩.



(178)

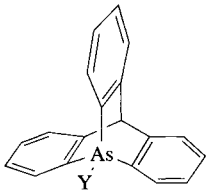


(179)

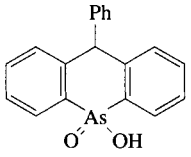


(180)

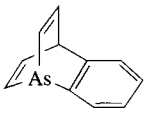
Several tri and tetraarsa adamantyl compounds have been described ⟨81ZN(B)1532⟩ together with some other related ring systems ⟨84ZN(B)1344⟩. The oxide of arsatriptycene (**181**) was prepared by the action of ppa on 10-phenyl-9-arsadihydroanthracene (**182**) ⟨62IC771⟩ and the crystal and molecular structure of the corresponding methiodide studied by XRD ⟨80AX(B)455⟩. Two-coordinate arsabenzene reacted with benzyne to give (33%) the benzo analogue of arsabarrelene (**183**) ⟨79CC880⟩. Stiba- and bismabenzenes (**184**; M = Sb, Bi) which were synthesized via stannacyclohexadienes as shown in Scheme 12, were found to be in equilibria with their dimers (**185**; M = Sb, Bi). The dimers react with hexafluorobutyne to give the corresponding barrelenes (**186**; M = Sb, Bi) (Equation (16)) ⟨82JA5693⟩. The perfluoro derivative of diarsatriptycene (**187**; M = As) can be prepared either from diiodotetrafluorobenzene and arsenic at 800 °C ⟨76JOM(112)9⟩ or by the reaction of tris(perfluorophenyl)arsine with trichloroarsine ⟨85JOM(287)57⟩. On the other hand, distibatriptycene (**187**; M = Sb) was prepared by the cyclization of an antimony phenylenemercury trimer ⟨85JOM(295)29⟩. The hexasilyl compounds (**188**; M = As, Sb, Bi) were made by reacting tetramethyldichlorosilane with mixed sodium and potassium arsenide, stibide, and bismuthide respectively ⟨88JOM(347)27⟩. The arsenite ⟨64IC884⟩ and thioarsenite analogues (**189**; X = O, S) of the much-studied phosphorus series have also been prepared. The latter was made (66%) by the reaction of the appropriate trimercaptan with hexamethylarsonotriamidite $As(NMe_2)_3$ ⟨68IC1469⟩. The mixed arsenic phosphorus compound (**190**) was prepared (61%) by the reaction of trimethyl arsenite with tris(hydroxymethyl)phosphine and converted to the phosphine oxide by dibenzoylperoxide ⟨70JOC2310⟩.



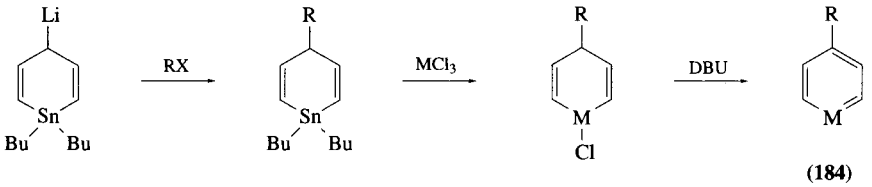
(181) Y = O, Me



(182)

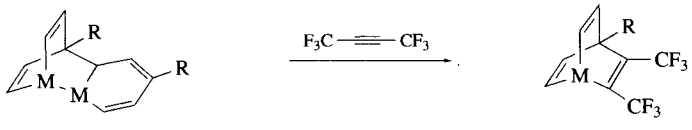


(183)



(184)

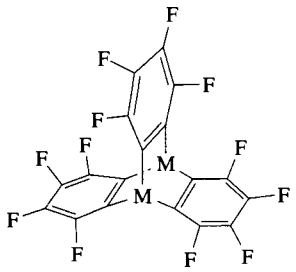
Scheme 12



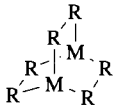
(185) M = Sb, Bi

(186)

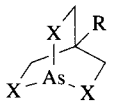
(16)



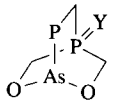
(**187**) M = As, Sb



(**188**) R = Me_2Si



(**189**)



(**190**) Y = lone pair, O

8.33.8 SYNTHETIC APPROACHES

Whilst the majority of the work described in this section involves the synthesis of cyclic phosphorus compounds, most of the chemistry could equally apply to arsenic and antimony and to a lesser extent bismuth. Most of the compounds synthesized have more than one heteroatom in the ring system, and not infrequently there are a number of heteroatoms, several of them often bound to the bridging metalloid atom, M. The methods most sucessfully applied to the synthesis of the parent and monoheterobicyclic compounds have been those involving addition and cycloaddition reactions.

8.33.8.1 MH Addition to Alkenes

The hydrides, MH_3, add to terminal C=C bonds under free radical conditions. This method has been used with some success for the synthesis of a number of the parent saturated phosphorus ring systems, by the intramolecular addition of a primary phosphine group to the terminal double bond of two alkenyl substituents. Examples are the synthesis of bicyclic phosphines (**16**), (**30**), (**50**), and (**99**). The phosphino group may be generated by reduction, e.g., LAH reduction of a phosphonate, or by alkylation of a phosphide, e.g., KPH_2. An interesting extension of this approach involves the generation of an iminium group in place of one of the alkenyl groups to synthesize the azaphosphine (**114**). Free radical-initiated reactions have been more successful than photochemical initiation.

8.33.8.2 Cycloaddition Reactions

The Diels–Alder reactions of two-coordinate metalloid compounds and their σ^3 Λ^5 derivatives have been one of the most useful applications of these compounds for the synthesis of unsaturated heterobicyclic compounds. The two-coordinate heterocycles have the potential to react as dienophiles or as dienes. As dienophiles, reaction across the M=C bond gives the possibility of synthesizing a range of fused-ring compounds. Thus dimethyl 2*H*-phosphole reacts with a diene to give [4,3,0] heterocycle (**34**) (Scheme 1). The 2*H*-phosphole, which can be kept conveniently as its dimer, was formed quite suprisingly by the protonation of the anions of the corresponding 1*H*-phosphole. A 2*H*-arsole (**166**) reacted similarly to give the [4,3,0] bicyclic heterocycle (**167**). 2*H*-Phospholes and arsoles will also react with 1,3 dipoles such as nitrile ylides and oxides, giving [3,3,0] heterocycles: for example, (**56**) and (**170**). A two-coordinate phosphole reacted with a diazoalkane to give a product indicative of a similar reaction (Scheme 4).

The σ^3 Λ^5 derivatives of phosphabenzene (e.g., sulfide (**21**)), also behave as dienophiles producing [4,4,0] heterocyclic phosphines. The only example of a two-coordinate phosphabenzene reacting across the P=C bond was its [3 + 2] reaction with its σ^3 Λ^5 sulphide to give (**45**). Phosphacyclopropanes (e.g., (**93**)), are formed in the cycloaddition reactions of diazoalkanes with two-coordinate diaza-2*H*-phospholes.

Conjugated two-coordinate phosphenes can also take on the role of a diene, the products being [2,2,1] and [2,2,2] heterocycles. The two-coordinate 2*H*-phosphole, which was used to make bicyclic compounds (**119**) and (**120**) (Scheme 8), was produced by a thermally promoted 1,2 phenyl migration from the *P*-phenylphosphole. A related product (**132**) is produced in the reaction of σ^3 Λ^5 2*H*-phosphole sulfides with acrylonitrile ⟨82TL1263⟩. Phospha-, arsa-, stiba- and bismabenzenes behave as dienes when reacted with alkynes to produce [2,2,2] heterocycles, (e.g., (**186**)), and phos-

phabenzene regenerated from adduct (**141**) was reacted with benzyne to give phosphine (**142**). Diphosphabenzenes react in a similar manner (Scheme 10). σ^3 Λ^5 Derivatives of phosphabenzene, for example, sulfide (**21**), will also take on the role of a diene with enol ethers to give [2,2,2] heterocycles (**144**) ⟨86BCJ2047⟩. There has been one example of a [6 + 2] cycloaddition reaction which involved the reaction of a phosphacyclohexadiene with DMAD to give the ylide (**111**).

8.33.8.3 Electrophilic Reactions

The arsinic acid (**182**) in the presence of ppa cyclizes with the phenyl ring to give the arsatriptycene oxide (**181**; Y = O). The reaction of tris(perfluorophenyl)arsine with arsenic trichloride gave diarsatriptycene (**187**; M = As) in a 40% yield. Cyclization reactions which involve the generation of electrophilic metalloid centers have not been studied to any extent.

8.33.8.4 Nucleophilic Attack at the Metalloid Atom

By far the most common leaving groups at the metalloid atoms are the halogens. Halo compounds of phosphorus, arsenic, antimony, and bismuth, $MHal_3$, $RMHal_2$, and R_2MHal, are readily available and they react readily with a wide range of nucleophilic reagents such as alcohols, amines, and organometallic centers. The phosphorus pentahalides and phosphoryl/thiophosphoryl halides have been used to a lesser extent: for example, in the synthesis of (**79**), (**106**), and (**165**). A base such as a tertiary amine is usually required when alcohols and amines are employed, in order to remove HX. The heterocyclic rings invariably include oxygen and nitrogen atoms usually bound to the metalloid atom. Thus trihydric nucleophiles such as diethanolamines or the corresponding diketoamines react with metalloid trihalides to lead directly to fused-ring [3,3,0] heterocycles (e.g., (**61**) and (**174**) respectively). The corresponding reactions of trihydric alcohols have been superseded by an ester exchange method (see below). Reactions of diols and diamines with cyclophosphazenes and cyclophosphazanes have produced a variety of bicyclic [*n*,3,1] compounds such as (**98**) and (**137**).

Phenoxy and ethoxy groups have been used as leaving groups. Thus triphenyl phosphite reacts with the trilithium derivative of triphenylamine which gave phosphazatriptycene (**153**), and the Grignard reagent from dibromide (**117**) gave the [2,2,1] oxide (**118**).

8.33.8.5 Transannular Reactions

Fused-ring bicyclic compounds have been formed by transannular attack of an amino group at phosphorus either to displace a phosphorus substituent, for example, formation of the salt (**53**), or by valence expansion to produce phosphorane (**68**). In the latter case the five-coordinate metalloid atom needs to be stabilized by the presence of electronegative substituents and the formation of small rings—preferably, five-membered rings.

8.33.8.6 Nucleophilic Metalloid Reagents

A variety of phosphines, phosphides, phosphoramidites, and phosphites have been used as nucleophilic reagents. Thus diphosphabicyclooctane (**50**) was prepared by an intramolecular alkylation of a cyclic secondary diphosphine. The parent diphosphabicyclo[2,2,2]octane (**151**) was synthesized in 1959 via a sequence of alkylations by 1,2-dibromoethane starting with tribenzylphosphine, removing the benzyl groups by LAH reductions. Trishydroxymethylphosphine has been utilized in a similar manner. In this case, after nucleophilic attack by phosphorus, formaldehyde is liberated to regenerate the nucleophilic phosphorus center, for example, conversion of diynol (**39**) to diphosphine (**40**). The phosphides are generally more reactive, diphosphine (**152**) being produced by the reaction of the disodium derivative of 1,2-diphosphinobenzene with 1,2-dihaloethane. Little use has been made of the enhanced nucleophilicity of the phosphorus atom when it possesses nitrogen substituents nor the nucleophilic potential of the anions of phosphinous acids, $R_2PO(OH)$, in cyclization reactions (see, however, the next section).

8.33.8.7 Transesterification and Transamination

Reactions of phosphites and triamides such as HMTP with compounds such as triols and primary or secondary triamines have been used with considerable synthetic success to make oxa and aza derivatives of bicyclic phosphorus heterocycles. Ester exchange between bis(neopentoxy)phosphine, $(RO)_2PH$, and diethanolamine gives the monoheterocycle (**69**) which undergoes a transannular interaction with valence expansion of phosphorus to produce the phosphorane (**70**). Ester exchange via intermediate (**155**) has been found to be a superior method for the preparation of [2,2,2] phosphite (**154**; X = O). The utilization of HMPA in amide ester exchange reactions with triols and trimercaptans have been used widely for the synthesis of the phosphites (**154**; X = O, S) and azaphosphatranes (**163**). The synthesis of the corresponding tetraazaphosphatranes (**164**) as well as the [4,4,0] triamidite (**27**) were achieved likewise. The approach has also been used to make arsenic analogues.

8.33.8.8 Silane Intermediates

The silanes have been used as intermediates (e.g., R_2M-TMS), in the conversion of metalloid halides R_2MHal to their hydrides R_2MH, which are then subjected to cyclization. They have also been used as leaving groups on heteroatoms such as nitrogen in their reactions with metalloid halides to give compounds such as the amides (**107**).

8.33.8.9 Ring Closure of Substituents

This approach involves cyclization which does not involve the metalloid atom. The metalloid atom may be used either to stabilize an adjacent reactive site (e.g., the generation of an anion (an ylide)) or to activate a leaving group. Intermediate ylides have been used to form stable oxaphosphoranes (**77**), and cyclic phosphonium amides (phosphazenes) have been either dimerized or reacted with ketenes and thiocycanates to produce [3,2,0] PN heterocycles such as (**78**). Also the reaction of chalcone with ethoxydiphenylphosphine proceeds via a conjugated ylide which reacts at the γ position with the carbonyl group of an aldehyde to produce a six-membered ring. Valence expansion completes the formation of phosphorane (**38**). 2,6-Bis(hydroxymethyl)phenylphosphine oxides and 2,6-diformylphenylphosphine oxides react likewise to give phosphoranes (**60**; Z = CH_2, CO). The addition of a dihydroxyalkyl phosphine to two equivalents of benzaldehyde produces labile hydroxy groups which can be condensed with the alcoholic groups (see Equation (10)). Nitrogen anions produced by the action of sodium hydride on phosphoramidates undergo intramolecular alkylation to produce [4,3,0] and [2,2,2] bicyclic heterocycles (**48**) and (**156**), respectively. The reaction shown in Scheme 5 shows that for five-membered ring formation an anion is not necessary. Cyclization can also be achieved at sites remote from the heteroatom: c.f. the bond formation induced by LDA between C-10 and the 2′ positions of 9(2-chlorophenyl)-9-phosphadihydroanthracene to produce phosphatriptycene (**140**) and the chlorine activation of the double bond of a dihydrophosphole oxide which induced cyclization with an adjacent hydroxymethyl group to give (**129**; R = CCl_2) as shown in Scheme 9.

8.33.8.10 Replacement of Heterocyclic Atoms

Phosphorus and arsenic atoms have been introduced into monocyclic rings by the substitution of oxonium groups and tetraalkyltin (Scheme 12). However, this type of reaction does not appear to have been explored for bridgehead situations. Since many of the methods available are reliant on the presence of additional heteroatoms, reactions which substitute these atoms for carbon groups could be useful. Thus the central phosphorus atom of the dithiadiphosphine (**57**; Z = P) reacts with acetyl chloride and aluminum chloride to produce the phosphine (**57**; Z = CHMe).

8.33.8.11 Miscellaneous Reactions

White phosphorus and red phosphorus as well as arsenic powder with iodine have been found to be useful starting materials for the preparation of a number of diphosphorus and diarsenic hetero-

cycles. Of special note are the reactions with alkynes and haloarenes to give the corresponding barrelenes and triptycenes. The former have found good use for the preparation of two-coordinate intermediates which can be used in cycloaddition reactions (see Scheme 10).

8.33.9 APPLICATIONS

Phosphorus compounds and to a lesser extent arsenic compounds are used in a very wide range of applications. Biological applications include their use as pesticides, antibiotics, cancer agents, antagonists for phosphorus agonists, and for weed control. There are many industrial applications; for example, as flameproofing agents for textiles and plastics, plastic stabilizers, lubricants, surfactants, metal extractants, water softening, ligands for petroleum catalysts ⟨92MI 833-01⟩.

A range of bicyclic phosphates (**154**; X = Y = O) have been the subject of biological assessment ⟨82ABC411⟩, and a 1-hydroxmethyl derivative (**154**; X = Y = O; R = $HOCH_2$) has been patented for its herbicidal properties ⟨66USP3287448⟩. The effects of various drug pretreatments on the convulsions and cerebellar cyclic nucleotide changes induced by the 4-isopropyl compound (**154**; X = Y = O; R = Pr^i) have been studied ⟨84MI 833-01⟩. The fireproofing properties of cyanotriazaphosphabicyclononane (**102**) have been patented ⟨73USP374584⟩. The inclusion of the metaloid atom at a bridgehead position in general reduces the nucleophilicity of the lone pair of the three-coordinate compounds, and applications which rely on this type of reactivity are unlikely to appear. However, the smaller ring systems can stabilize five-coordinate compounds and as such could provide a route to some interesting rigid molecules.

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8.34
Bicyclic Systems with Ring Junction Boron Atoms

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Russian Academy of Sciences, Moscow, Russia

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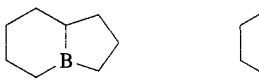
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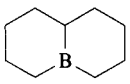
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8.34.1 INTRODUCTION

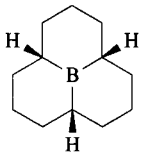
Several different groups of compounds are consistent with the title of this chapter: saturated heterocycles, unsaturated heterocycles, carboranes, etc. However, only the studies of saturated boron-containing heterocycles with ring junction boron atoms connected to three carbon atoms are discussed here (structures (**1**)–(**6**)).



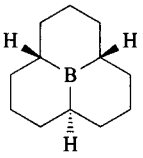
(**1**)



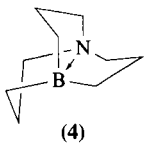
(**2**)



(**3a**)



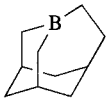
(**3b**)



(**4**)

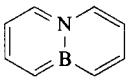


(**5**)

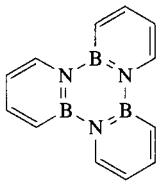


(**6**)

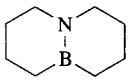
A detailed account of the chemistry of the fully conjugated rings containing boron and nitrogen was given in the first edition of *Comprehensive Heterocyclic Chemistry* ⟨84CHEC-I(1)629⟩, and systems of the type (**7**) and (**8**) are not discussed here. Also excluded are compounds of the type (**9**), i.e., heterocycles containing a noncoordinative bond between boron and another heteroatom; such compounds are only occasionally mentioned in this chapter for comparison.



(**7**)



(**8**)



(**9**)

No special review of the chemistry of boron-containing heterocycles with ring junction boron atoms has been made; however, compounds (**1**)–(**4**) ⟨77T2331⟩ and 1-boraadamantane (**5**) ⟨80MI 834-01, 83PAC1439⟩ were reviewed separately as parts of more general surveys.

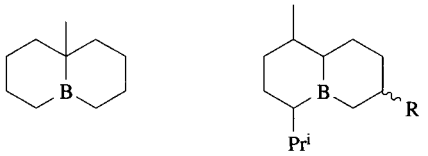
A number of books are recommended for a better understanding of the properties and reaction patterns of organoboron compounds ⟨B-73MI 834-01, B-75MI 834-01, 79COC(3)689, B-81MI 834-01, 84HOU(13,3c)215, B-84MI 834-01, B-88MI 834-01⟩.

8.34.2 8-BORAHYDRINDANE AND 9-BORADECALINS

8.34.2.1 Thermodynamics, Theoretical Methods, and Experimental Structural Methods

Five compounds in this series are mentioned in the literature: 8-borahydrindane (**1**), 9-boradecalin (**2**), 10-methyl-9-boradecalin (**10**), and two 10-methyl-2-isopropyl-9-boradecalins (**11a,b**). However, only 9-boradecalin (**2**) was isolated in the pure state; b.p. 102–103 °C (100 mm Hg), n_D^{20} 1.4792, d_4^{20}

0.8684 ⟨65LA(682)21⟩. Compounds (**1**), (**10**), and (**11a,b**) were prepared *in situ* and used for further transformations ⟨B-64MI 834-01, 65LA(682)21, 81T2441, 85JOC520⟩.



(**10**)

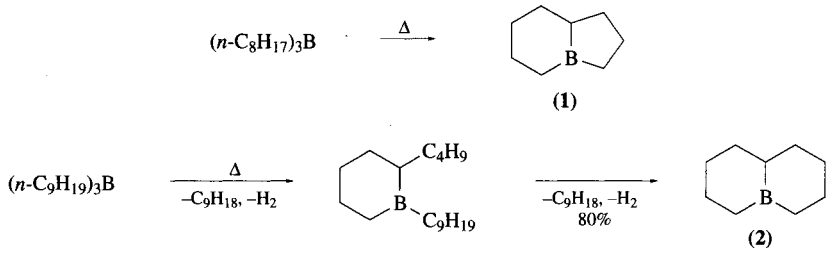
(**11a**) R = H
(**11b**) R = Me

No thermochemical or structural data are known for compounds (**1**), (**2**), (**10**), and (**11**), nor were any theoretical calculations done. The ^{1}H NMR spectrum of (**2**) (60 MHz) was described as "multiplet at 0.5–2.3 ppm" ⟨85JOC520⟩; ^{13}C and ^{11}B NMR spectra are unknown for any of the compounds (**1**), (**2**), (**10**), and (**11**).

Compounds (**1**), (**2**), (**10**), and (**11**) are extremely air-sensitive; they are insoluble in water and soluble in hydrocarbons and chlorinated hydrocarbons.

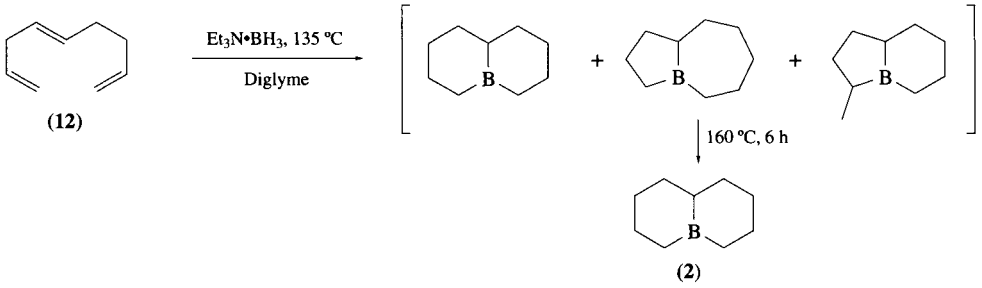
8.34.2.2 Synthesis

Pyrolysis of trialkylboranes containing alkyl groups with eight and more carbon atoms leads to bicyclic boranes. This reaction provides an approach to the synthesis of 8-borahydrindane (**1**) from trioctylborane and of 9-boradecalin (**2**) from trinonylborane (Scheme 1) ⟨60AG563, B-64MI 834-01, 65LA(682)21⟩. Synthesis of 8-borahydrindane (**1**) is complicated by side reactions ⟨B-64MI 834-01⟩.



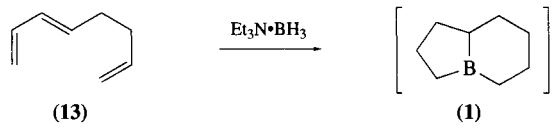
Scheme 1

Another method of the synthesis of bicyclic boranes (**1**), (**2**), (**10**), and (**11**) involves hydroboration of trienes. Thus, the hydroboration of 1,4,8-nonatriene (**12**) with triethylamine–borane at 130–140 °C in Diglyme followed by heating for 6 h at 160 °C affords isomerically pure 9-boradecalin (**2**) in 77% yield (Scheme 2) ⟨85JOC520⟩.

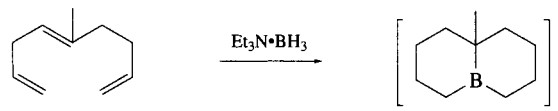


Scheme 2

8-Borahydrindane (**1**) and 10-methyl-9-boradecalin (**10**) were prepared *in situ* by hydroboration of 1,3,7-octatriene (**13**) and 5-methyl-1,4,8-nonatriene (**14**), respectively (Equations (1) and (2)) ⟨85JOC520⟩.



(13) (1) (1)

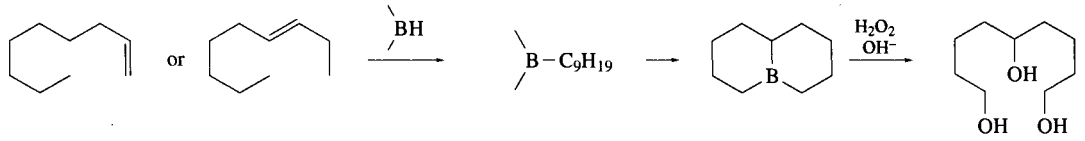


(14) (10) (2)

8.34.2.3 Reactivity

8.34.2.3.1 Oxidation

Oxidation of bicyclic borane (**2**) with hydrogen peroxide in the presence of base leads to 1,5,9-nonanetriol (**15**) (Scheme 3) ⟨B-64MI 834-01, 65LA(682)21⟩. It should be stressed that the combination of the three consequent reactions (hydroboration–pyrolysis–deboration) results in a unique approach for the transformation of monoalkenes to organic compounds containing three functional groups. Thus, a mixture of nonenes can be converted to 1,5,9-nonanetriol (**15**).

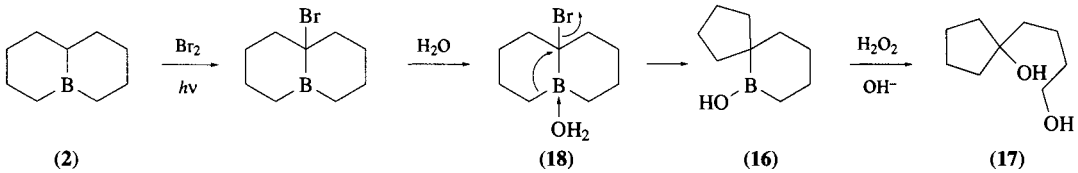


(2) (15)

Scheme 3

8.34.2.3.2 Bromination

The photochemical light-induced reaction of 9-boradecalin (**2**) with bromine in the presence of water yields 6-hydroxy-6-boraspiro[4.5]decane (**16**). The structure (**16**) was confirmed by oxidation with alkaline hydrogen peroxide, which gave 1-(4-hydroxybutyl)cyclopentanol (**17**) (Scheme 4) ⟨74JOC861⟩. It is evident that the radical α-bromination occurs selectively at the α-tertiary hydrogen atom, rather than at the α-secondary position. Under the action of water, the intermediate α-bromoborane (**18**) undergoes a rapid and facile migration of the C—B bond from boron to α-carbon, and the new C—C bond is formed (Scheme 4).



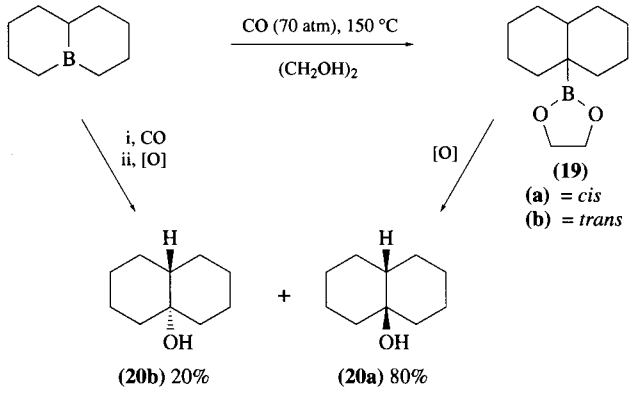
(2) (18) (16) (17)

Scheme 4

8.34.2.3.3 Carbonylation

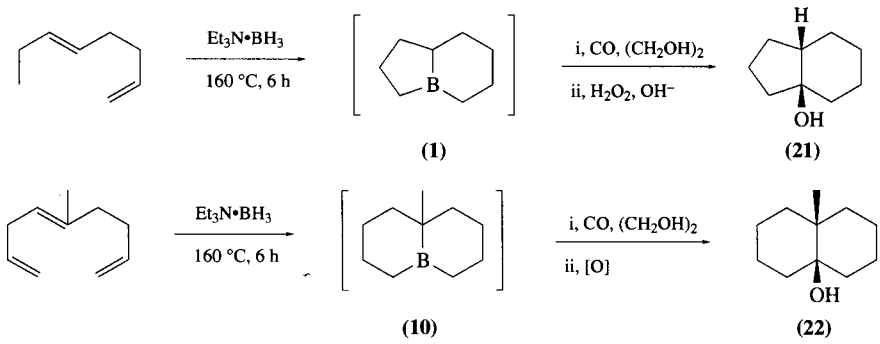
Carbonylation is a convenient method for the replacement of the boron atom in boracyclanes with a carbon atom. Carbonylation of 9-boradecalin (**2**) under 70 atm of CO (50 → 150 °C) in the presence of ethylene glycol results in a mixture of *cis*- and *trans*-2-(9-decalyl)-1,3,2-dioxaboroles

(**19a,b**) (*cis*: *trans* ~ 4 : 1) in 89% overall yield. *cis*-Isomer (**19a**) was isolated by chromatography and deboronated (H_2O_2, OH^-) to *cis*-9-decalol (**20a**) (Scheme 5) ⟨85JOC520⟩.



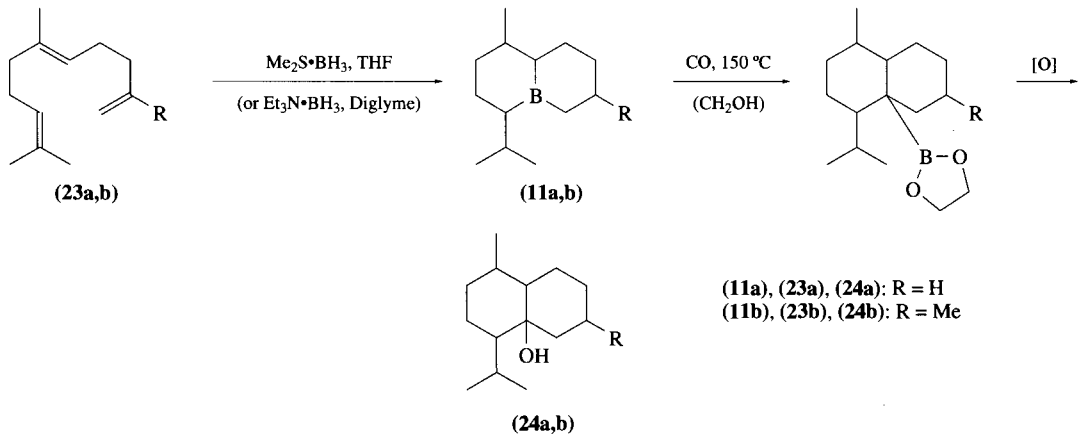
Scheme 5

Tertiary alcohols, *cis*-8-hydrindanol (**21**) (33%) and *cis*-10-methyl-9-decalol (**22**) (62%), were synthesized similarly from 8-borahydrindane (**1**) and 10-methyl-9-boradecalin (**10**), prepared *in situ* by hydroboration of 1,3,7-octatriene and 5-methyl-1,4,8-nonatriene, respectively (Scheme 6) ⟨85JOC520⟩.



Scheme 6

Bicyclic compounds (**11a**; R = H) and (**11b**; R = Me) were obtained as mixtures of stereoisomers by hydroboration of trienes (**23a,b**) with $H_3B \cdot SMe_2$ in THF or $Et_3N \cdot BH_3$ in diglyme and were transformed to the corresponding cadenane sesquiterpenes (**24a,b**) via carbonylation–oxidation (Scheme 7) ⟨81T2441⟩.

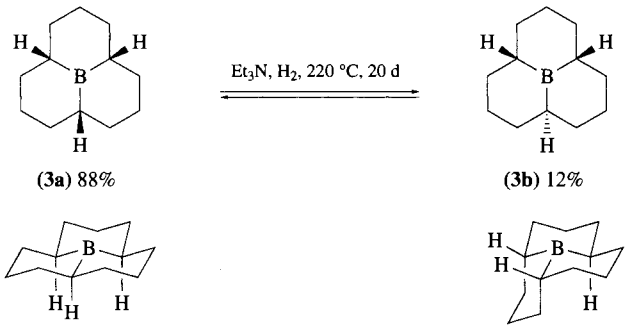


Scheme 7

8.34.3 PERHYDRO-9b-BORAPHENALENES

8.34.3.1 Thermodynamics, Theoretical Methods, and Experimental Structural Methods

Two isomers of perhydro-9b-boraphenalene are known: *all-cis*-perhydro-9b-boraphenalene (**3a**) and *cis,trans*-perhydro-9b-boraphenalene (**3b**). In the molecules of (**3a**) and (**3b**) the boron atom is imbedded in the center of a relatively rigid symmetrical circle of carbon atoms. Up to 1995 there are no conformational or structural studies of these interesting molecules. Nevertheless, taking into account the trigonal planar nature of the trivalent boron atom, approximate conformations of *cis,cis*- and *cis,trans*-perhydro-9b-boraphenalenes are shown in Scheme 8.

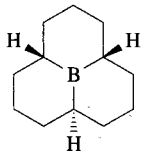
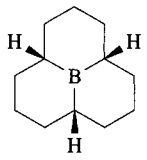


Scheme 8

cis,cis-Perhydro-9b-boraphenalene (**3a**) is a solid compound (m.p. 31 °C); the *cis,trans*-isomer (**3b**) is a moderately viscous liquid. Both isomers are thermally stable and extremely sensitive to air. They are insoluble in water, but soluble in carbon tetrachloride, benzene, carbon disulfide, or cyclohexane. The IR ⟨60JCS2922, B-64MI 834-01, 65LA(686)153⟩ and ^{1}H NMR (60 MHz) ⟨85JOC520⟩ spectra of (**3a,b**) have been described.

Both isomers form the corresponding 1 : 1 adducts with ammonia, pyridine, and piperidine ⟨60JCS2922, 65LA(686)153⟩ (see Table 1). No complexes with tetrahydrofuran, water, or triethylamine were detected ⟨60JCS2922⟩.

Table 1 Physicochemical properties of perhydro-9b-boraphenalenes and their complexes.

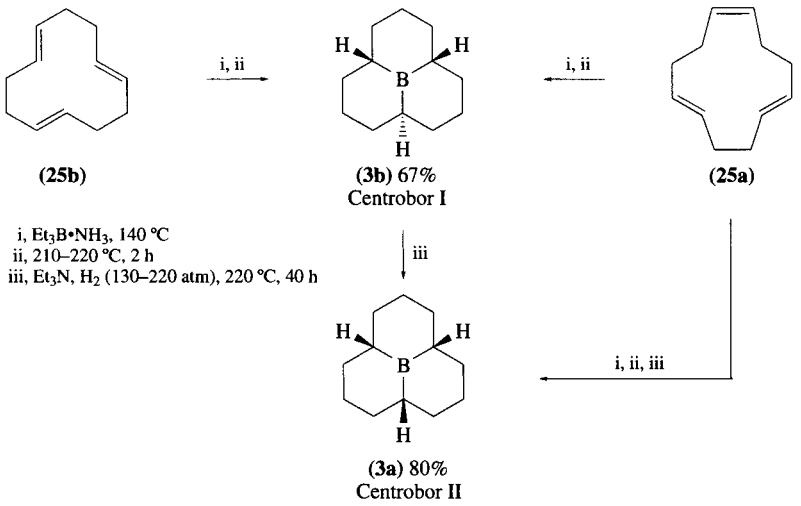
Compound	*Yield* (%)	*b.p.* (°C/mm)	*m.p.* (°C)	d_4^{35}	n_D^{35}
	57.4	115/10 55/0.1		0.9358	1.1510
(**3b**)·NH_3	97		38		
(**3b**)·Py	86	104–108/90			
	85.3		31.0	0.9221	1.5030
(**3a**)·NH_3	90		108		
(**3a**)·Py	85		80.5–82		

An equilibrium mixture containing 87% of (**3a**) and 13% of (**3b**) is formed when a pure sample of the *cis,trans*-isomer (**3b**) is heated at 220 °C in an autoclave in the presence of triethylamine and hydrogen (100 atm of H_2 at 20 °C). If the pure *all-cis*-isomer (**3a**) is subjected to the similar hydroisomerization, an equilibrium mixture of (**3a**) and (**3b**) (89% and 11%, respectively) is obtained (Scheme 8). From these data the difference between the free energies of (**3a**) and (**3b**) was found to be 1.9 ± 0.1 kcal mol^{-1} ⟨85JOC520⟩.

8.34.3.2 Synthesis

Perhydro-9b-boraphenalenes (**3a,b**) were prepared for the first time by Köster in 1957 by hydroboration of 1,5,9-dodecatriene ⟨57AG684⟩. However, the original stereochemical assignment has been reinvestigated. Koster's Centrobor I was proved to be *cis,trans*-perhydro-9b-boraphenalene (**3b**) and Centrobor II is the *cis,cis*-isomer (**3a**) ⟨85JOC520⟩.

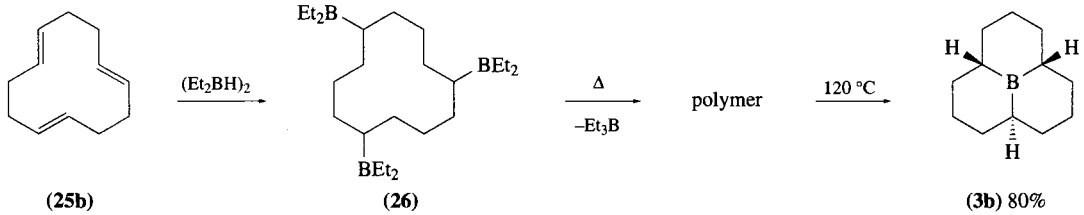
The most developed approach to *cis,trans*-perhydro-9b-boraphenalene (**3b**) consists of hydroboration of *cis,trans,trans*- or *trans,trans,trans*-1,5,9-dodecatriene with triethylamine–borane at 140 °C with subsequent heating in a sealed tube or an autoclave under nitrogen at 200–220 °C in the presence of triethylamine (Scheme 9) ⟨57AG684, 60JCS2922, 62AG329, 63AG1079, B-64MI 834-01, 65LA(686)153, 74AJC2593, 83OS(61)103, 85JOC520⟩.



Scheme 9

cis,cis-Isomer (**3a**) is obtained by thermal isomerization of (**3b**) at 210–220 °C under pressure in the presence of triethylamine and hydrogen (hydrogenation–dehydrogenation equilibria) (Scheme 9) ⟨57AG684, 62AG329, B-64MI 834-01, 85JOC520⟩. Pure *cis,cis*-perhydro-9b-boraphenalene (**3a**) can also be prepared in 70–80% yield by heating 1,5,9-cyclododecatrienes (**25a,b**) with $Et_3N \cdot BH_3$ (140–160 °C) followed by thermal treatment in an autoclave at 220 °C (40 h) in the presence of triethylamine and hydrogen (100–200 atm) ⟨B-64MI 834-01, 65LA(686)153, 74AJC2593⟩. Strict control of the experimental conditions is necessary during the preparation of *cis,cis*-perhydro-9b-boraphenalene (**3a**). The optimal temperature for the thermal treatment is 220 °C; at higher temperatures the yield of the product is reduced, reaching zero at temperatures >270 °C, probably owing to irreversible hydrogenolysis of the B—C bonds. At temperatures <190 °C a mixture of (**3a**) and (**3b**) is formed ⟨74AJC2593⟩.

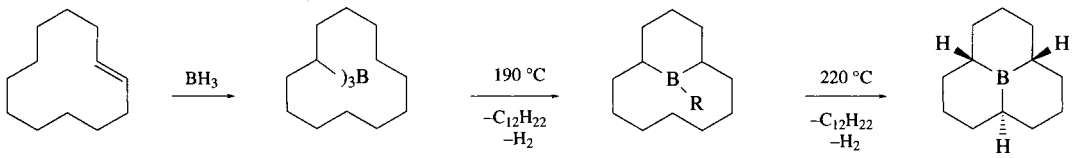
cis,trans-Perhydro-9b-boraphenalene (**3b**) can also be obtained by hydroboration of 1,5,9-dodecatriene with tetraethyldiborane (Scheme 10) ⟨61AG171, 64LA(672)1, 65LA(686)153⟩. Triboron compound (**26**) formed initially undergoes symmetrization to give triethylborane and polymer; pyrolysis of the latter gives (**3b**).



Scheme 10

Pyrolysis of tricyclododecylborane (**27**) gives B-cyclododecyl-13-borabicyclo[7.3.1]tridecane (**28**) together with a mixture of cyclododecenes. On further heating, compound (**28**) loses one mole of

hydrogen and one mole of cyclododecene giving *cis,trans*-perhydro-9b-boraphenalene (**3b**) in 70–80% yield (Scheme 11) ⟨62AG252, 65LA(682)21, 65LA(686)153⟩.



(**27**) (**28**) R = $C_{12}H_{23}$ (**3b**) 70–80%

Scheme 11

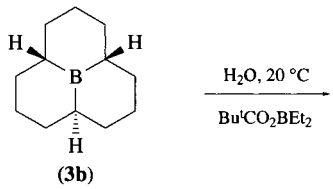
It should be mentioned that *cis,cis*-perhydro-9b-boraphenalene (**3a**) is less reactive than *cis,trans*-perhydro-9b-boraphenalene (**3b**). Thus, in contrast to (**3b**), (**3a**) does not react with water in the presence of $Bu^tCO_2BEt_2$ up to 70 °C, remains virtually unattacked by ethylene at 150–200 °C, and reacts only slowly with hydrogen under pressure. These reactions can be used for the removal of (**3b**) from (**3a**) in a mixture ⟨62AG329, 65LA(686)153, 74LA54⟩.

8.34.3.3 Reactivity

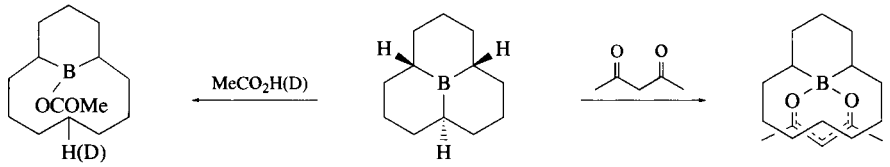
8.34.3.3.1 Protolysis: Cleavage of one B—C bond

Both isomers of perhydro-9b-boraphenalene (**3a,b**) are inert to water and probably to alcohols at ambient temperature. However in the presence of pivaloyl(diethyl)borane, *cis,trans*-perhydro-9b-boraphenalene (**3b**) reacts with water at room temperature to give anhydride, $(C_{12}H_{22}B)_2O$ (**29**) (Equation (3)) ⟨74LA54⟩.

One B—C bond of (**3b**) is also split on heating with acetic acid (or MeCOOD) at 20–80 °C ⟨65LA(686)153, 71BCJ2827⟩ or with acetylacetone (80–130 °C) ⟨65LA(686)153⟩, to form the corresponding 13-borabicyclo[7.3.1]tridecane derivatives (**30**) and (**31**), respectively (Scheme 12).



(**3b**) (**29**) (3)



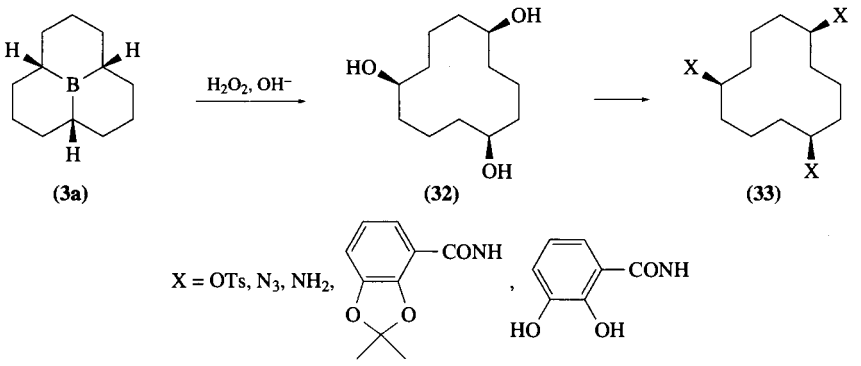
(**30**) (**3b**) (**31**)

Scheme 12

8.34.3.3.2 Oxidation

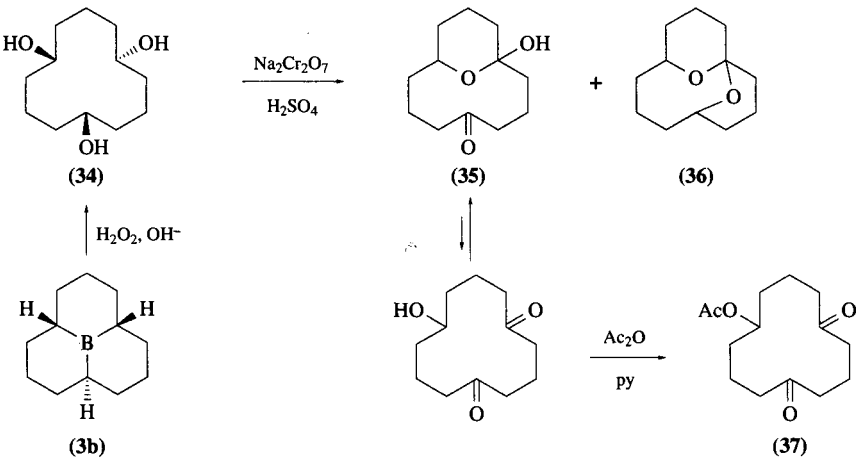
Oxidation of *cis,cis*-isomer (**3a**) with hydrogen peroxide leads to *all-cis*-cyclododecan-1,5,9-triol (**32**) ⟨65LA(686)153, 74AJC2593⟩, which was used as a starting compound for the preparation of the 1,5,9-cyclododecane derivatives (**33**) (X = OTS, N_3, NH_2, 2,3-$(HO)_2C_6H_3CONH$) (Scheme 13) ⟨65LA(686)153, 74AJC2593, 77TL3923⟩.

cis,trans-Cyclododecan-1,5,9-triol (**34**) was prepared similarly from (**3b**) ⟨60JCS2922, 65LA(686)153⟩. Transannular interaction takes place in oxidation of (**34**) with a sodium dichromate–sulfuric acid–



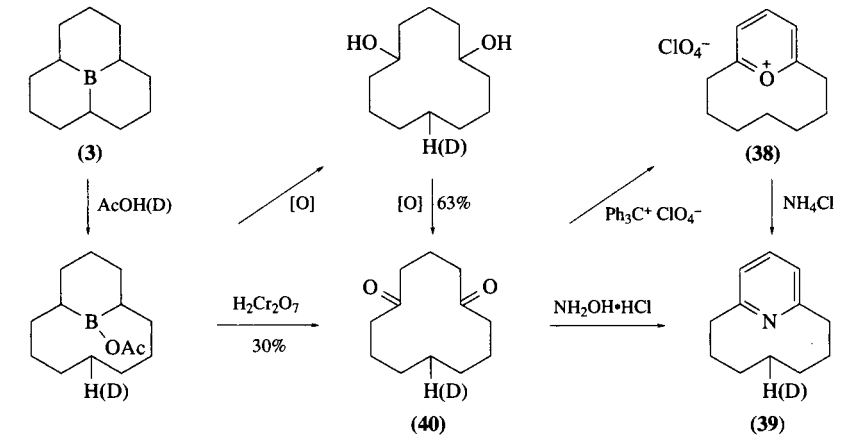
Scheme 13

ether mixture to give a hemiacetal (**35**) and an acetal (**36**) in a 43 : 57 ratio. The ratio between products was considerably changed (74 : 26) in the Cornforth oxidation (CrO_3–pyridine–H_2O) of (**34**). Acylation of a mixture of (**35**) and (**36**) led to diketone (**37**) (Scheme 14) ⟨70BCJ2995⟩.



Scheme 14

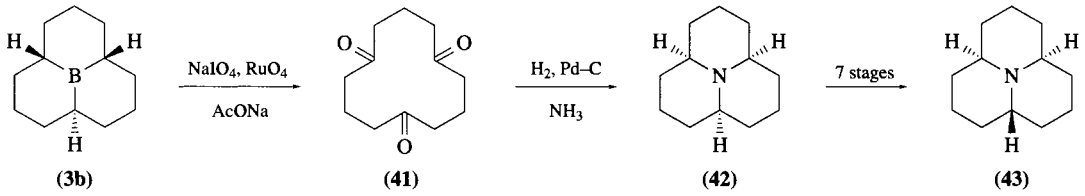
Two interesting cyclophanes (**38**) and (**39**) were synthesized from perhydro-9b-boraphenalene (**3**) (Scheme 15). Heating of 1,5-diketone (**40**) with hydroxylamine hydrochloride in ethanol for 15 h at 150–175 °C gave [7]2,6-pyridinophane (**39**) in 44% yield. 4-Deuterated pyridinophane was prepared in 42% yield in a similar way. Pyrylophanium perchlorate (**38**) was obtained by the dehydration of the 1,5-diketone accompanied by hydride elimination. Compound (**38**) was also transformed into pyridinophane (**39**) ⟨71BCJ2827⟩.



Scheme 15

Treatment of *cis,trans*-perhydro-9b-boraphenalene (**3b**) with $NaIO_4$ in the presence of ruthenium tetroxide results in triketone (**41**) (44%), which was converted to *cis,cis*-perhydro-9b-azaphenalene (**42**) by reductive amination. This compound was transformed to *cis,trans*-isomer (**43**) via seven stages (Scheme 16) ⟨75CC565, 84JOC2217⟩. In contrast, *cis,trans*-isomer (**43**) gives (**42**) (97%) on heating at 190°C for 21 h (Pd/C, H_2, Pr^iOH) ⟨84JOC2217⟩.

Aza-derivative (**43**) was also obtained via direct amination of (**3b**) (see Section 8.34.3.3.5).

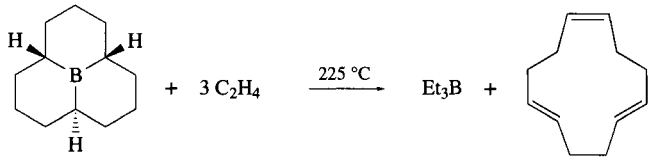


(**3b**) (**41**) (**42**) (**43**)

Scheme 16

8.34.3.3.3 Reaction with alkenes

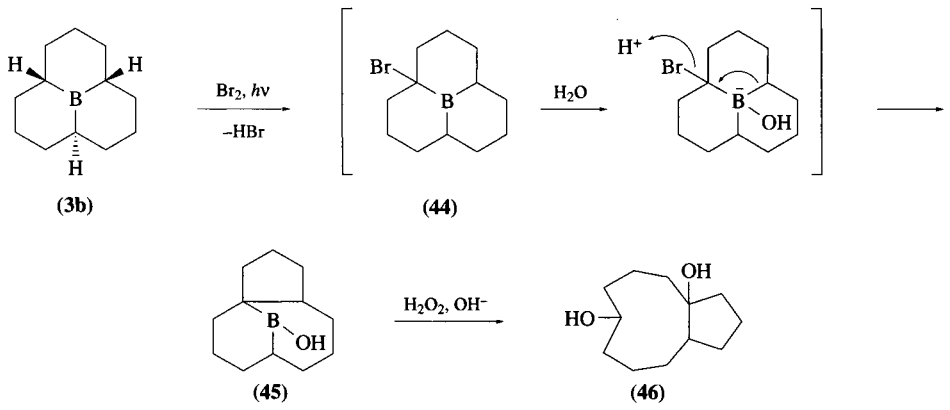
Transalkylation of *cis,trans*-perhydro-9b-boraphenalene (**3b**) takes place when it is reacted with ethylene at 220–225°C (50 atm of C_2H_4, 18 h). Triethylborane and *cis,trans,trans*-1,5,9-cyclododecatriene (**25a**) (15%) were found among the products (Equation (4)) ⟨65LA(686)153⟩.



(**3b**) (**25a**) (4)

8.34.3.3.4 Bromination

The light-induced bromination of *cis,trans*-perhydro-9b-boraphenalene (**3b**) in the presence of water proceeds selectively at the α-tertiary hydrogen atom (bromide (**44**)) to produce a polycyclic borinic acid (**45**) under the action of water. Oxidation of the latter provides bicyclo[7.3.0]dodecane-1,5-diol (**46**) in 70% yield (Scheme 17) ⟨74JOC861⟩.

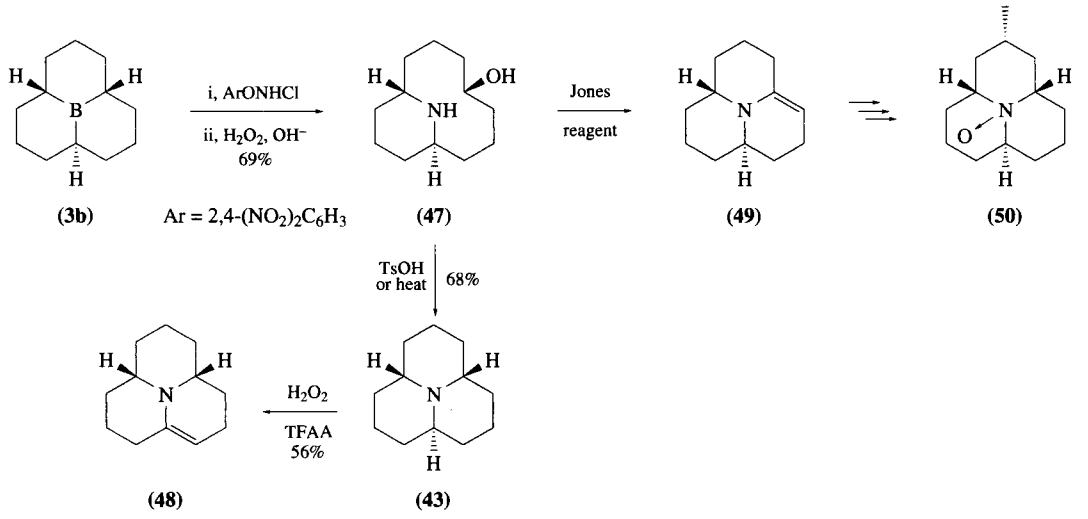


(**3b**) (**44**) (**45**) (**46**)

Scheme 17

8.34.3.3.5 Amination

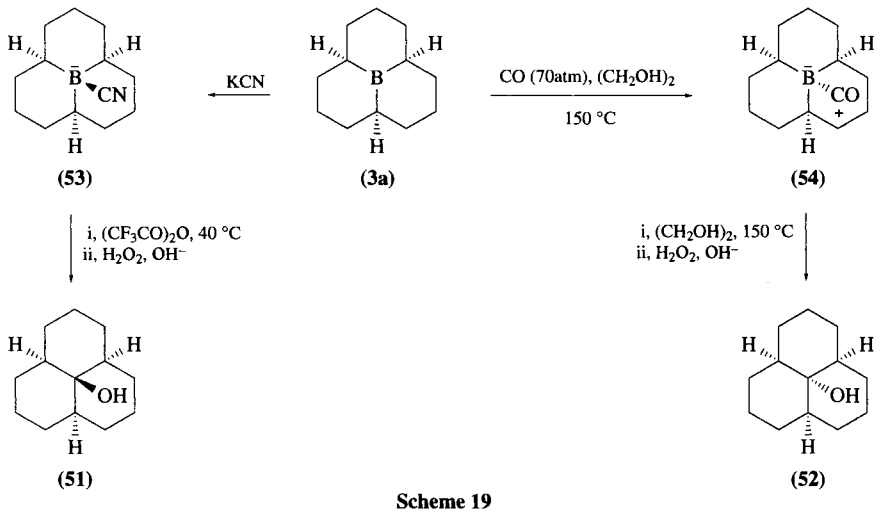
Treatment of (**3b**) with *N*-chloro-*O*-2,4-dinitrophenylhydroxylamine (generated *in situ* from *O*-2,4-dinitrophenylhydroxylamine) and subsequent oxidation of the intermediate boronic derivative resulted in *trans*-13-azabicyclo[7.3.1]tridecane-5-ol (**47**), from which perhydro-9b-azaphenalene (**43**) and unsaturated compounds (**48**) and (**49**) were prepared ⟨76TL2925, 84JOC2217⟩. In this reaction, the direct replacement of two B—C bonds by the nitrogen atom takes place. Compound (**49**) was used in the total synthesis of coccinelline (**50**) (Scheme 18) ⟨79TL1991, 80TL1093, 84JOC2217⟩.



Scheme 18

8.34.3.3.6 Carbonylation and cyanoboration

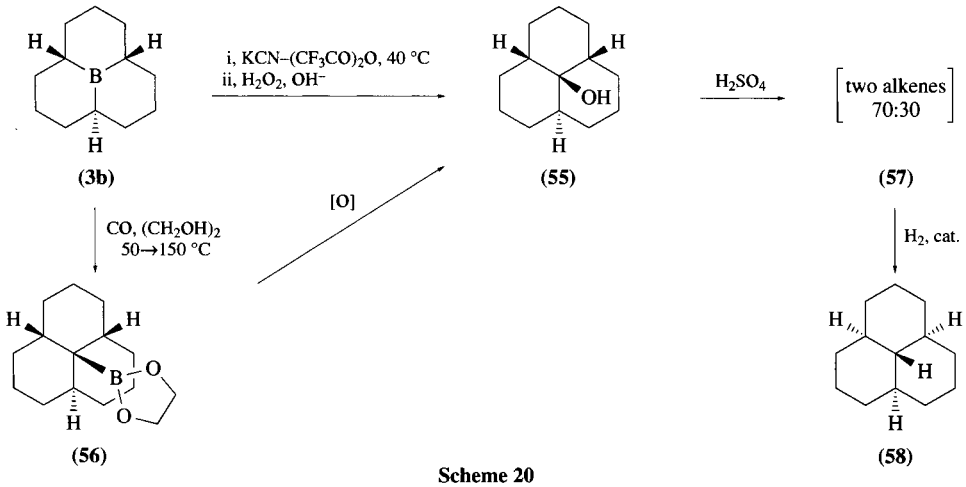
The reaction of *cis,cis*-perhydro-9b-boraphenalene (**3a**) with potassium cyanide and then with trifluoroacetic anhydride followed by oxidation gives *trans,trans,trans*-perhydrophenalene-9-ol (**51**) in 41% yield. The *cis,cis,cis*-isomer (**52**) is obtained by carbonylation–oxidation of (**3a**) (Scheme 19) ⟨78CC805⟩. The cyanoborate reaction seems to proceed through the more stable adduct (**53**), whereas the carbonylation reaction is channeled through the less stable adduct (**54**) (Scheme 19).



Scheme 19

On the other hand, the cyanoborate process applied to *cis,trans*-perhydro-9b-boraphenalene (**3b**) gives *cis,cis,trans*-perhydro-9b-phenalenol (**55**) (75%) ⟨78CC805⟩, the same product as that obtained via the carbonylation–oxidation of (**3b**) (Scheme 20) ⟨67JA5478⟩.

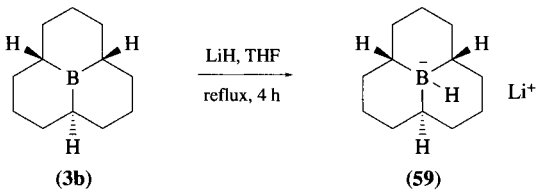
Carbonylation of *cis,trans*-perhydro-9b-boraphenalene (**3b**) in the presence of $(CH_2OH)_2$ results in the formation of essentially a single product identified as an ethylene glycol ester of the boronic acid (**56**) (90%). Oxidation of this ester produces *cis,cis,trans*-perhydro-9b-phenalenol (**55**) (70%) ⟨67JA5478, 83OS(61)103⟩. *all-trans*-Perhydrophenalene (**58**) was prepared via dehydration–hydrogenation of (**55**) via mixed alkenes (**57**) (Scheme 20).



Scheme 20

8.34.3.3.7 Reaction with metal hydrides and organometallic compounds

Finely dispersed lithium hydride readily reacts with *all-cis*- and *cis,trans*-perhydro-9b-boraphenalenes (**3a,b**) in refluxing tetrahydrofuran to give lithium perhydro-9b-boraphenalenylhydride (**59**) (Equation (5)) ⟨68LA(717)21, 70JA709⟩. Compound (**59**) is an active reducing agent which exhibits remarkably high stereoselectivity in the reduction of cyclic and bicyclic ketones (see Section 8.34.3.3.8).

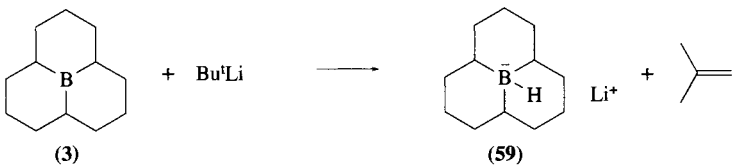


(5)

The lithium borohydride (**59**) (pair of isomers) is also obtained by the treatment of perhydro-9b-boraphenalene (**3**) with $LiAlH_4$ in diethyl ether in the presence of 1,4-diazabicyclo[2.2.2]octane (dabco). The adduct $H_3Al \cdot$ dabco precipitates quantitatively and can easily be separated by filtration or centrifugation to give a solution containing two isomers (Scheme 21) ⟨81T2359⟩.

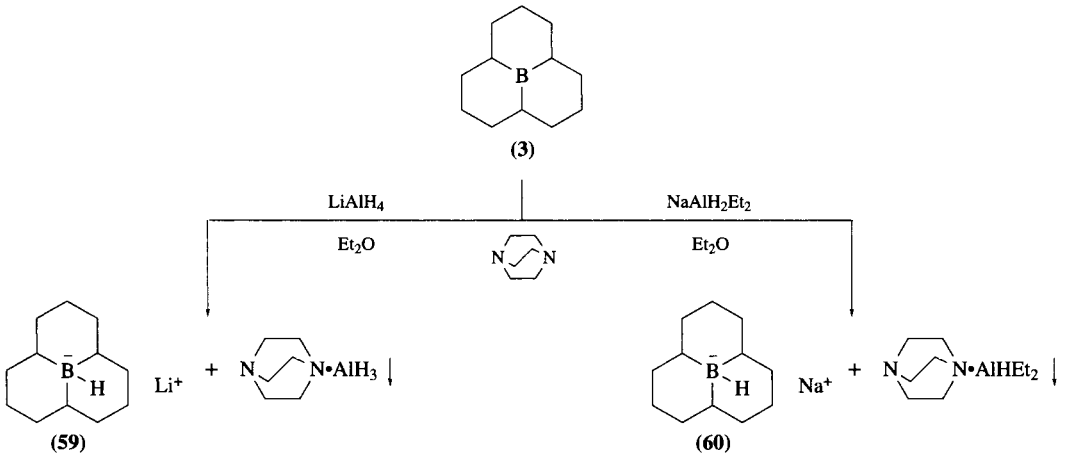
The sodium borohydride (**60**) can be prepared by interaction of (**3**) with sodium diethyldihydroaluminate, $NaAlH_2Et_2$, in the presence of dabco in toluene ⟨89CC1639⟩ or ether ⟨93T8311⟩ (Scheme 21).

Another method for the synthesis of the lithium borohydride (**59**) is the reaction of (**3**) with Bu^tLi; 2-methylpropene is the second product of the reaction (Equation (6)) ⟨80JOM(188)1⟩.



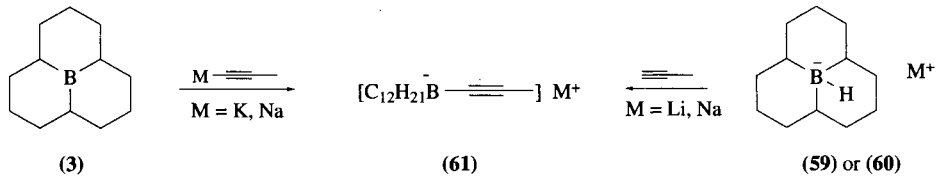
(6)

The potassium analogue of (**59**) and (**60**) is readily prepared by the treatment of perhydro-9b-boraphenalene (**3**) with potassium hydride in tetrahydrofuran at 25 °C ⟨78JOM(156)111⟩.



Scheme 21

Both isomers of perhydro-9b-boraphenalene (**3a,b**) react with sodium and potassium propynyl to form the corresponding ate-complexes, i.e., tetracoordinated anionic organoboron compounds (**61**). The latter are also prepared by the reaction of methylacetylene with the corresponding hydroborates (Scheme 22) ⟨68LA(717)21⟩.



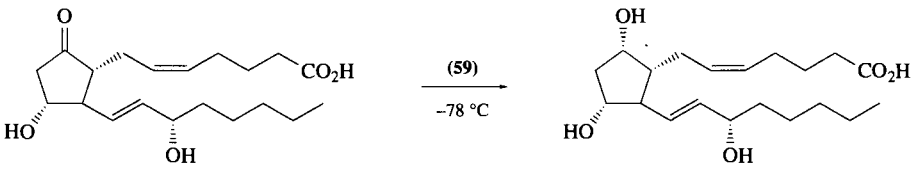
Scheme 22

8.34.3.3.8 Reduction with metal hydrides

One of the remarkable features of lithium perhydro-9b-boraphenalenylhydride (**59**) is its unusual ability to perform the steric control of the reduction of cyclic ketones ⟨70JA709⟩. Thus, 2-methylcyclopentanone gives 94% of *cis*-2-methylcyclopentanol and 2-methylcyclohexanone gives the corresponding *cis*-alcohol in 97% epimeric purity.

Predominant attack of the reagent from the equatorial direction is observed even in the case of a simple cyclohexanone containing a single substituent in the 3- or 4-position. Thus, 3-*t*-butylcyclohexanone gives 72% of the *trans* isomer as compared to only 15% with $LiAlH_4$. From 3,3,5-trimethylcyclohexanone, *trans* alcohol (99%) is obtained. In all cases, even in the reduction of the highly hindered camphor structure, the reaction is 100% complete within 0.5 h at 0 °C ⟨70JA709⟩.

The reducing agent (**59**) was used in a prostaglandin synthesis (Equation (7)) ⟨71JA7319, 73TL129, 73TL141⟩.



8.34.4 1-AZA-5-BORATRICYCLO[3.3.3.0^{1,5}]UNDECANE

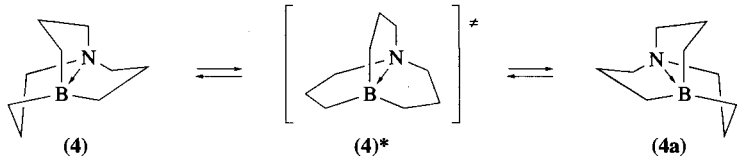
8.34.4.1 Thermodynamics, Theoretical Methods, and Experimental Structural Methods

1-Aza-5-boratricyclo[3.3.3.0^{1,5}]undecane (**4**), m.p. 123 °C, is readily soluble in organic solvents (alcohols, acetone, CCl_4, CS_2, cyclohexane) and insoluble in water, and it is steam-volatile. It has a

camphor-like smell, is stable in the air and towards peroxidic oxidizing agents (H_2O_2) ⟨64JCS4753, 85JA5901⟩.

Azaboratricycloundecane (**4**) is monomeric in the gas phase and associated in nonpolar solvents (hexameric, as estimated by the Rast method). Its vapor pressure corresponds to the equation $\log P(\text{mm}) = 8.743 - 2845/T$, from which the heat of vaporization is 13.02 kcal mol^{-1} ⟨64JCS4753⟩.

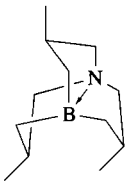
Rapid interconversion of enantiomers of (**4**) occurs at room temperature, as was shown by the NMR data. Each of the two protons of each CH_2 group is equivalent to the other. The ^1H NMR spectrum is unchanged when the temperature is decreased to −95 °C (Scheme 23) ⟨85JA5901⟩.



(**4**) (**4**)* (**4a**)

Scheme 23

According to MNDO calculations, transition state (**4**)*, in which all of the three B—C—C—C—N bridges are planar, is only 2 kcal mol^{-1} higher in energy than (**4**). Pathways involving flips of one bridge at a time would have barriers even lower than 2 kcal mol^{-1}. The low barrier to racemization indicates a substantial amount of strain in (**4**) ⟨85JA5901⟩. A barrier of 1.2 kcal mol^{-1} was calculated for (**62**) ⟨85JA5901⟩.



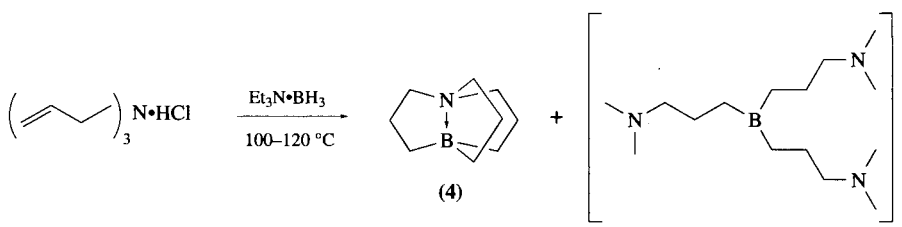
(**62**)

NMR investigations show that in the molecule of (**4**) the nitrogen atom acts as a weak Lewis base (complexes with BBr_3 and $SbCl_5$), whereas acidic properties of the boron atom were not found (compound (**4**) does not form an adduct with NH_3) ⟨85JA5901⟩.

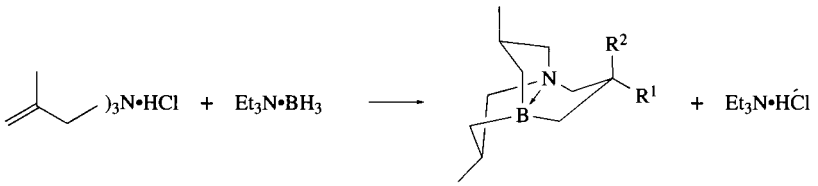
8.34.4.2 Synthesis

1-Aza-5-boratricyclo[3.3.3.$0^{1,5}$]undecane (**4**) was synthesized in 18% yield (with a polymer as a side product) by hydroboration of triallylamine hydrochloride with triethylamine–borane in light petroleum (Equation (8)) ⟨64JCS4753⟩. The yield of (**4**) was much lower when toluene was used as the solvent ⟨85JA5901⟩.

Hydroboration of tris(2-methylallyl)amine hydrochloride gave the tricyclic product (**62**) (16%) (Equation (9)). The two diastereomers of (**62**) were separated by either HPLC or GC ⟨85JA5901⟩.



(**4**) (8)



(9)

(**62a**) R^1 = H, R^2 = Me
(**62b**) R^1 = Me, R^2 = H

8.34.5 1-BORAADAMANTANES

1-Boraadamantane (**5**) is a unique compound, possessing a series of features unusual both to organoboron compounds and to other caged heterocycles. The reason for this is an uncommon geometry of the boron atom involved in the inflexible framework that leads to an additional strain in the nearest environment of the boron atom. This particular feature appears in structural and physicochemical properties of 1-boraadamantane (**5**) and its homologues, as well as in their high complexing capacity and unusually high reactivity. The latter is especially interesting, because such structurally interesting and reactive compounds as 1-boraadamantanes provide rare opportunities for the synthesis of carbon and heterocyclic caged systems, bicycles, and other compounds difficult of access. A number of the 1-boraadamantane complex compounds show pronounced antiviral activity ⟨79MI 834-01⟩.

8.34.5.1 Theoretical Methods

In 1-boraadamantane (**5**) the trivalent boron atom, which is usually trigonal (R_3B, BX_3), has a tetrahedral configuration. In this respect it resembles the 1-adamantyl cation (**63**) (Table 2); *ab initio* calculations of the latter indicate the bond angles at the carbocation center to be 117.5° ⟨79JA6163⟩. This is an intermediate value between the characteristic angles for sp^3- and sp^2-hybridized atoms. *Ab initio* calculations of the 1-boraadamantane molecule were done at the RMP2(fc)/6-31G* level of theory ⟨95UP 834-01⟩. The calculations show that 1-boraadamantane resembles the 1-adamantyl cation in similar distortion of the adamantane framework, viz. the flattening of the upper part of the molecule (Figure 1).



(**63**)

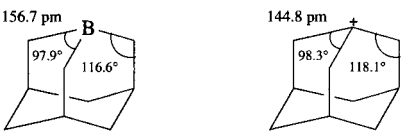


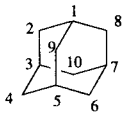
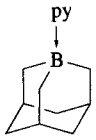
Figure 1 Comparison of calculated geometric parameters of 1-boraadamantane and adamantyl cation ⟨95UP 834-01⟩.

8.34.5.2 Experimental Structural Methods

8.34.5.2.1 X-ray analysis

Up to 1995 the attempts to determine the structure of free 1-boraadamantane by x-ray analysis have been unsuccessful, because the diffraction pattern of well-shaped crystals of the compound contain a very small number of diffuse reflections. Raman spectroscopic studies showed that at

Table 2 ^{13}C Chemical shifts (δ, ppm) for adamantane, adamantyl cation, 1-boraadamantane, and its pyridine complex.

Compound	*C-1*	*C-2,8,9*	*C-3,5,7*	*C-4,6,10*
	28.75	38.24	28.75	38.24
	298.8	64.8	85.8	32.8
		33.1	33.1	40.4
		39.7	45.1	38.5

ambient temperature the solid 1-boraadamantane (**5**) occurs as a plastic *meso*-phase with isotropic reorientations of the molecules ⟨89IZV483⟩. At 183 K (−90°C) the *meso*-phase transforms into organized crystals. Thus, the x-ray analysis of (**5**) can only be made below 183 K. X-ray analysis of the complexes of 1-boraadamantane with pyridine, quinoline ⟨81IZV595⟩, and methylenetriphenylphosphorane ⟨85IZV2483⟩ showed that introducing the tetracoordinated boron atom into the adamantane system only slightly affects the geometry of the framework.

8.34.5.2.2 NMR spectroscopy

The ^{1}H NMR spectrum of 1-boraadamantane is shown in Figure 2.

Effects similar to those observed for the 1-adamantyl cation are observed in the ^{13}C NMR spectrum of 1-boraadamantane ⟨80MI 834-01⟩ (see Table 2). A strong deshielding effect for β-carbon atoms was explained for the 1-adamantyl cation by overlapping of the reverse sides of the orbitals of the junction carbon atoms (the so-called "cage effect") ⟨64CRV277⟩.

Both naturally occurring boron isotopes, ^{11}B and ^{10}B, are appropriate for NMR measurement. However, only the former is usually studied owing to its higher degree of abundance (about 80%) and its lower nuclear spin ⟨B-78MI 834-01⟩. The ^{11}B chemical shifts of 1-boraadamantane and alkylated 1-boraadamantanes vary from 82 to 84 ppm (see Table 3), whereas for the complexes much lower values (0–30 ppm) are characteristic (see Table 4). The ^{11}B chemical shift of the complexes is indicative of their stability. Exchange of a complex compound with free triorganoborane is usually fast on the NMR timescale and only one averaged signal is observed; the more stable the complex, the lower the chemical shift. This allows the quantitative determination of the stability of the complexes of 1-boraadamantanes ⟨80MI 834-01⟩.

8.34.5.2.3 Mass spectroscopy

Fragmentation patterns of free 1-boraadamantanes are unknown. For the complexes of 1-boraadamantanes with amines, the most characteristic are $[M - H]^+$ ions formed as a result of easy hydride elimination ⟨88IZV2282⟩.

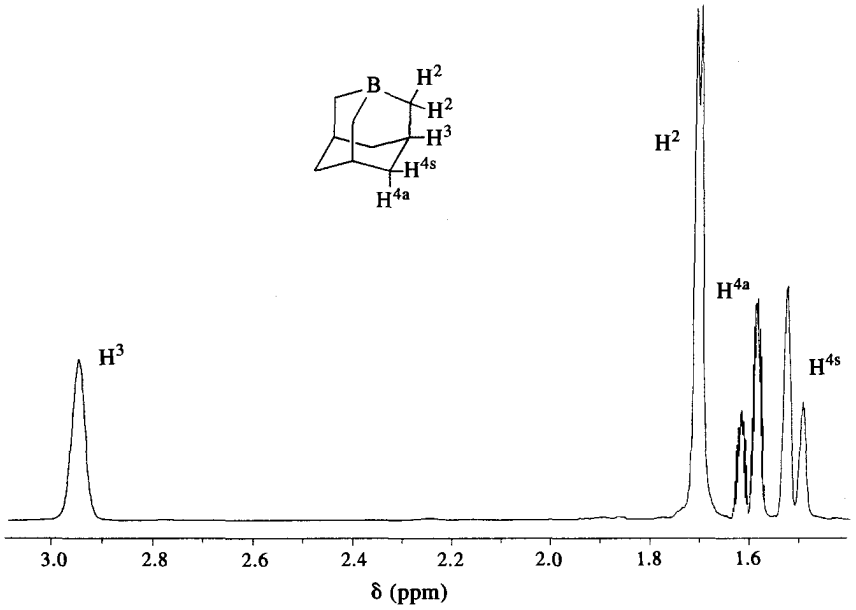


Figure 2 ^{1}H NMR spectrum of 1-boraadamantane (**5**) (400 MHz, $CDCl_3$, 25 °C).

8.34.5.3 Thermodynamic Aspects

The parent compound 1-boraadamantane (**5**) is a colorless crystalline compound readily oxidized in the air. It can be sublimed *in vacuo* to give ideal prisms (or tetrahedrons), which start to melt at 80 °C, but under further heating transforms into a glacial mass. Alkyl derivatives of 1-boraadamantane are colorless liquids flammable in air.

1-Boraadamantanes are readily soluble in chlorinated hydrocarbons (chloroform, methylene chloride, carbon tetrachloride) and in benzene. The parent 1-boraadamantane (**5**) can be recrystallized from hydrocarbons (pentane), whereas alkyl derivatives are soluble in these solvents. More polar solvents either react or give complexes with 1-boraadamantanes.

The molecule of 1-boraadamantane is highly strained owing to the unusual tetrahedral configuration of the boron atom. This additional strain manifests itself in the higher complexing ability of 1-boraadamantanes compared with other triorganoboranes. The difference in the enthalpies of formation of the complexes of 1-boraadamantane and trimethylborane with pyridine was evaluated to be 5.7 kcal mol^{-1}. This value is considered to estimate the energy of sp^2–sp^3 reorganization for the boron atom ⟨80MI 834-01⟩.

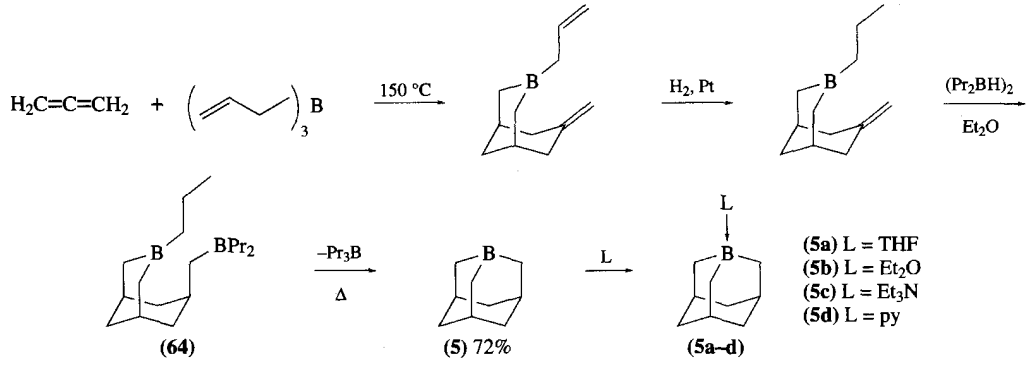
8.34.5.4 Synthesis

1-Boraadamantane (**5**) was originally synthesized in 1971 ⟨72IZV1672⟩ by hydroboration of 3-propyl-7-methylene-3-borabicyclo[3.3.1]nonane (**64**) prepared via a thermal reaction of allene with triallylborane (Scheme 24) ⟨72DOK(206)125⟩.

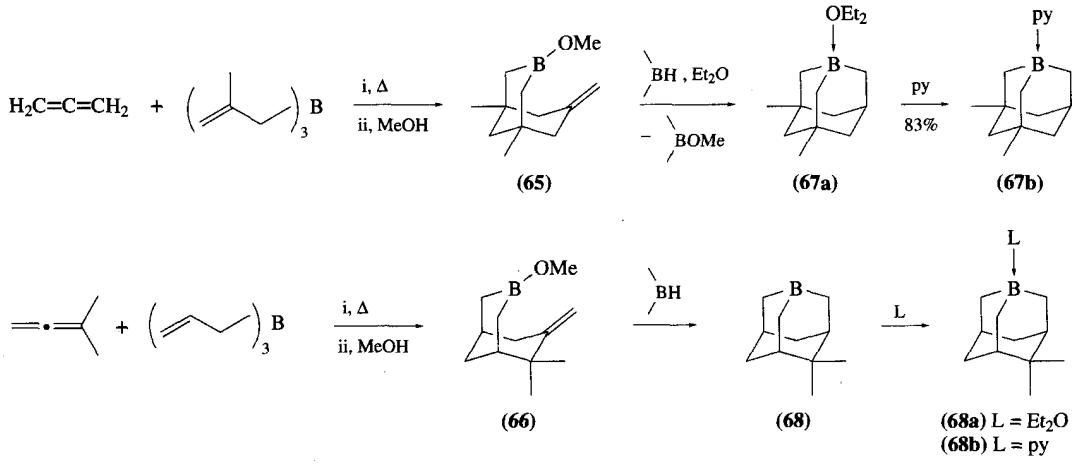
Similarly, from exomethylene bicyclic boranes (**65**) and (**66**), 3,5- and 4,4-dimethyl-1-boraadamantanes (**67**) ⟨76IZV2302⟩ and (**68**) ⟨79IZV2340⟩ were prepared (Scheme 25).

THF and pyridine complexes of 4-chloro-1-boraadamantane (**69**) were prepared from 6-chloro-3-alkyl-3-borabicyclo[3.3.1]nonane (**70**) according to Scheme 26 ⟨83JOM(246)9⟩.

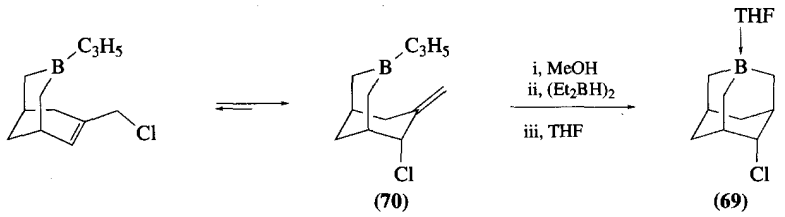
Another approach to 1-boraadamantane and its derivatives is based on hydroboration of 3-borabicyclo[3.3.1]non-6-enes (**71**), which are obtained by heating of triallylborane (or trimethallylborane) with terminal acetylenes. The reaction was originally carried out in 1965 and was called allylboron–acetylenic condensation (Scheme 27) ⟨65IZV1310, 67IZV2290⟩. The allylboron–acetylenic condensation proceeds in three consecutive stages ⟨B-84MI 834-01⟩: (i) allylboration of a triple bond (proceeds with the rearrangement of the allylic moiety); (ii) intramolecular allylboration of the terminal double bond leading to 1,5-diallyl-3-*R*-1-boracyclohex-2-enes (**72**); (iii) intramolecular cyclization resulting in 3-allyl-3-borabicyclo[3.3.1]non-6-enes (**73**). Methanolysis of the latter gives bicycles (**71**) used in the synthesis of 1-boraadamantanes.



Scheme 24



Scheme 25



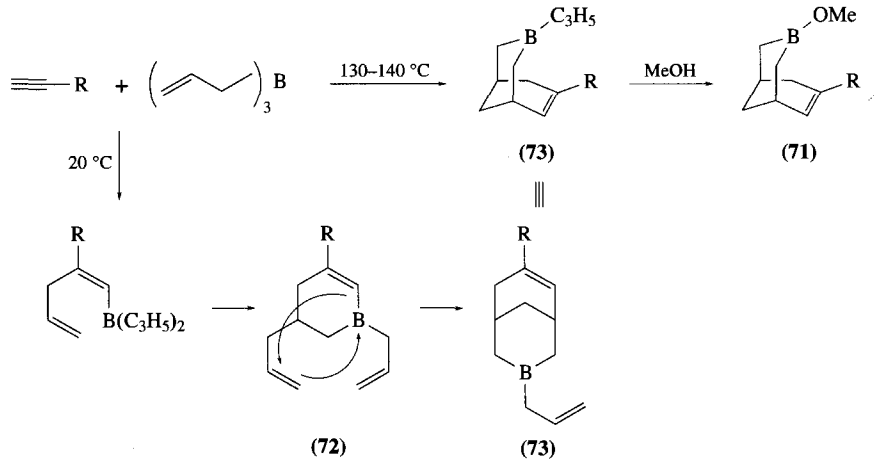
Scheme 26

Either diborane or its complexes ($BH_3 \cdot THF$, $BH_3 \cdot NEt_3$) were used as hydroborating reagents to prepare 1-boraadamantane (**5**) from bicycles (**71**) (Scheme 28) ⟨76IZV2056, 79IZV2544, 79IZV2551, 79IZV2724, 79IZV2729, 81JOM(219)295⟩. This method of synthesis of 1-boraadamantane is based on the inclination of organoboron compounds to undergo thermal isomerization. For example, at 150–160 °C secondary and tertiary organoboranes isomerize to primary (Equation (10)) ⟨57JA5190⟩. The presence of the compounds with B—H bonds catalyzes the process ⟨B-84MI 834-01⟩. During hydroboration of some steroids, the same process was observed at 40–60 °C ⟨73CC942⟩.

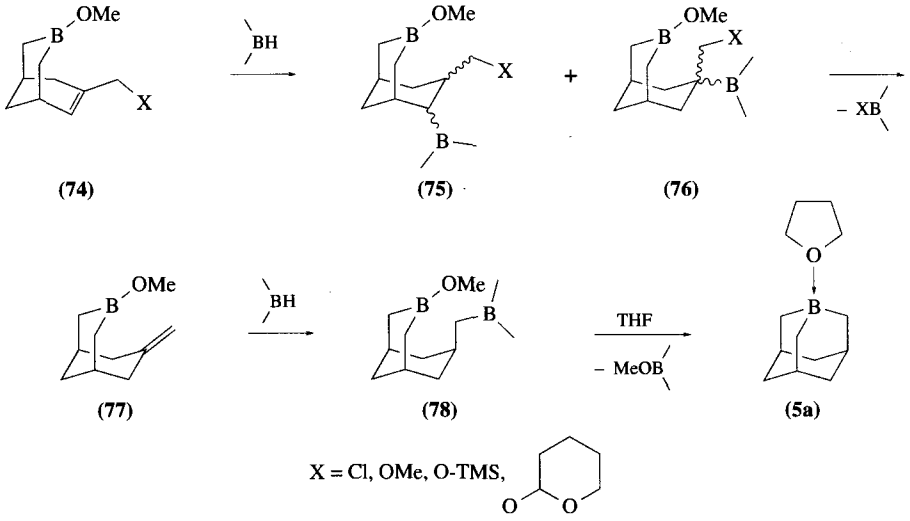


(10)

Borane (**75**) formed initially in the course of the hydroboration of bicycle (**74**) readily isomerizes to compound (**76**) even at 0 °C ⟨81JOM(219)295⟩. Bicycle (**76**) immediately undergoes β-elimination



Scheme 27



Scheme 28

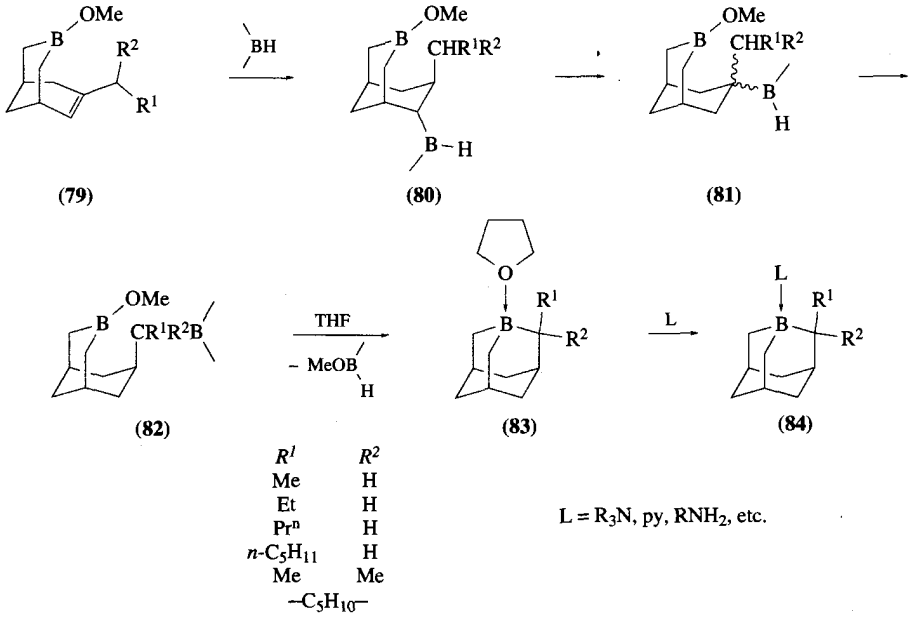
to give 3-methoxy-7-methylene-3-borabicyclo[3.3.1]nonane (**77**). The hydroboration of the latter gives THF complex of 1-boraadamantane (**5a**) via compound (**78**) (Scheme 28).

2-Alkyl and 2,2-dialkyl derivatives of 1-boraadamantanes (**84**), including spiro-compound and side chain-functionalized 1-boraadamantanes, can be synthesized by the same method via hydroboration–isomerization of corresponding compounds of type (**79**) containing at least one α-hydrogen atom in the substituent located in the 7-position (Scheme 29) ⟨86IZV1451, 86T1079, 87PAC895⟩.

A solution of $BH_3 \cdot THF$ in tetrahydrofuran is used as a hydroborating reagent. Isomerization of (**80**) to (**81**) and the further migration of boron to the side chain (compound (**82**)) followed by ring closure giving 1-boraadamantane–THF complex (**83**) proceed under reflux in tetrahydrofuran (2–3 h), or even at room temperature (4–5 days). It should be stressed that in theory the boron atom can migrate from the ring along the side chain to the terminal carbon atom. In this case one could expect the formation of homo- and polyhomoadamantanes or their oligomers (polymers). However, formation of these compounds was not detected. This means that the ring closure giving (**83**) occurs immediately after the boron atom appears at the appropriate position, i.e., at the first carbon atom of the side chain.

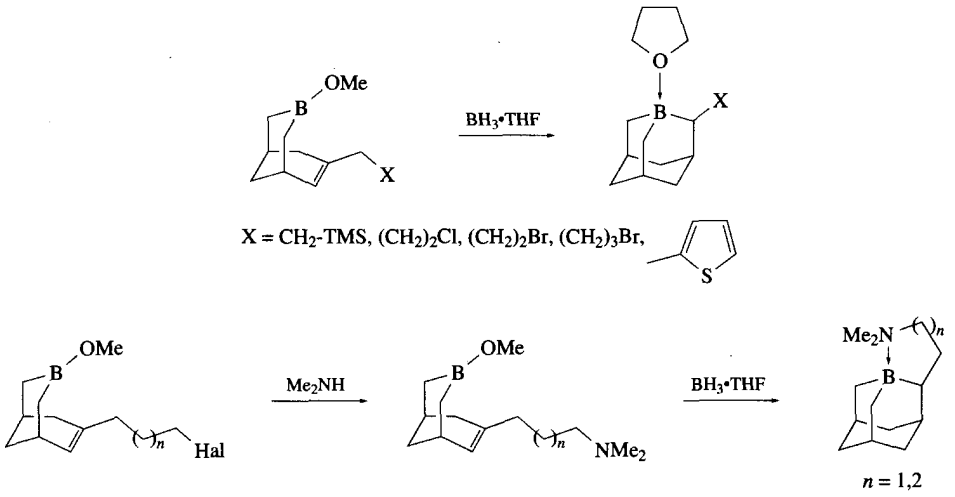
The same reaction applied to corresponding 7-substituted-3-methoxy-3-borabicyclo[3.3.1]non-6-enes was used for the synthesis of the functionally substituted 1-boraadamantanes (Equation (11)) ⟨84IZV1197, 84IZV1837, 88IZV415⟩.

It is also possible to carry out preliminary functionalization in a starting 3-borabicyclo[3.3.1]non-



Scheme 29

6-ene in order to synthesize intramolecular complexes of 1-boraadamantane (Scheme 30) ⟨91JOM(412)311⟩.

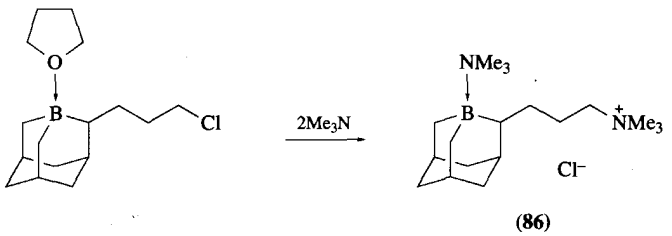


(11)

Scheme 30

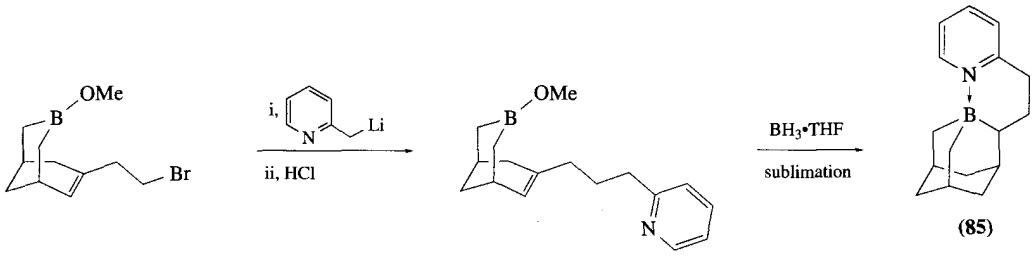
The same approach was applied for the three-stage synthesis of the elegant 2[2-(2-pyridyl)ethyl]-1-boraadamantane (**85**); the overall yield is 35% (Scheme 31) ⟨91JOM(412)311⟩.

One example of side chain ω-function modification in 1-boraadamantane is known (Equation (12)). It should be noted that the trimethylammonium salt (**86**) is readily soluble in water ⟨91JOM(412)311⟩.



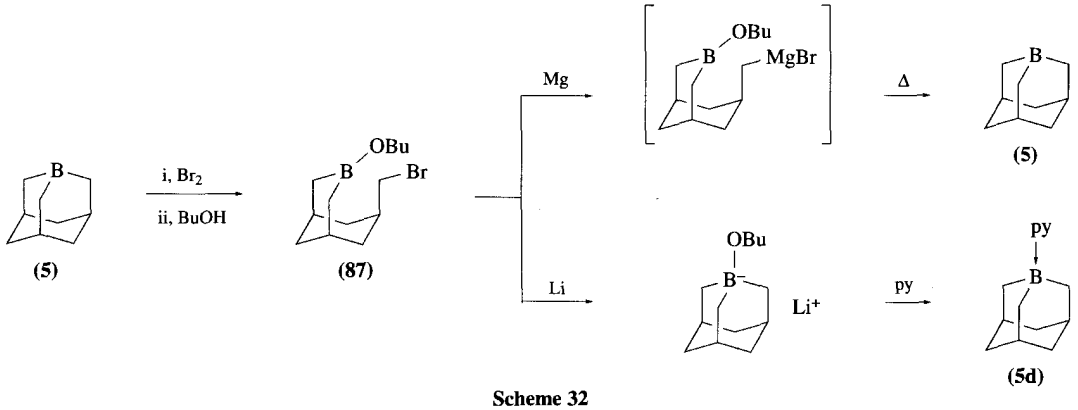
(12)

(**86**)



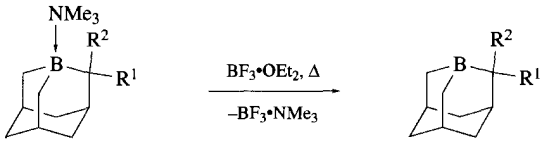
Scheme 31

There is also one example of the synthesis of 1-boraadamantane structure via organometallic derivatives of 3-butoxy-7α-bromomethyl-3-borabicyclo[3.3.1]nonane (**87**) (Scheme 32). However, since the only real source of the starting compound (**87**) is the 1-boraadamantane itself, this process is of theoretical interest only ⟨82JOM(226)115⟩.



Scheme 32

The data on the synthesis of 1-boraadamantanes are collected in Table 3. Treatment of the ether or THF complexes of 1-boraadamantanes with amines or with pyridine leads to the substitution of the ether molecule, affording corresponding amine complexes of 1-boraadamantane with yields up to 98% ⟨80MI 834-01⟩. Many of these amine and pyridine complexes are air-stable compounds ⟨74PAC505⟩. Free 1-boraadamantanes are usually prepared by the double vacuum sublimation (for solid compounds) or distillation (for liquids) of the etherates, or by treatment of the amine complexes with $BF_3 \cdot OEt_2$ followed by sublimation (Equation (13)). The data on the known complexes of 1-boraadamantanes are given in Table 4.



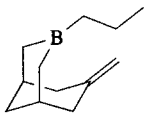
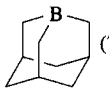
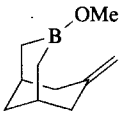
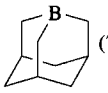
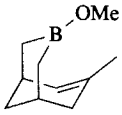
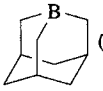
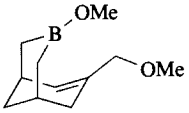
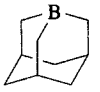
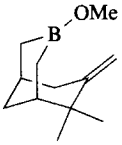
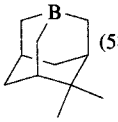
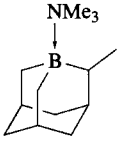
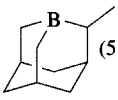
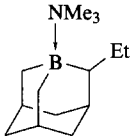
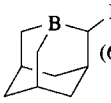
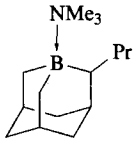
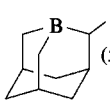
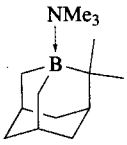
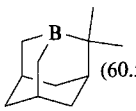
(13)

8.34.5.5 Reactivity

8.34.5.5.1 Complexing ability

The simplest and apparently the most important reaction of 1-boraadamantanes (**5**) is the formation of complexes with nucleophiles (Equation (14)). Owing to the unusual tetrahedral configuration of the trivalent boron atom in 1-boraadamantane, it acquires a very strong complexing ability. Thus, it forms adducts even with such weak donors as diethyl ether, tetrahydrofuran, and ethyl acetate, which do not give complexes with trialkylboranes, R_3B. Adducts with Et_2O, THF, or Me_3N can be directly isolated during the synthesis of 1-boraadamantane; they can be easily transformed to other various 4-coordinated complexes of 1-boraadamantane via exchange reactions. A

Table 3 Preparation of 1-boraadamantanes.

Starting compound	*Reagents; conditions*	*Isolated compound* (%)	$\delta^{11}B$ (ppm); *b.p.* (mm Hg) *or m.p.* (°C)	*Ref.*
	$B_2H_2Et_4$, pure; sublimation *in vacuo*	 (72%)	82 ppm; decomposes at 80 °C	76IZV2302
	B_2H_6, ether; sublimation *in vacuo*	 (75%)		76IZV2302
	B_2H_6, ether; sublimation *in vacuo*	 (70%)		95UP 834-02
	B_2H_6, ether; 3.5 h, 20–34 °C, sublimation	 (70%)		79IZV2544
	B_2H_6, ether; sublimation	 (58%)	83.5 ppm; 73–78 °C (1)	79IZV2340
	$BF_3 \cdot OEt_2$; distillation	 (51%)	83.9 ppm; 74–76 °C (1.5)	95UP 834-02
	$BF_3 \cdot OEt_2$; distillation	 (64.7%)	84.3 ppm; 65–67 °C (1.5)	95UP 834-02
	$BF_3 \cdot OEt_2$; distillation	 (58.7%)	84.6 ppm; 66–68 °C (1.5)	95UP 834-02
	$BF_3 \cdot OEt_2$; distillation	 (60.5%)	82.8 ppm; 65–66 (1.5)	95UP 834-02

great number of complexes were obtained by this method. Many among these compounds are exceptionally stable. For example, the complex with pyridine (**5d**) is unchanged in air for years and does not dissociate at 200 °C.

Similar complexes were also prepared for various substituted 1-boraadamantanes (see Table 4).

Table 4 Synthesis of the 1-boraadamantane complexes.

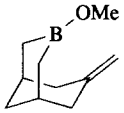
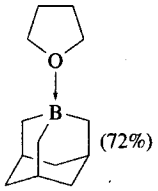
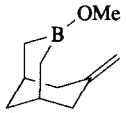
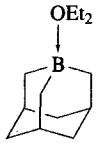
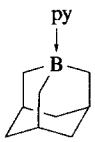
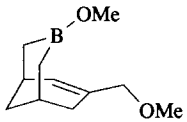
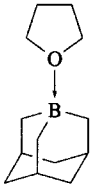
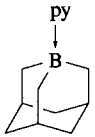
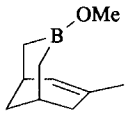
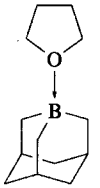
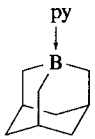
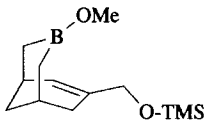
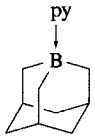
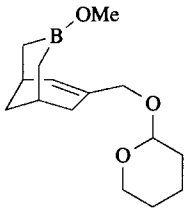
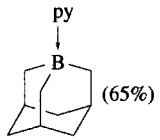
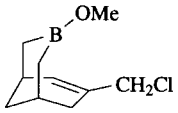
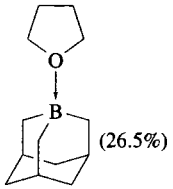
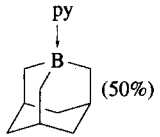
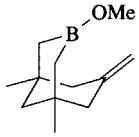
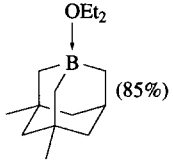
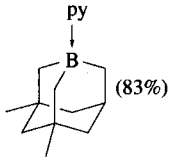
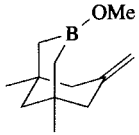
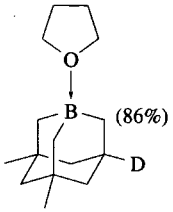
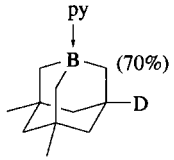
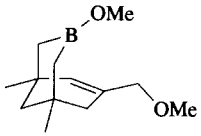
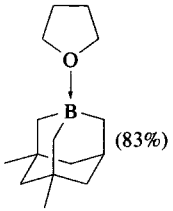
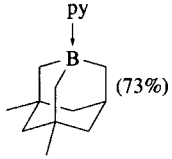
Starting compound	*Reagent, conditions*	*Isolated compound (%)*	$\delta^{11}B$ (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Pyridine complex (yield)*	$\delta^{11}B$ (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Ref.*
	$BH_3 \cdot THF$, THF	 (72%)	8	79–85				76IZV2302
	B_2H_6, ether		15.6	oil	 (84%)	–4.1	160–162	76IZV2302
	$BH_3 \cdot THF$, THF; 1 h boiling	 (90%)		84–88	 (84%)		164–167	79IZV2544
	$BH_3 \cdot THF$, THF; 3 h boiling	 (97.5%)	12.8	90–92	 (97.2%)	–4.1	163–165	95UP 834-02
	$BH_3 \cdot THF$, THF; 1.5 h boiling				 (53%)		164–166	81JOM(219)295

Table 4 (continued)

Starting compound	*Reagent, conditions*	*Isolated compound (%)*	*$\delta^{11}B$* (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Pyridine complex (yield)*	*$\delta^{11}B$* (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Ref.*
	$BH_3 \cdot THF$; 3 h, 20				 (65%)		159–161	79IZV2729
	B_2H_6, ether; 12 h; then THF	 (26.5%)		79–83	 (50%)		159–162	83JOM(246)9
	$B_2H_2Et_4$, ether	 (85%)			 (83%)		162–164 (1), 51–52	76IZV2302
	$BD_3 \cdot THF$, THF	 (86%)		73–74 (1)	 (70%)		56–57	80JOM(201)81
	$BH_3 \cdot THF$, THF; 2 h	 (83%)		72–74 (1)	 (73%)		156–158 (1), 54–56	79IZV2724

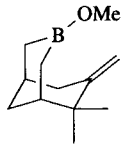
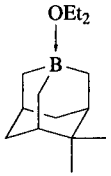
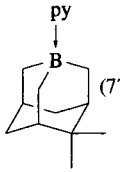
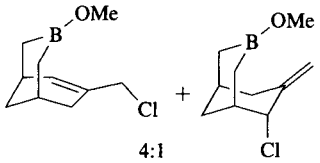
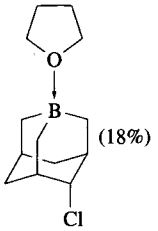
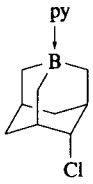
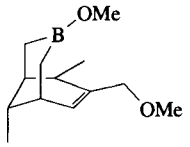
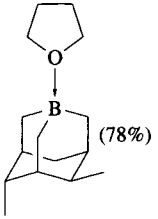
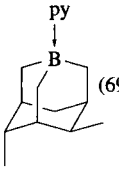
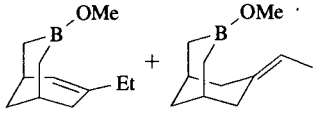
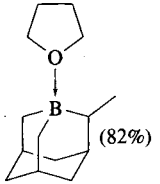
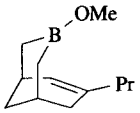
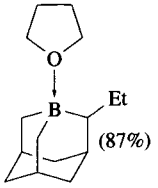
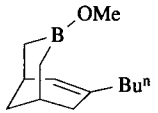
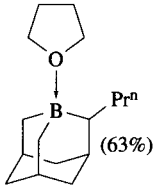
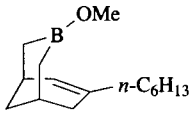
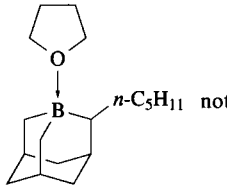
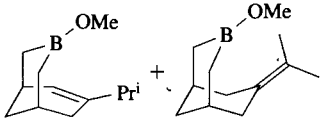
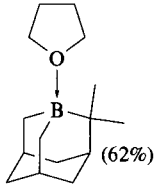
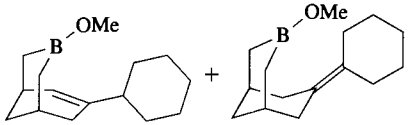
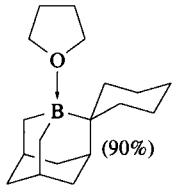
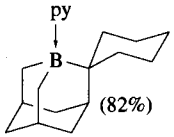
	$B_2H_2Et_4$, ether		15	oil	 (77%)		87–89	79IZV2340
 4:1	$B_2H_2Et_4$, THF; 20°C, 12 h	 (18%)	9.8	47–49	 (88%)	–5.6	107–107.7	83JOM(246)9
	$BH_3 \cdot THF$, THF; 20°C, 12 h	 (78%)		53–56.5	 (69%)		90–90.5	79IZV2551
	$BH_3 \cdot THF$, THF; 3 h	 (82%)		83–85 (2–5)				86T1079
	$BH_3 \cdot THF$, THF; 3 h	 (87%)		77–78.5 (2)				95UP 834-02

Table 4 (continued)

Starting compound	*Reagent, conditions*	*Isolated compound (%)*	*$\delta^{11}B$ (ppm)*	*b.p. (°C) (mm Hg) or m.p.*	*Pyridine complex (yield)*	*$\delta^{11}B$ (ppm)*	*b.p. (°C) (mm Hg) or m.p.*	*Ref.*
	$BH_3 \cdot THF$, THF; 3 h			76–78 (1.5)				95UP 834-02
	$BH_3 \cdot THF$, THF; 3 h		not isolated					95UP 834-02
	$BH_3 \cdot THF$, THF; 3 h			62–63.5				86T1079, 86IZV1451
	$BH_3 \cdot THF$, THF; 3 h			>80 decomp.			198–200	86T1079, 86IZV1451

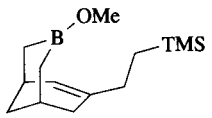
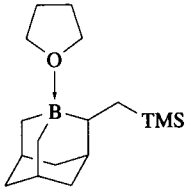
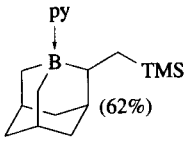
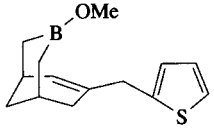
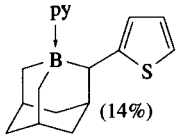
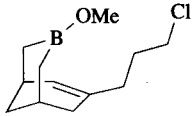
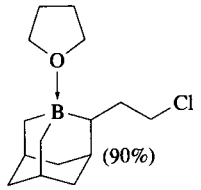
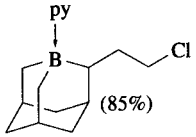
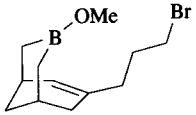
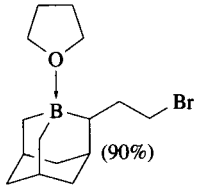
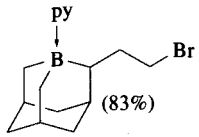
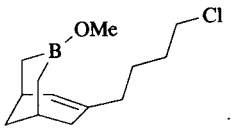
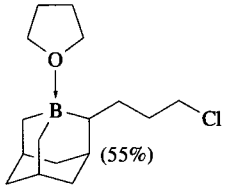
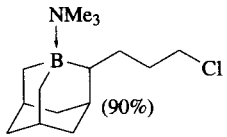
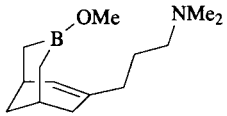
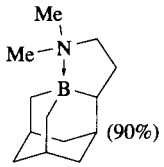
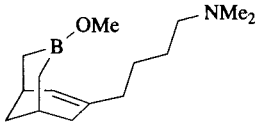
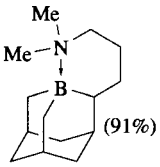
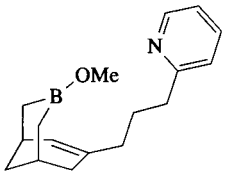
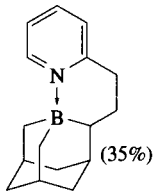
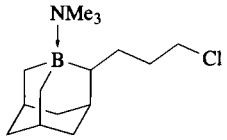
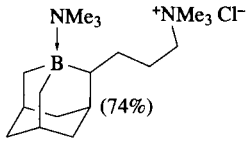
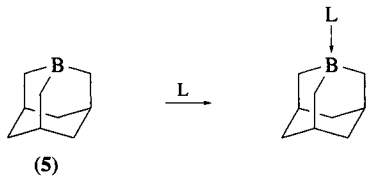
	$BH_3 \cdot THF$, THF	 not seperated	liquid	 (62%)		59–61	84IZV1197
	$BH_3 \cdot THF$, THF; 11 h boiling			 (14%)		102–103	84IZV1837
	$BH_3 \cdot THF$; 3 h boiling in THF	 (90%)	oil	 (85%)	−3.3	90.5–92	88IZV415
	$BH_3 \cdot THF$; 3 h boiling in THF	 (90%)	oil	 (83%)	−3.1	90–91	88IZV415
	$BH_3 \cdot THF$; 2 h boiling in THF	 (55%)	12.5	108–110 (0.6)	 (90%)	−1.05	87–88	91JOM(412)311

Table 4 (continued)

Starting compound	*Reagent, conditions*	*Isolated compound (%)*	$\delta^{11}B$ (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Pyridine complex (yield)*	$\delta^{11}B$ (ppm)	*b.p.* (°C) (mm Hg) *or m.p.*	*Ref.*
	$BH_3 \cdot THF$, 3 h boiling in THF, sublimation				 (90%)	−2.0	119–120	91JOM(412)311
	$BH_3 \cdot THF$; 3 h boiling in THF, sublimation				 (91%)	−3.7	65–66	91JOM(412)311
	$BH_3 \cdot THF$, 1.5 h boiling in THF, sublimation				 (35%)	−5.0	149–150	91JOM(412)311
	Me_3N, C_6H_6; 100°C, 8 days				 (74%)	−0.8	168 (decomp.)	91JOM(412)311



(5) (14)

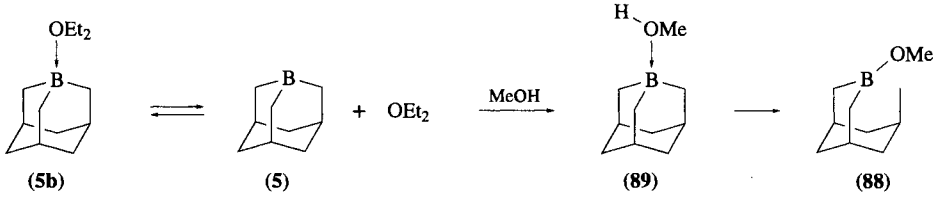
L = Et_2O, THF, $MeCO_2Et$, Me_3N, Et_2NH, $EtNH_2$, Et_3N, Pr_2NH, C_5H_5N, 2-MeC_5H_4N, 3-MeC_5H_4N, 4-$NH_2C_5H_4N$, γ,γ-$(C_5H_4N)_2$

8.34.5.5.2 Reactions with electrophiles

The chemical properties of 1-boraadamantanes clearly indicate a relatively stronger "metallic" character of its boron atom compared to that in acyclic organoboron compounds. Thus, 1-boraadamantanes react with electrophiles (ROH, $R_2C{=}O$, $RC{\equiv}N$, Br_2) similarly to the classical organometallic compounds (RLi, RMgX) with the cleavage of the B—C bond, although it is known that acyclic triorganoboranes are inert at ambient temperature to the reagents mentioned above ⟨B-81MI 834-01⟩.

(i) Protolysis

Acyclic trialkylboranes, R_3B, react with alcohols at 150–170 °C giving the corresponding borinic esters, $R^1{}_2BOR^2$, mixtures of saturated and unsaturated hydrocarbons and hydrogen ⟨B-84MI 834-01⟩. In contrast, the weak ether complex of 1-boraadamantane (**5b**) readily affords 3-methoxy-7α-methyl-3-borabicyclo[3.3.1]nonane (**88**) on treatment with methanol at room temperature (Scheme 33) ⟨76IZV2302⟩. Protolysis of the B—C bond proceeds through the formation of methanol complex (**89**). This follows from the fact that a strong pyridine complex of (**5**) does not react with methanol even at 70–80 °C, which is explained by the impossibility of substitution of pyridine by methanol ⟨76IZV2302⟩. Protolysis of the 1-boraadamantane–THF complex (**5a**) requires prolonged reflux in methanol ⟨84JOM(270)9⟩.

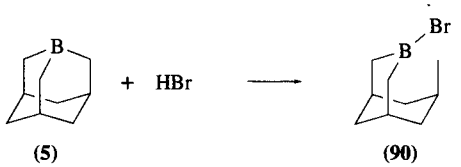


(**5b**) (**5**) (**89**) (**88**)

Scheme 33

In contrast to Bu_3B, which is cleaved by hydrogen bromide at 55–60 °C ⟨38JA115⟩, (**5**) reacts with HBr at 0 °C giving 3-bromo-7-methyl-3-borabicyclo[3.3.1]nonane (**90**) (Equation (15)) ⟨80IZV1106⟩.

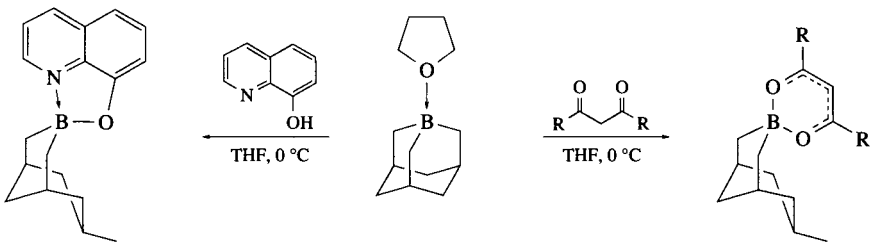
Reactions of THF complex (**5a**) with β-diketones ⟨81IZV394⟩ and with 8-hydroxyquinoline ⟨86IZV1645⟩ also proceed in mild conditions affording the corresponding chelates (**91**) and (**92**) in good yields (Scheme 34).



(**5**) (**90**) (15)

(ii) Halogenation

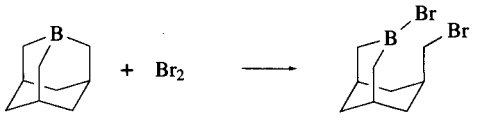
Two possible directions of the reaction of triorganoboranes with halogens are known, viz. the radical and the ionic halogenations ⟨B-84MI 834-01⟩. However, probably only the latter is realized in



(91) (5a) (92) R = Me, Ar

Scheme 34

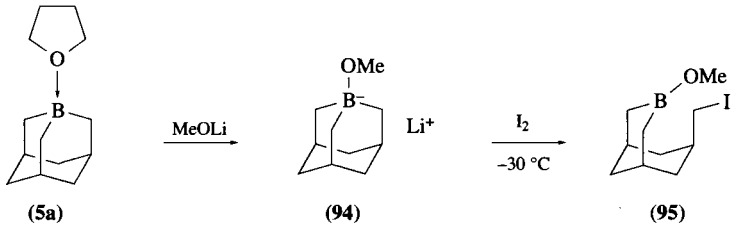
the case of 1-boraadamantane (**5**). Reaction of (**5**) with bromine readily occurs at −50 to −40°C, with the cleavage of one of the B—C bonds yielding 3-bromo-7α-bromomethyl-3-bora-bicyclo[3.3.1]nonane (**93**) (Equation (16)) ⟨80IZV1106⟩.



(5) (93) (16)

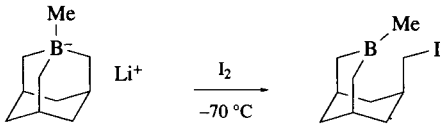
1-Boraadamantane (**5**) does not react with iodine at room temperature. However, in the presence of bases, e.g., alcoholates, the reaction rate increases dramatically. Coordination of a base at the boron atom leads to increase in the polarity of the B—C bond, facilitating its heterolytic cleavage. For example, ate-complex (**94**), prepared by the treatment of (**5a**) with lithium methoxide, reacts with iodine at −30°C giving 3-methoxy-7α-iodomethyl-3-borabicyclo[3.3.1]nonane (**95**) (Scheme 35) ⟨83JOM(246)19⟩.

The reactivity of a tetraorganoborate complex (**96**) is higher than that of (**94**); the reaction of (**96**) with iodine proceeds even at −70°C (Equation (17)) ⟨83JOM(246)19⟩.



(5a) (94) (95)

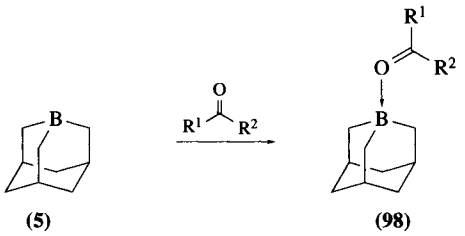
Scheme 35



(96) (97) (17)

(iii) Reactions with carbonyl compounds and aromatic nitriles

Owing to a strong polarization of the B—C bonds in 1-boraadamantane (**5**), it reacts with aldehydes and ketones in a similar manner to Grignard reagents. The intermediate formation of adducts with carbonyl compounds (**98**) (Equation (18)) was detected by spectral methods (IR and ^{11}B NMR) ⟨81JOM(219)301⟩.

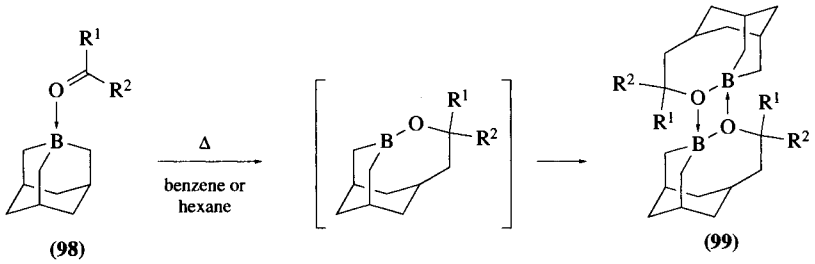


(a) $R^1 = H$, $R^2 = Ph$
(b) $R^1 = H$, $R^2 = 4\text{-}MeOC_6H_4$
(c) $R^1 = H$, $R^2 = 3,4\text{-}(MeO)_2C_6H_4$
(d) $R^1 = H$, $R^2 = Pr^i$
(e) $R^1 = R^2 = Me$

(18)

(5) (98)

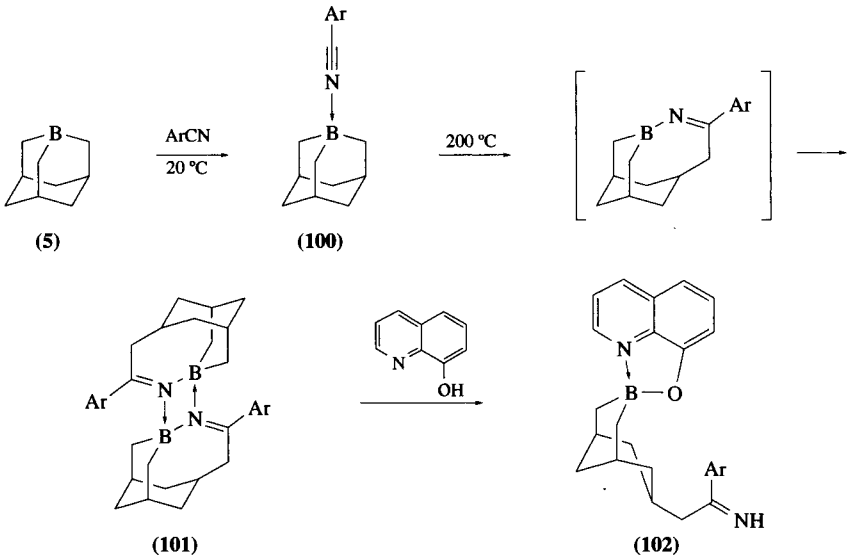
When heated, complexes (**98**) undergo a rearrangement with the formation of a new C—C bond to give the dimeric 5-substituted-4-oxa-3-bora-1,1-bihomoadamantanes (**99**) (Scheme 36). Dimers (**99**) form colorless crystals, stable in the air ⟨81JOM(219)301⟩.



(98) (99)

Scheme 36

The reaction of 1-boraadamantane (**5**) with aromatic nitriles also proceeds according to the organometallic synthesis scheme. As in the reaction with carbonyl compounds, the initially formed complexes (**100**) (Scheme 37) transform to dimers of 5-aryl-4-aza-3-bora-1,1-bihomoadamantane-4-enes (**101**) when heated higher than 200 °C ⟨84JOM(260)25⟩. Compounds (**101**) are stable in the air and do not react with alcohols; however, they can be cleaved with 8-hydroxyquinoline to give bicyclic compounds (**102**) ⟨84JOM(260)25⟩.



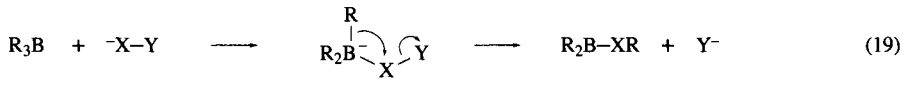
(5) (100) (101) (102)

Scheme 37

8.34.5.5.3 Anionotropic rearrangements

1,2-Anionotropic rearrangements make a large group of reactions of organoboron compounds ⟨B-81MI 834-01⟩. These reactions involve the migration of an organic group from the negatively charged boron atom to the neighboring electrophilic center according to Equation (19).

In the chemistry of 1-boraadamantane, reactions of this type provide the most selective and general method for framework transformation leading to its homologues, heteroanalogues, and various compounds of the adamantane series ⟨83PAC1439, B-84MI 834-01⟩.

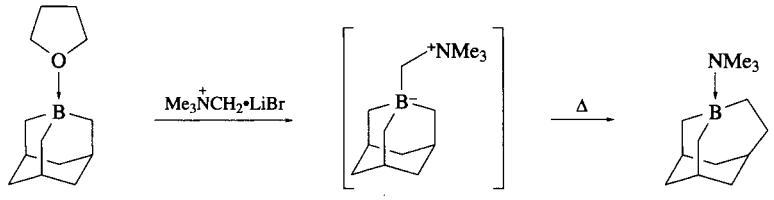


(19)

(i) Reactions with ylides

Insertion reaction of 1-boraadamantane with ylides permits extension of one of the rings by a CH_2 group to obtain another strained organoboron polyhedral system, viz. 3-borahomoadamantane (**6**).

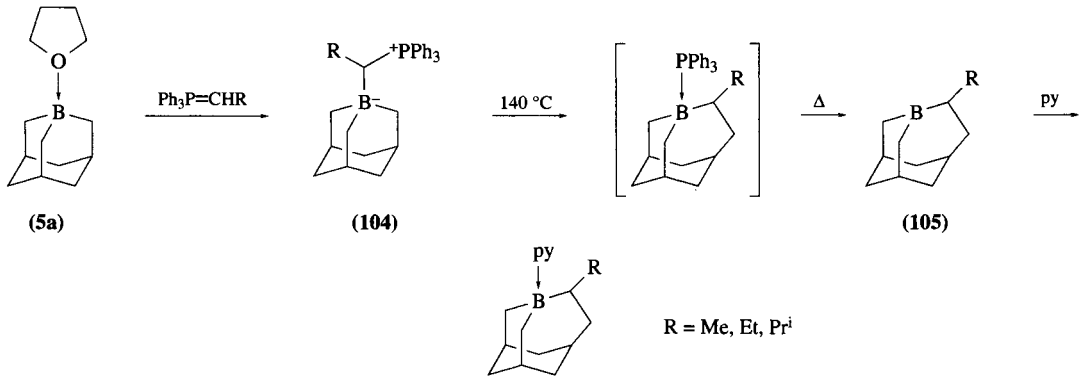
Thus, the reaction of trimethylammonium methylylide with the 1-boraadamantane-THF complex (**5a**) gives the trimethylamine complex of 3-borahomoadamantane (**6a**) via the unstable betaine (**103**) (Scheme 38) ⟨80IZV1621⟩.



(**5a**) (**103**) (**6a**)

Scheme 38

In contrast to the nitrogen ylide, alkylidenetriphenylphosphines give air-stable crystalline compounds (**104**) with 1-boraadamantane (**5**) (Scheme 39) ⟨84JOM(260)17⟩. Adducts (**104**) rearrange to 4-alkyl-3-borahomoadamantane series (**105**) under reflux in chlorobenzene; these form complexes (**106**).



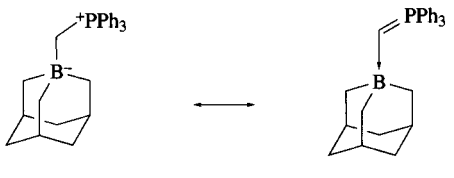
(**5a**) (**104**) (**105**)

R = Me, Et, Pr^i

(**106**)

Scheme 39

X-ray structural investigation showed that adduct (**104b**) has a zwitterionic structure, although some contribution of the "ylide form" (**104a**) cannot be excluded (Equation (20)) ⟨85IZV2483⟩.

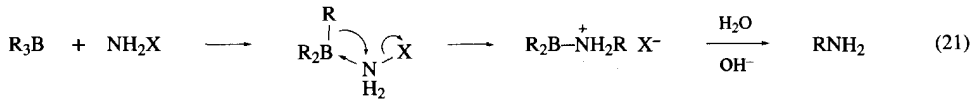


(20)

(**104b**) (**104a**)

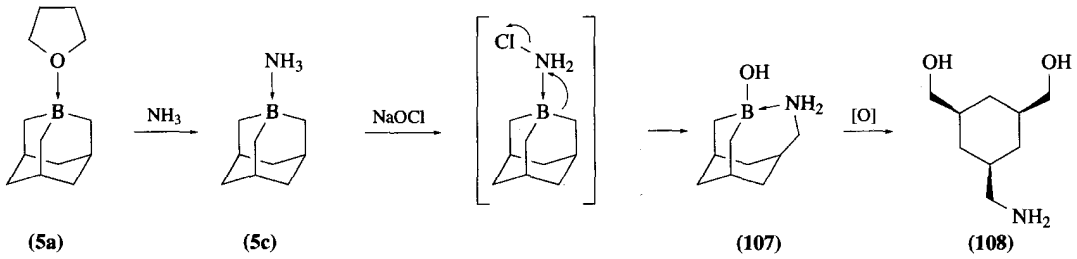
(ii) Amination

Organoboranes can be used for the synthesis of various organic compounds containing an amino group ⟨B-88MI 834-01⟩. The most common procedures involve the reaction of organoboranes with azides, with hydroxylamine derivatives, or with chloroamines. All amination reactions proceed via intermediate formation of a borate complex followed by anionotropic rearrangement to form the new C—N bond (Equation (21)).



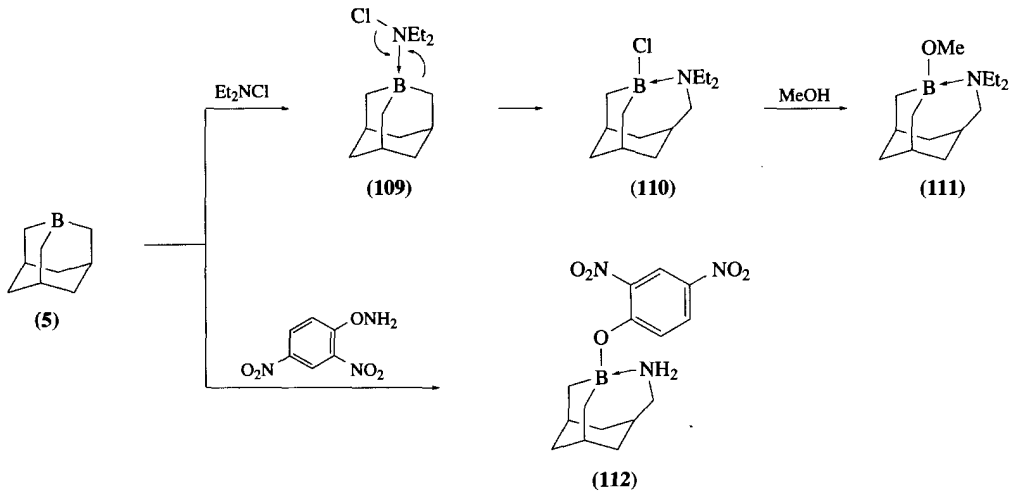
$$R_3B + NH_2X \longrightarrow R_2B{-}N(R)H_2X \longrightarrow R_2B{-}\overset{+}{N}H_2R\ X^- \xrightarrow[OH^-]{H_2O} RNH_2 \qquad (21)$$

The ammonia complex of 1-boraadamantane (**5c**) at ambient temperature readily reacts with NaOCl in the two-phase system H_2O–CH_2Cl_2, giving 3-hydroxy-7α-aminomethyl-3-borabicyclo-[3.3.1]nonane (**107**) ⟨89MI 834-01⟩. The latter is a direct precursor of *cis,cis*-aminodiol (**108**) (Scheme 40).



Scheme 40

Free 1-boraadamantane (**5**) also readily reacts with dimethyl- ⟨94CB1105⟩ or diethylchloroamine, hydroxylamine-*O*-sulfonic acid, or *O*-2,4-dinitrophenylhydroxylamine to give intramolecular complex compounds (**110**)–(**112**) via adducts of the type (**109**) (Scheme 41) ⟨81JOM(220)1⟩.

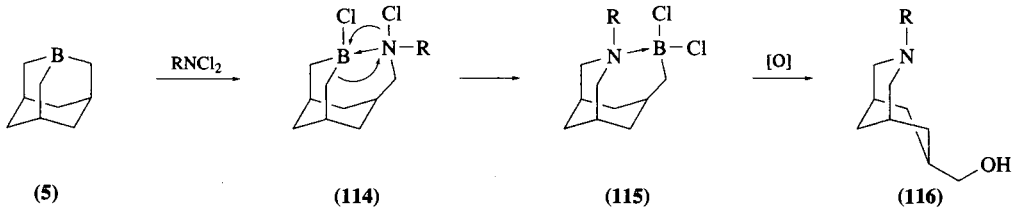


Scheme 41

The structural closeness of 1-boraadamantane (**5**) and 1-azaadamantane (**113**) induced the attempts to convert (**5**) into (**113**). The first reported synthesis has been carried out according to the following synthetic scheme. Treatment of (**5**) with *N,N*-dichloroamines leads to the formation of an intramolecular complex compound (**114**). A second anionotropic migration in (**114**) gives rise to compound (**115**); standard oxidation of the latter provides 3-alkyl-3-azabicyclo[3.3.1]nonanes (**116**) (Scheme 42) ⟨81JOM(220)1⟩.



(113)

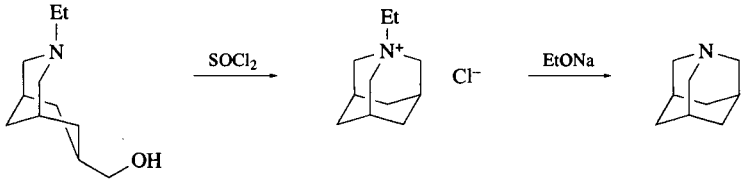


(5) **(114)** **(115)** **(116)**

(a) R = Me; **(b)** R = Et; **(c)** R = Pr^n; **(d)** R = Bu^n

Scheme 42

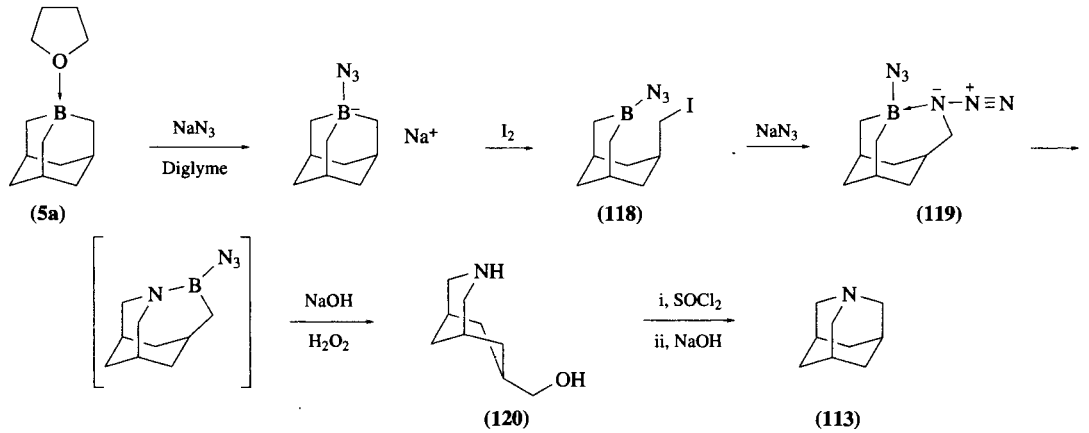
Treatment of aminoalcohol (**116b**) with thionyl chloride followed by Hoffmann cleavage of the quaternary salt (**117**) afforded azaadamantane (**113**) with a yield of 29% based on the 1-boraadamantane (**5**), or 10% (six stages) starting from allyl bromide (Scheme 43) ⟨83JOM(258)131⟩.



(116b) **(117)** **(113)**

Scheme 43

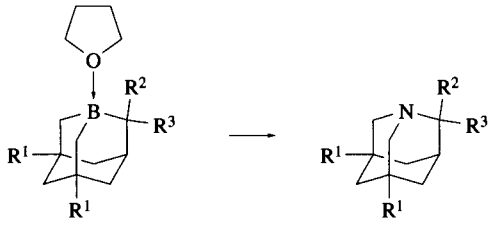
A more convenient procedure for the synthesis of (**113**) from (**5**) was later elaborated ⟨91JOM(412)1⟩. It is based on the intramolecular version of the reaction of organoboranes with organic azides. The THF complex of 1-boraadamantane (**5a**) is treated with iodine in the presence of an excess of sodium azide. The iodine atom in the intermediately formed borabicycle (**118**) undergoes an easy nucleophilic substitution by azide ions. The subsequent anionotropic rearrangement in the borabicyclic azide (**119**) leads (after the oxidation of the reaction mixture) to amino-alcohol (**120**), which is smoothly converted to 1-azaadamantane (**113**). The yield of (**113**) in this synthesis is 40–45% based on (**5a**), or 20–22% based on triallylborane (Scheme 44).



(5a) **(118)** **(119)** **(120)** **(113)**

Scheme 44

Up to 1995 this is the most effective method of synthesis of 1-azaadamantane (**113**), being significantly better than any previously known methods ⟨70CC197⟩. The same procedure was applied to the synthesis of the three alkylated 1-azaadamantanes from the corresponding 1-boraadamantanes (Equation (22)) ⟨94MC43⟩.

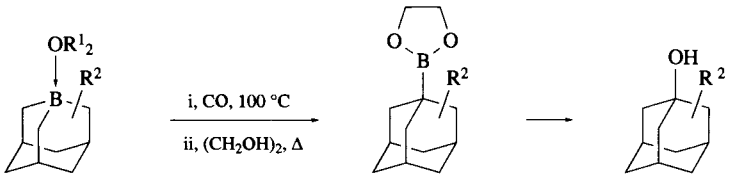


(22)

R^1	R^2	R^3	*Yield* (%)
Me	H	H	15
H	H	Me	36
H	Me	Me	30

(iii) Carbonylation

Trialkylboranes give trialkylcarbinols on Hilmann carbonylation followed by oxidation ⟨B-84MI 834-01, B-88MI 834-01⟩. One of the most effective applications of this reaction in organic synthesis is the conversion of 1-boraadamantanes to the corresponding 1-adamantanols (Scheme 45) ⟨76IZV2302⟩.



$OR^1{}_2$ = Et_2O, THF; R^2 = alkyl, cycloalkyl

Scheme 45

The scope of this reaction was illustrated with a great number of examples (see Figure 3); this is probably the most general and convenient method for the preparation of substituted adamantanols ⟨76IZV2056, 76IZV2302, 79IZV2340, 83JOM(246)9, 95UP 834-02⟩.

The transformation of 1-boraadamantane to 1-adamantanol (**121**) was also carried out by the Pelter method ⟨B-88MI 834-01⟩ (Equation (23)) ⟨76IZV2056⟩.

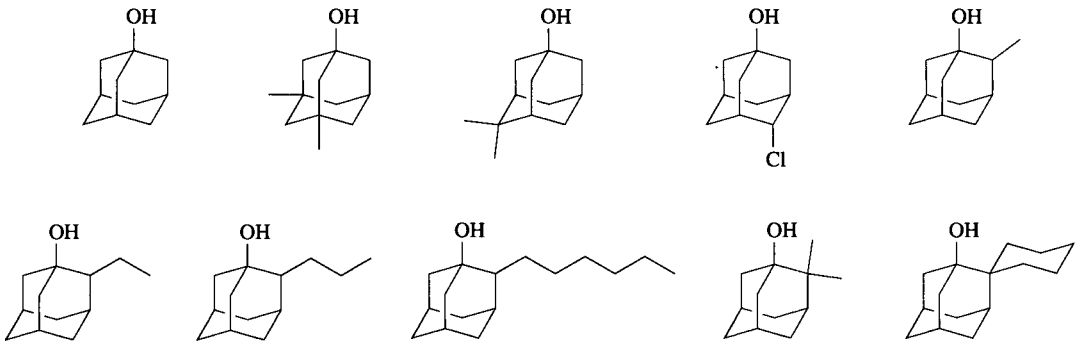
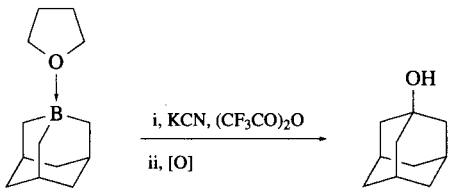


Figure 3 Representative adamantanols prepared from corresponding boraadamantanes.

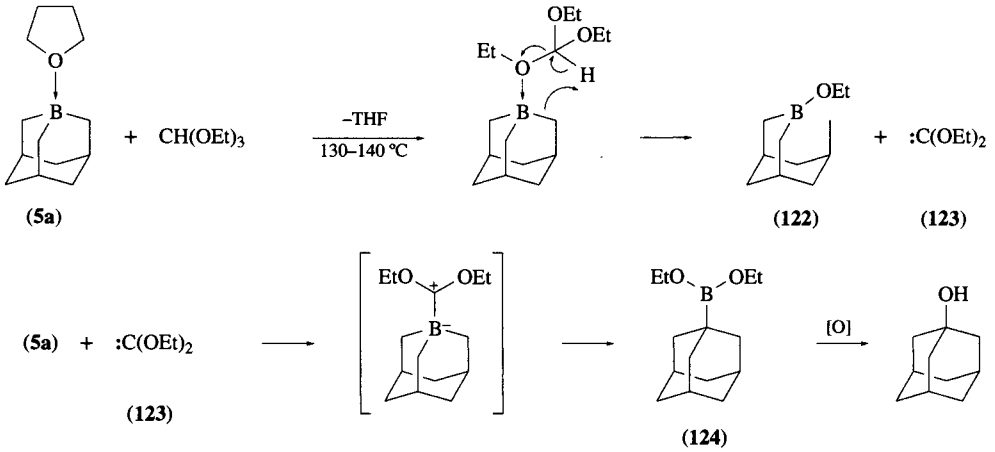


(5a) (121) (23)

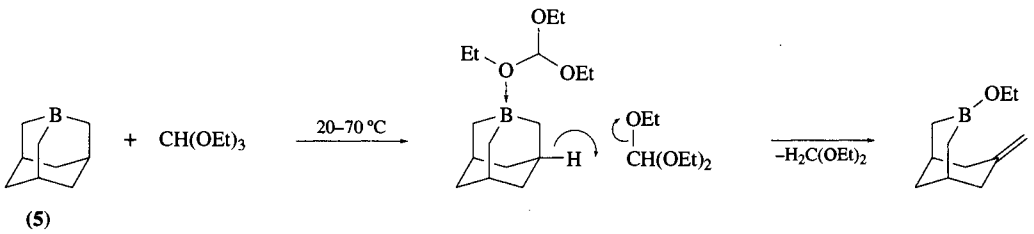
An interesting reaction occurs when the THF complex of 1-boraadamantane is heated (130–140 °C) with ethyl orthoformate. These conditions give rise to 3-ethoxy-7α-methyl-3-borabicyclo-[3.3.1]nonane (**122**) and adamantylboronic derivative (**124**). The reaction was thought to proceed via intermediate diethoxycarbene complex (**123**) (Scheme 46) ⟨90MI 834-01⟩.

In contrast, the reaction of free 1-boraadamantane (**5**) with ethyl orthoformate proceeds at 20–70 °C via hydride elimination (Scheme 47) ⟨90MI 834-01⟩.

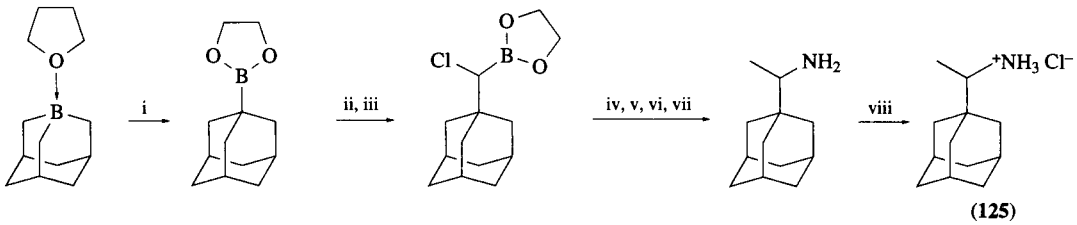
The combination of the carbonylation and the amination of 1-boraadamantane (**5**) was used in the synthesis of the known antiviral compound, rimantadine (**125**) (Scheme 48) ⟨93MC56⟩.



Scheme 46



Scheme 47



i, CO, $(HOCH_2)_2$; ii, Pr^i_2NLi; iii, CH_2Cl_2; iv, MeLi; v, AcCl; vi, H_2NOSO_3H; vii, NaOH; viii, HCl

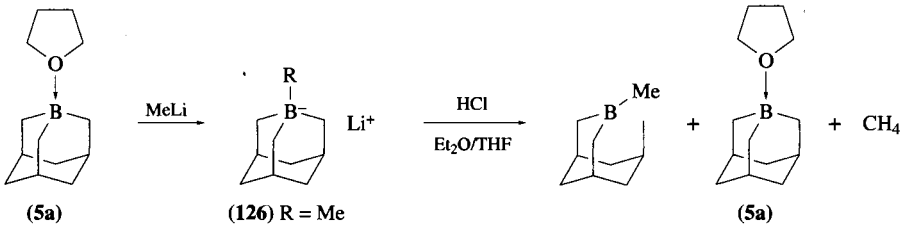
Scheme 48

8.34.5.5.4 Reactivity of the 1-boraadamantane ate-complexes

Formation of the four-coordinate intermediates is the first and the determining stage of most of the reactions of organoboron compounds ⟨B-81MI 834-01⟩. It is also the key stage of all anionotropic rearrangements discussed above. A specific reactivity of tetraorganoborates is indicated by their electronic structure, viz. the marked anionic nature of the ligands in the ate-complexes.

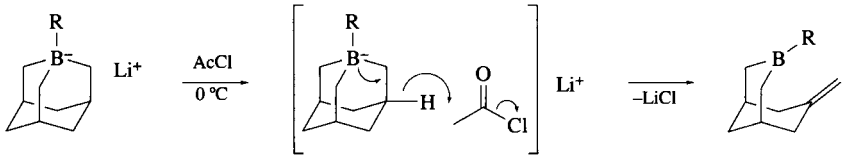
1-Boraadamantane ate-complexes (e.g., (**126**)) are readily formed when treating (**5**) (or its THF complex (**5a**)) with lithium alkyls or alkali metal alcoholates (Scheme 49). The process can conveniently be monitored by the value of the ^{11}B chemical shift, because a strong high-field shift is characteristic for the ate-complexes (to −20 ppm in the case of RLi, and to −3 ppm in the case of ROMe). Protolysis of the ate-complexes with HCl in ether proceeds under very mild conditions to give a borabicyclic compound, THF complex (**5a**) and methane (Scheme 49). The ratio of the products attests the relative rates of cleavage of the B—C^{cycl} and B—Me bonds ⟨83JOM(246)129⟩.

Treatment of borate complexes of the type (**126**) with acetyl chloride affords 3-substituted 7-methylene-3-borabicyclo[3.3.1]nonanes (**127**) (Scheme 50) ⟨80JOM(201)81⟩.



(**5a**) (**126**) R = Me (**5a**)

Scheme 49

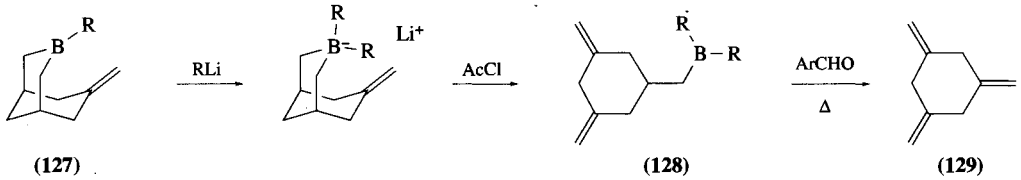


(**126**) R = Me, Bu^n, Ph (**127**)

Scheme 50

The unusual facility of the β-elimination is presumably caused by the *anti* arrangement of the eliminating hydrogen and the boryl fragment in the intermediate state. Formally this dehydroboration process can be regarded as a reversed ring-closure reaction observed during the creation of the 1-boraadamantane system via hydroboration.

It is interesting to note that ate-complexes obtained from a 3-alkyl-7-methylene-3-borabicyclo-[3.3.1]nonane (**127**) react with acetyl chloride in a similar way, giving 3,5-dimethylene-cyclohexylmethyl(dialkyl)boranes (**128**). If compounds (**128**) are used in the known reaction with aromatic aldehydes ⟨65IZV898, 66ZOB62⟩, the complete dehydroboration of 1-boraadamantane (**5**) is achieved, affording 1,3,5-trimethylenecyclohexane (**129**) (Scheme 51) ⟨83JOM(246)129⟩.

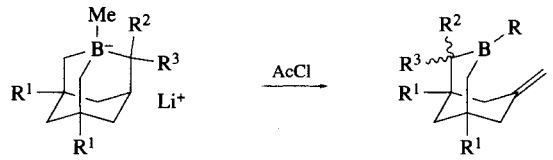


(**127**) (**128**) (**129**)

Scheme 51

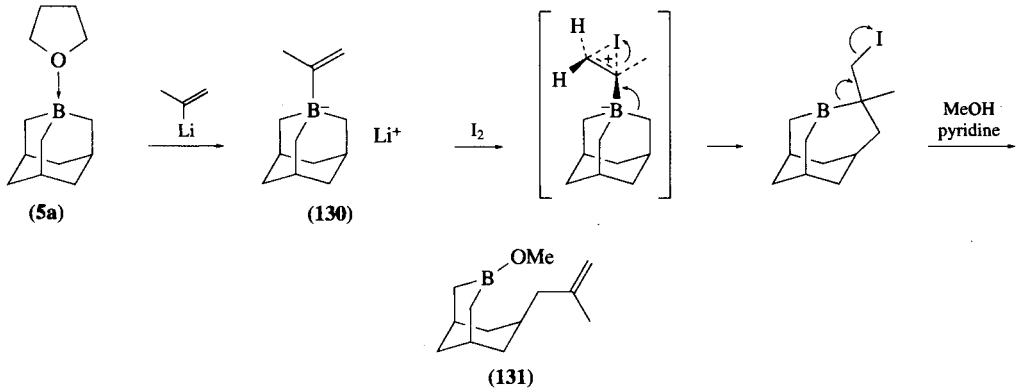
Similar reaction with acetyl chloride is known for ate-complexes of 3,5-dimethyl-, 2-methyl-, and 2,2-dialkyl-1-boraadamantane. In the two latter cases a complete regiospecificity is observed, i.e., the elimination of a hydride ion occurs only from the unsubstituted side (Equation (24)) ⟨86T1079⟩.

Iodination of an isopropenyl ate-complex of 1-boraadamantane (**130**) gives 3-methoxy-7α-isobutenyl-3-borabicyclo[3.3.1]nonane (**131**) after an appropriate workup of the reaction mixture (Scheme 52) ⟨83JOM(246)19⟩.



(24)

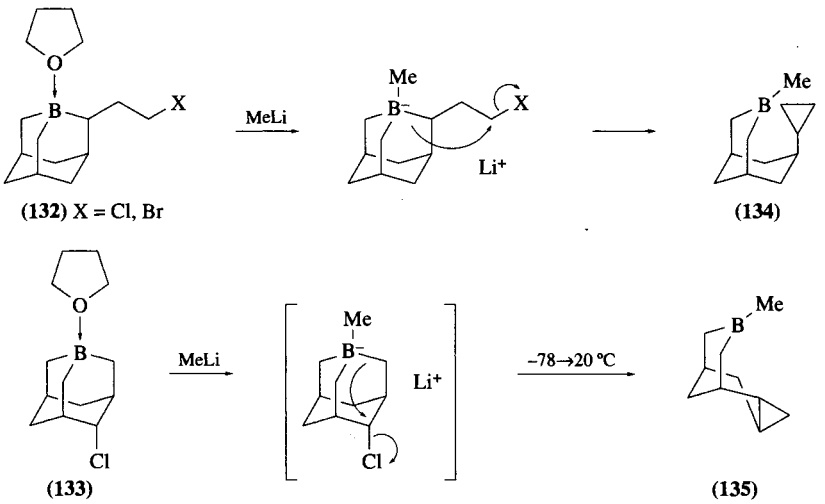
R^1 = Me, R^2 = R^3 = H;
R^1 = H, R^2 = R^3 = Me;
R^1 = H, R^2 = Me, R^3 = H;
R^1 = H, R^2 + R^3 = $(CH_2)_5$



(5a) (130) (131)

Scheme 52

Ate-complexes of 1-boraadamantane containing a halogen atom in the γ-position of either the side chain (**132**) or of the adamantane framework (**133**) undergo γ-elimination at room temperature leading to the formation of cyclopropanes (**134**) and (**135**), respectively (Scheme 53). These 1,3-elimination reactions presumably proceed synchronously, i.e., simultaneously with the halogen elimination the B—C bond is cleaved and the cyclopropane ring is created. Moreover, the elimination proceeds with the inversion of both of the reaction centers (Scheme 53) ⟨88IZV415⟩.



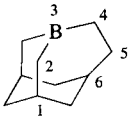
(132) X = Cl, Br (134) (133) (135)

Scheme 53

8.34.6 3-BORAHOMOADAMANTANES

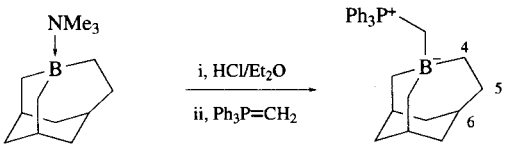
8.34.6.1 Structural Aspects

3-Borahomoadamantane (**6**) is the nearest structural homologue of 1-boraadamantane (**5**). Similarly to (**5**), (**6**) is a highly strained framework system with the boron atom almost sp^3 hybridized (although probably (**6**) is not so strained as (**5**)).



(**6**)

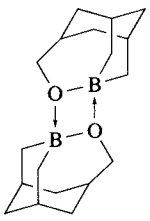
One of the most important features of the geometry of homoadamantane derivatives is the conformation of a "homo-link" of the polyhedron framework. Dreiding models predict a twisted configuration of the "homo-link," whereas the calculations and scarce structural studies attest to the eclipsed arrangement of the 4,5-bridge ⟨75AX(B)585⟩. X-ray study of 3-borahomoadamantane adduct with methylenetriphenylphosphorane (**136**) prepared according to Equation (25) has been carried out ⟨91MI 834-01⟩.



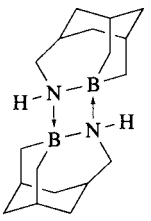
(25)

(**6a**) (**136**)

Introduction of a dimethylene link into the polyhedral boraadamantane system causes the appearance of a strain in (**136**), which manifests itself in the distortion of the geometric parameters. Thus, the bonds C-4—C-5 1.511 Å and C-5—C-6 1.487 Å are shortened compared to the standard length of a C(sp^3)—C(sp^3) of 1.540 Å. Concerning the conformation of the C-4—C-5 link, it is interesting to note that in boron–oxygen framework (**137**) ⟨81IZV353⟩ the "homo-bridge" is practically flat, whereas in boron–nitrogen derivative (**138**) ⟨89MI 834-01⟩ a notable twisting of the bridge was observed; i.e., the torsion angle BNCC equals 42°. The molecule of (**136**) has an intermediate character: the twisting of the dimethylene bridge over the C-4—C-5 bond is 10.3° ⟨91MI 834-01⟩.



(**137**)

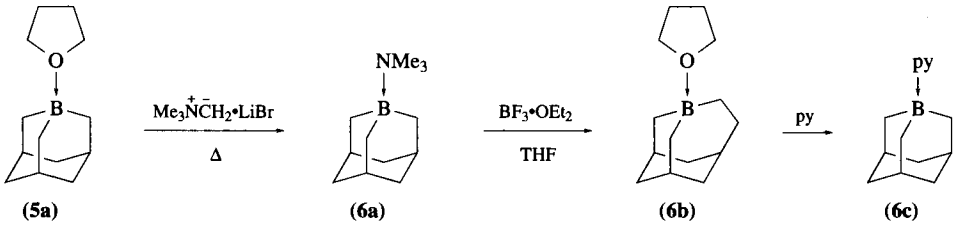


(**138**)

8.34.6.2 Synthesis

3-Borahomoadamantanes are prepared from the corresponding 1-boraadamantanes. As was discussed in Section 8.34.5.5.3, complexes of the parent 3-borahomoadamantane (**6a–c**) (Scheme 54) were prepared by the reaction of THF complex of 1-boraadamantane (**5a**) with trimethylammonium methylylide (Scheme 54, see also Scheme 38) ⟨80IZV1621⟩.

Reaction of (**5a**) with phosphorus ylides affords free 4-alkyl-substituted 3-borahomoadamantanes (**105**) without contamination by the starting compound (**5**) (see Scheme 39). However, the parent compound (**6**) was not prepared by this method, because the corresponding adduct of (**5**) with methylenetriphenylphosphorane is exceptionally stable and rearranges only at temperatures

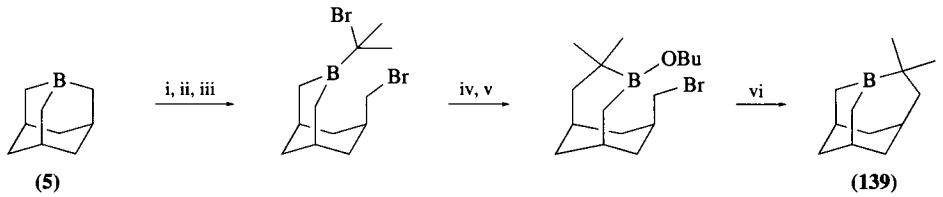


(5a) (6a) (6b) (6c)

Scheme 54

higher than 200°C. Apparently, 3-borahaomoadamantane (**6**) is unstable under such harsh conditions.

One more approach to the 3-borahomoadamantane system was developed (Scheme 55) ⟨82JOM(226)115⟩ giving the dimethyl derivative (**139**).

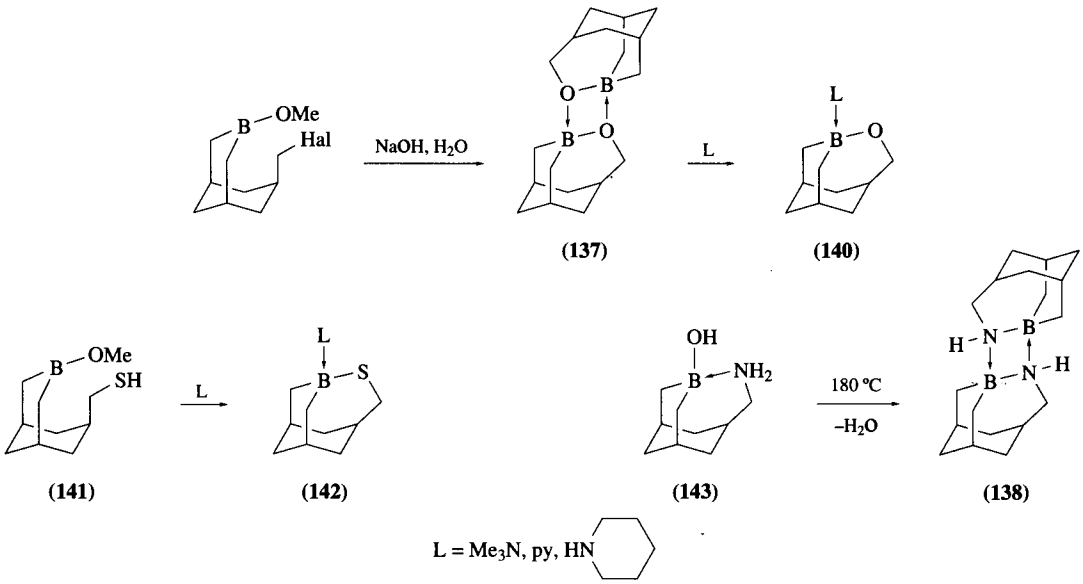


(5) (139)

i, Br_2; ii, Pr^iMgBr; iii, Br_2, *hν*; iv, Δ; v, BuOH; vi, Li

Scheme 55

Besides the 3-borahomoadamantane system itself, a series of 4-hetero-3-borahomoadamantane compounds are known. These skeletons were obtained as dimers (**137**), (**138**) ⟨80IZV1106, 81IZV353, 89MI 834-01⟩ or amine complexes (**140, 142**) (Scheme 56) ⟨92MC153⟩.



(137) (140) (141) (142) (143) (138)

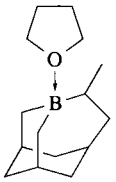
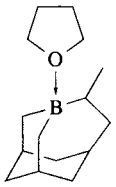
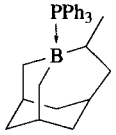
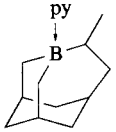
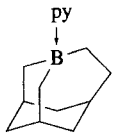
L = Me_3N, py, HN⟨ ⟩

Scheme 56

8.34.6.3 Reactivity

Among the chemical properties of 3-borahomoadamantanes, their ability to form complexes with THF and amines should be underlined (see Table 5). Such complexes are less stable than in the case of 1-boraadamantanes owing to the flexibility of the dimethylene bridge ⟨92MC153⟩.

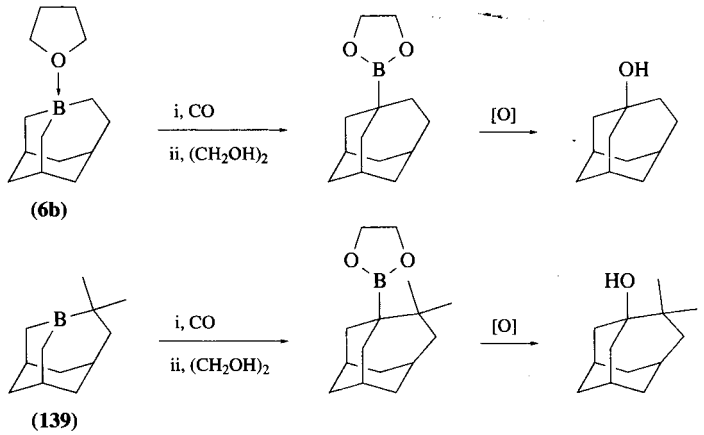
Table 5 ^{11}B Chemical shifts of the 3-borahomoadamantane derivatives.

Compound	$\delta^{11}B$ *(solvent)* (ppm)
	79.5
	22.4 (THF)
	10.3 ($CDCl_3$)
	0.0 ($CDCl_3$)
	−1.5 (Diglyme)

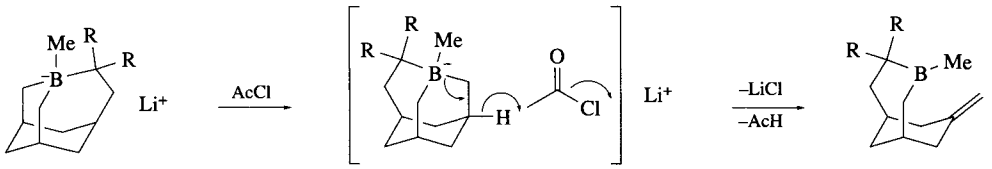
py = pyridine

Carbonylation–oxidation of 3-borahomoadamantanes gives the corresponding homoadamantane-3-ols ⟨80IZV1621, 82JOM(226)115⟩ (Scheme 57).

Ate-complexes of 3-borahomoadamantanes undergo a reaction of hydride elimination when treated with AcCl, giving 8-methylene-3-methyl-3-borabicyclo[4.3.1]decanes (Scheme 58). The hydride elimination occurs regioselectively only from the bridgehead β-position of the caged compounds ⟨86T1079⟩.



Scheme 57

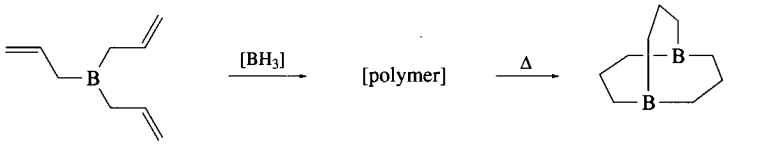


R = Me, H

Scheme 58

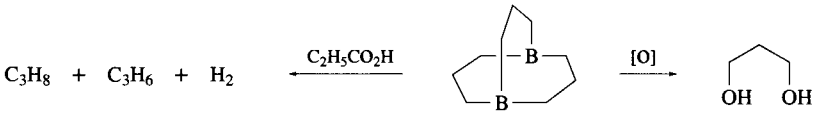
8.34.7 RELATED SYSTEMS

Hydroboration of triallylborane with diborane ⟨62IZV1475⟩ or triethylamine–borane ⟨64JCS4753⟩ leads to a polymer (Equation (26)). However, pyrolysis of this polymer yields a mixture of at least eight volatile products, the main component of which is believed to be 1,5-diborabicyclo[3.3.3]undecane (**144**). Compound (**144**) is extremely sensitive to air, water, and ethanol, suggesting that both boron atoms are 3-coordinated. It reacts with ammonia at −78 °C to form a 2 : 1 adduct, $(NH_3)_2C_9H_{18}B_2$, which dissociates completely into its components below 0 °C. Oxidation of (**144**) with hydrogen peroxide gives 1,3-propanediol uncontaminated with 1,2-propanediol; protonolysis with propionic acid gives propane in low yield together with small amounts of propylene and hydrogen (Scheme 59) ⟨64JCS4753⟩.



(26)

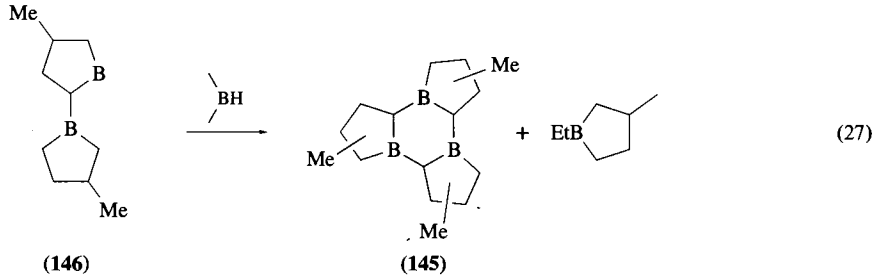
(**144**)



(**144**)

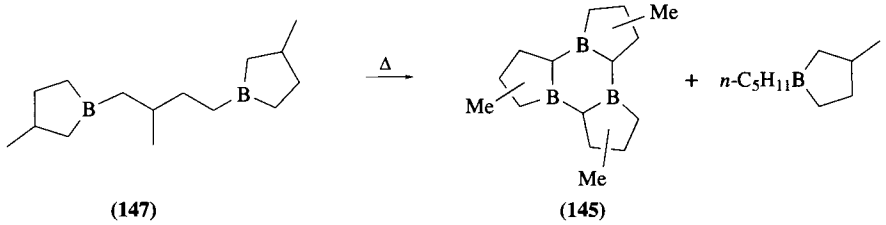
Scheme 59

Tetracyclic compound (**145**) was obtained as a mixture of isomers (b.p. 85 °C/0.3 mm Hg) by dimerization of bicycle (**146**) in the presence of B—H bonds (Equation (27)) ⟨63AG346⟩ or by thermolysis of diboron compound (**147**) (Equation (28)) ⟨63AG1079⟩.



(27)

(**146**) (**145**)



(28)

(**147**) (**145**)

8.34.8 IMPORTANT COMPOUNDS AND APPLICATIONS

Perhydro-9b-boraphenalenes (**3a**,**b**) proved to be useful synthons for the preparation of various polycyclic heterocycles (see Section 8.34.3.3.5). Borohydrides of the type (**59**) made from (**3**) are successfully used as stereoselective reducing reagents (see Section 8.34.3.3.8 for details).

1-Boraadamantane (**5**) is used as a starting compound in the most effective synthesis of 1-azaadamantane (Section 8.34.5.5.3). Several complexes of 1-boraadamantane (**5**) reveal significant therapeutic and prophylactic activity against influenza ⟨79MI 834-01⟩.

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8.35
Three Heterocyclic Rings Fused (5 : 5 : 5)

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and

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8.35.1 INTRODUCTION

A fairly large number of different three five-membered heterocyclic ring systems fused (5 : 5 : 5) are known. Surprisingly a comprehensive treatment along with the development of systematic classification and recognition for recording various properties is absent. In order to understand all these properties systematically, it is highly desirable to have an unambiguous idea about the structural patterns of different representative members of this unique heterocyclic ring system.

8.35.1.1 Classification

The compounds of this series so far encountered, logically belong to the following two distinct classes:

(i) linearly fused (5 : 5 : 5) systems,

(ii) angularly fused (5 : 5 : 5) systems.

In addition to these two distinct classes, there are more compounds reported bearing *spiro* and propellane moieties which are classified under the heading "miscellaneous".

Taking first the linearly fused system, it is obvious that it should incorporate at least two heteroatoms of the types A–E (see Figure 1) so as to generate a (5 : 5 : 5) heterocyclic system. It can be noted that further representatives of this class are reported which incorporate three, four, five and up to six heteroatoms in linearly fused three heterocyclic rings fused (5 : 5 : 5).

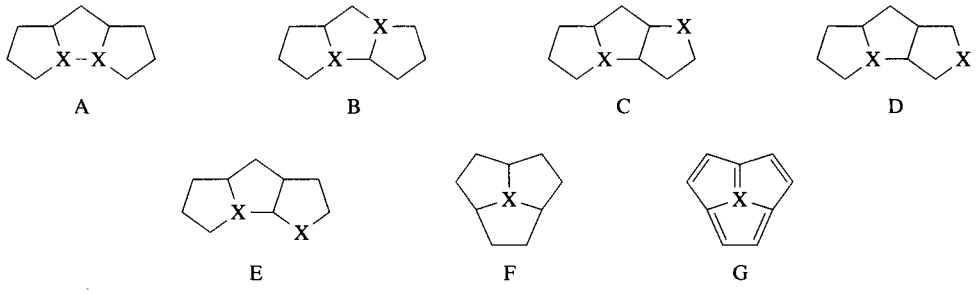


Figure 1 Typical structures of three heterocyclic rings fused (5:5:5).

Among the different members of the angularly fused system, the central position may be occupied by a single heteroatom (type F). The central atom is usually nitrogen in the compounds reported up to 1995. This represents a unique well-known class designated as "cyclazine" following a proposal by Boekelheide who reserved the term cyclazine for the general case of a conjugated unsaturated cyclic molecule held planar by three covalent bonds to an internal nitrogen atom ⟨78AHC(22)321⟩.

Besides cyclazines, there are a large number of examples of this angularly fused heterocycle containing up to six heteroatoms leading to three heterocyclic rings fused (5 : 5 : 5). When $X = N^+$ in G, the nitrogen atom will carry a positive charge and such cationic cyclazines have not been described so far.

Considering the above-mentioned classification, it is highly pertinent to list the more important compounds reported in the literature in tabular form (Tables 1–9) as there is no specific review available in the literature on the subject.

Table 1 Linearly fused (5 : 5 : 5) heterocycles with two heteroatoms.

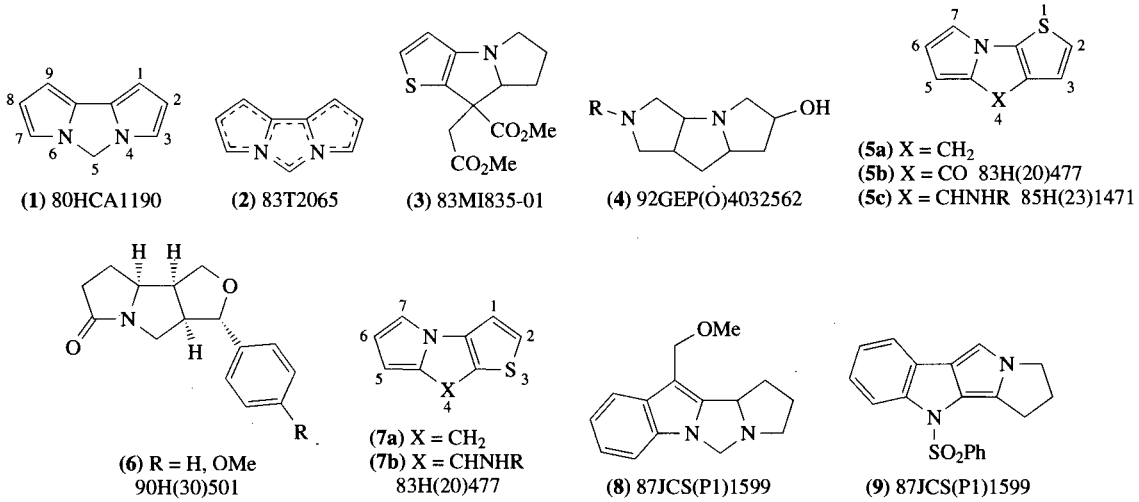
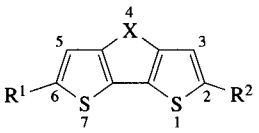


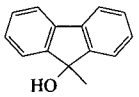
Table 2 Linearly fused (5 : 5 : 5) heterocycles with three heteroatoms.



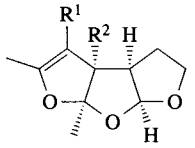
(**10a**) $R^1 = R^2 = H$, X = NH 83JCS(P1)2551
(**10b**) $R^1 = R^2 = Br$, X = S 87CL2339
(**10c**) $R^1 = R^2 = CHO$, X = S 73JCS(P2)1816

(**10d**) $R^1 = R^2 = C(OH)(C_6H_{11})_2$, $-CH(OH)PH_2$,

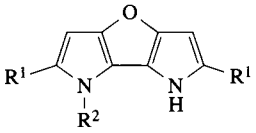
(**10e**) $R^1 = R^2 = H$, X = SO_2 82JCS(P2)301
(**10f**) $R^1 = R^2 = -OBu^t$, X = S 91CL1117



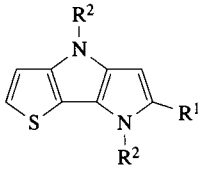
, X = S 92CC1381



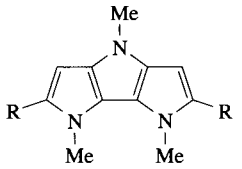
(**11**) $R^1 = R^2 = Ac$, CO_2Et
92T5883



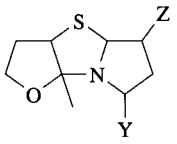
(**12**) 92M807
Benzo deriv.
84CCC1529



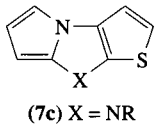
(**13**) 89TL1655
89JAP(K)6786



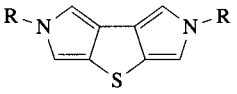
(**14a**) R = H 89TL1655
(**14b**) R = CO_2Et 89JAP(K)172387



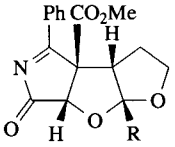
(**15a**) Y = COR, Z = R
(**15b**) Y = COX, 81TL2727
(**15c**) Carbocyclic deriv. 94EUP600741
(**15d**) Y = Z = CO_2Et
(**15f**) Y = COR 85T3537



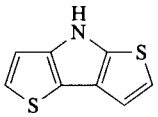
(**7c**) X = NR
85H(23)1471



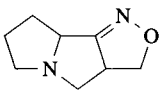
(**16**) 93T6831



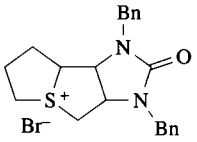
(**17**) R = H, Me
87CPB4730



(**18**) 83JCS(P1)2551



(**19**) 91OMS(26)667



(**20**) 81EUP36030

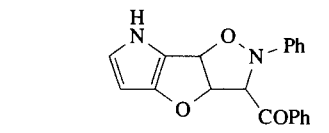
8.35.1.2 Nomenclature

The naming of these three heterocyclic fused (5 : 5 : 5) ring systems has been done according to the IUPAC system of nomenclature. Some examples are given below. Compound (**1**) (Table 1) is named 5*H*-dipyrrolo[1,2-*c* : 2′,1′-*e*]imidazole. Compound (**10b**) (Table 2) is 2,6-dibromodithieno[3,2-*b* : 2′,3′-*d*]thiophene. Compound (**23**) (Table 3) is 5λ^4-[1,2]dithiolo[1,5-*b*]thieno[2,3-*d*][1,2]dithiole. The names of compounds (**41b**) and (**43**) (Table 5) are 2a-aza-1-phenyl[2.2.2]cyclazine and 5-phenyl-1-thia[2.2.2]cyclazine respectively. Compounds (**45**) and (**46**) (Table 6) have been given the names hexahydro-6b*H*-2a,4a,6a-triazacyclopenta[*cd*]pentalene and 2-alkyl-3,4-dicarbomethoxy-1,6a-diaza[2,2,2]cyclazine respectively. Finally compound (**50**) (Table 7) is named 2,2a,4,4a,6,6a-hexahydro-1,3,5-trithia-7-azacyclopenta[*cd*]pentalene.

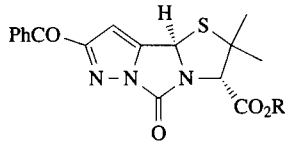
8.35.2 THEORETICAL METHODS

Hückel molecular orbital (HMO) calculations on acepentylene (**63**) and its comparison with cycl[2,2,2]azinium salts (**64**) ⟨78AHC(22)321⟩ show that the cyclazinium salts should be represented as an annulenone derivative of the $(4n + 1)\pi$ type ⟨65CCC3529⟩. HMO treatment further points out

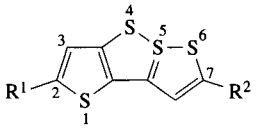
Table 3 Linearly fused (5 : 5 : 5) heterocycles with four heteroatoms.



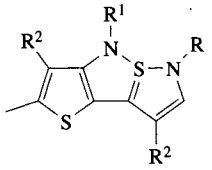
(**21**) 81EUP36030



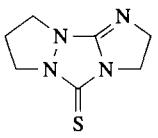
(**22**) 82TL2813



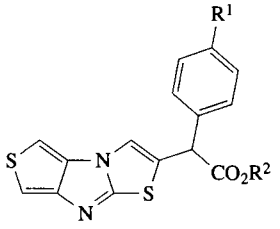
(**23**) 80AHC(27)177



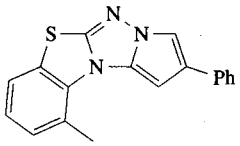
(**24**) 92JPR25



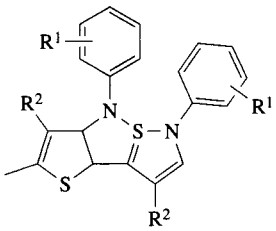
(**25**) 92PHA416



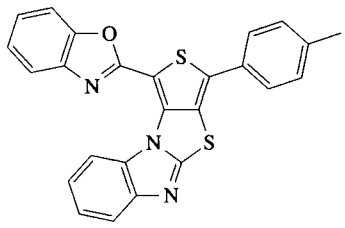
(**26**) R^1 = H, halo, CF_3, R^2 = H
90EUP358116



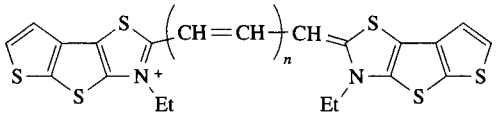
(**27**) 92MI 835-01



(**28a**) R^1 = H, Me, R^2 = Me
(**28b**) R^1 = H, R^2 = Ph
89GEP(E)264697



(**29**) 91JHC1449



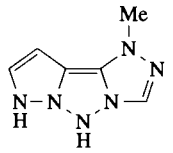
(**30**) 76AHC(19)123

a closed shell system for the dianion of (**63**) suggesting stabilization for isoelectronic cycl[2,2,2]azines with an additional nitrogen in a peripheral position, for example, (**65**). HMO theory was also applied to explain the reactivity of the anion (**66**) with chlorocarbene to afford (**67**) ⟨80HCA1190, 83T2065⟩.

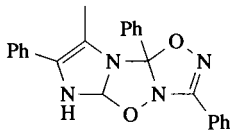
The reaction corroborates the reactivity of the center with the observed largest excess of charge (−0.38) and the HOMO of the ion has a large coefficient at this center.

The results from the *ab initio* calculations on (**50**) (Table 7), a hexahydrotrithiaazacyclopentapentalene derivative ⟨84JCS(D)2073⟩, reveal that the four highest orbitals are predominantly combinations of the p_z orbitals on the nitrogen and sulfur atoms. All these orbitals are centered on nonbonded atoms. Any electronic communication between them is probably a through-space π-interaction. The energy of HOMOs which consist of a degenerate set is -1.05×10^{-18} J. Primarily these are composed of $3p_z$ orbitals on the sulfur atoms. These orbitals are responsible for carrying 75% of the electron density. Furthermore, the $2p_z$, $3p_x$ and $3p_y$ atomic orbitals on the sulfur nuclei carry the remaining electron density in the degenerate molecular orbitals. The bonding and antibonding combinations of p_z orbitals on the three sulfur atoms and nitrogen atom produce the next two lower occupied orbitals, at -1.13×10^{-18} J and -1.22×10^{-18} J. It should be emphasized that the p_z orbitals bear 93% of the electron density in the bonding combination and 57% in the antibonding combination.

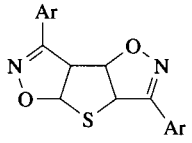
Table 4 Linearly fused (5 : 5 : 5) heterocycles with five or six heteroatoms.



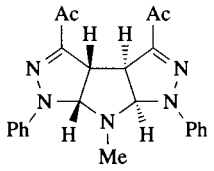
(31) 74MI 835-01



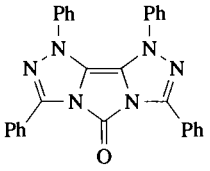
(32) 83JCR(S)172



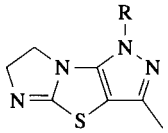
(33) 77JCS(P2)706
78T3545
Ar = 3,5-Cl_2-2,4,6-Me_3C



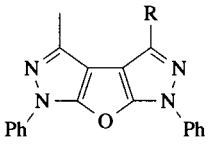
(34) 72TL4703



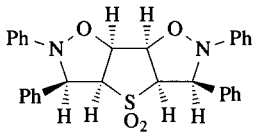
(35) 81KGS694



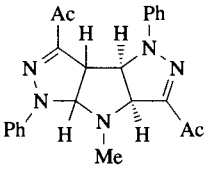
(36) 90JIC610



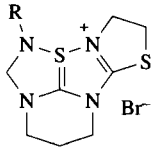
(37) 92BCJ1652



(38) 81JOC3502

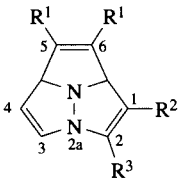


(39) 72TL4703

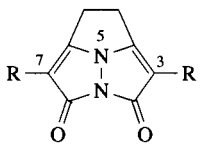


(40) R = Me, Et, allyl
90CE145

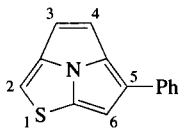
Table 5 Angularly fused (5 : 5 : 5) heterocycles with two heteroatoms.



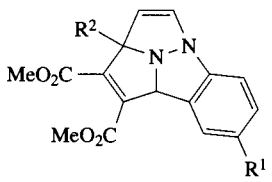
(41a) R^1 = CO_2Me, R^2 = Ph, R^3 = COPh
(41b) R^1 = R^3 = H, R^2 = Ph 66PNA(55)1385
(41c) R^1 = COPh, R^2 = alkyl, R^3 = COR 90CE1841
(41d) Benzo deriv. 88H(27)1207



(42) 90JA7315

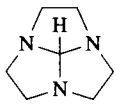


(43) 77 USP 4033978
75 USP 3920672

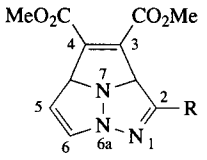


(44) 87H(26)133

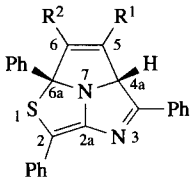
Table 6 Angularly fused (5 : 5 : 5) heterocycles with three heteroatoms.



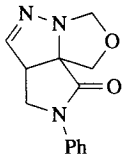
(**45**) 93TL3691
80JA6364
80JA6365



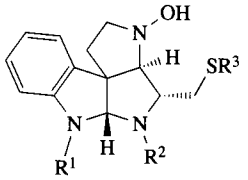
(**46**) 78TL1291



(**47**) 83CL763

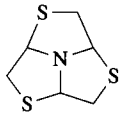


(**48**) 93BCJ1496

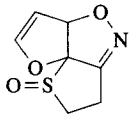


(**49**) R^1 = H, Me, CH_2OMe
R^2 = CO_2Bn, $CO_2CH_2CCl_3$, CO_2Me
R^3 = CO_2Me, Me, CO_2Bz, CO_2CHCCl_3, $CH_2OCH_2CH_2OMe$ 88CC463

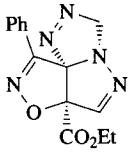
Table 7 Angularly fused (5 : 5 : 5) heterocycles with more than three heteroatoms.



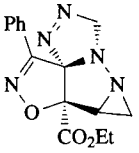
(**50**) 84JCS(D)2073



(**51**) 89TL5013

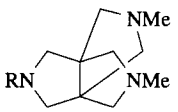


(**52**) 89JOC706

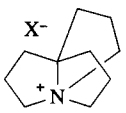


(**53**) 89JOC706

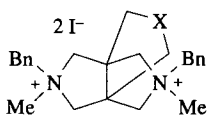
Table 8 Propellane-type (5 : 5 : 5) heterocycles.



(**55**) R = H 92ACS60



(**54**) X = Cl, Br
54CCC298

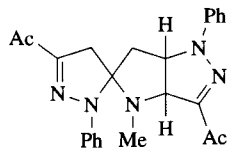


(**56**) X = O, NBn
87G451

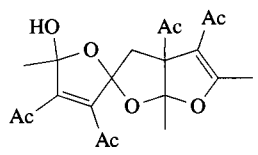
The *ab initio* calculations support a very interesting observation. The crystal structure of (**50**) shows that there is some electronic interaction between the sulfur and nitrogen atoms. Calculations also suggest that there is a slight stabilization arising from the interaction of the p_z lone pair orbitals on nitrogen and sulfur atoms.

According to theoretical calculations ⟨77CCA107, 77JA1692, 83JA1979⟩, (**68**) turns out to be a highly unstable heteroaromatic ring system, but it has successfully been prepared ⟨90H(31)603⟩ (Section 8.35.9).

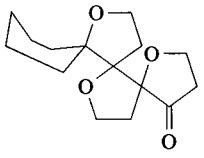
Table 9 Miscellaneous and *spiro* (5 : 5 : 5) heterocycles.



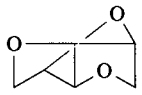
(**57**) 78JHC293



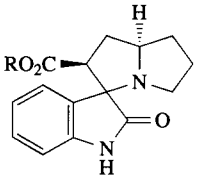
(**58**) 80CJC1645



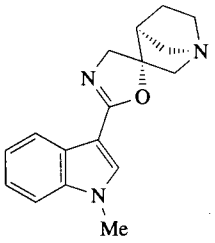
(**59**) B–81MI 835-01



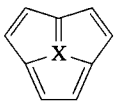
(**60**) 75AX(B)552



(**61**) R = menthyl
91TL5417



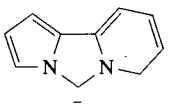
(**62**) 90JCS(P1)3183



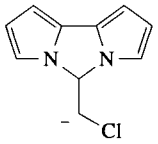
(**63**) X = C
(**64**) X = N^+



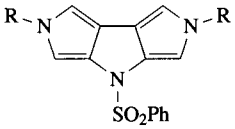
(**65**)



(**66**)



(**67**)



(**68a**) R = H
(**68b**) R = Bn

8.35.3 EXPERIMENTAL STRUCTURAL METHODS

8.35.3.1 Electronic and IR Spectroscopy

Electronic (UV and visible) spectroscopy has not been utilized in a routine manner, most likely due to the fact that the nature of heterocycles is rather difficult to correlate correctly with the chromophoric absorption; IR spectroscopy, however, has been applied almost routinely, as this technique can establish unequivocally the presence of various functionalities.

The *spiro*-heterocycles (**58**) (Table 9) have IR absorptions at 3420 cm^{-1}, 1715 cm^{-1}, 1700 cm^{-1}, and 1605 cm^{-1} fully consistent with their structure ⟨80CJC1645⟩. This indicates the presence of a conjugated —CO—C=C—O— moiety ⟨76H(4)1775⟩. This was further confirmed by the UV absorption at 266 nm. The presence of a further conjugated Ac—C=C—Ac moiety was indicated by the record of a second maximum at 220 nm ⟨57BSF997⟩.

More applications of UV and IR spectroscopic techniques have been recorded ⟨83CL763, 83H(20)477, 83H(20)1021, 83JCS(P1)2551, 89TL1655, 90H(31)603, 90JHC1805⟩.

8.35.3.2 NMR Spectroscopy

Proton NMR spectroscopy has been extensively used in order to obtain unambiguous structural assignments. It is interesting to note that compound (**50**), obtained from the reaction of dithiocarbamate with chloroacetaldehydehydrate by Craig *et al.* ⟨55JA1283⟩, was initially assigned the

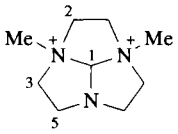
wrong structure. Its correct structure was assigned as hexahydro-1,3,5-trithia-6b-azacyclopenta[*c*,*d*]pentalene, on the basis of its ^{1}H NMR spectra taken in different solvents ($CDCl_3$, C_6D_6 and CF_3CO_2H) by Fort and Semon ⟨67JOC3685⟩. The ^{1}H NMR spectrum in $CDCl_3$ solution exhibited the presence of an ABX spin system having $J_{AB} = 11.5$ Hz, $J_{AX} = 5.5$ Hz and $J_{BX} = 6.1$ Hz. Interpretation of the ^{1}H NMR spectrum became much easier in benzene as solvent as the nonequivalency of H_A and H_B was removed and the spin system was changed from ABX to A_2X with $J_{AX} = 6.6$ Hz. In CF_3CO_2H solvent, the nitrogen atom undergoes extensive protonation which gives rise to a clear distinction between methylene protons. There are some changes in J values which may most plausibly be attributed to the changes in bond lengths and bond angles caused by the positive charge on nitrogen. It is interesting to note that the structure determined by ^{1}H NMR spectroscopy has unequivocal support from x-ray crystallography (*vide intra*).

Since ^{1}H NMR spectral analysis has become an almost routine affair in structure elucidation, ^{1}H NMR spectral data is available for different types of three heterocyclic ring systems fused (5 : 5 : 5). Salient features of all ^{1}H NMR data available are being determined which will be very useful for structural studies.

With compounds (**47**; R^1,R^2 = CO_2Me and R^1,R^2 = COPh) (Table 6) the H at position 4a appeared as a singlet at δ 5.72 and δ 6.31 respectively. With other derivatives (**47**; R^1 = H, R^2 = CO_2Me and COPh) the same H as at 4a appeared as a doublet at δ 5.42 (J = 1.2 Hz) and δ 5.52 (J = 2.0 Hz) respectively, whereas H5 appeared as a doublet at δ 7.01 and δ 6.53 respectively ⟨83CL763⟩.

In ^{1}H NMR spectra of compounds (**5a**) and (**7a**) (Table 1), the signal for the C-4 methylene group appeared at δ 3.70 and δ 3.83 respectively, whereas when X = CHOH in (**5a**) and (**7a**) the methine signal appeared at δ 3.40 and δ 5.70 respectively. All other alkenic protons appeared at δ 6.00 to δ 8.03 ⟨83H(20)477⟩. H-2 in (**7a**; X = CO) moves to a maximum downfield position at δ 8.03, most likely due to the electron-withdrawing mesomeric effect of the carbonyl group.

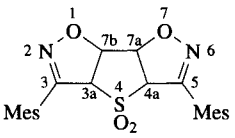
The protons of compound (**10a**) (Table 2) appeared at δ 6.65 and δ 6.74 as 2H doublets, J = 5.1 Hz, whereas compound (**18**) (Table 2) showed signals at δ 6.61 and δ 6.69 as 2H doublets, J = 5.1 Hz and at δ 6.81 (2H, d, J = 5.1 Hz) along with a broad singlet for H1 at δ 7.30 ⟨83JCS(P1)2551⟩. More ^{1}H NMR spectral data are reported for a large number of linearly fused (5 : 5 : 5) compounds with three heteroatoms ⟨83H(20)1021, 90H(31)603, 90JHC1805⟩; the configuration of (**11**) (Table 2) was determined by Nuclear Overhauser Effect (NOE) studies ⟨92T5883⟩. The 220 MHz ^{1}H NMR spectrum of tricyclic trisaminomethane (**45**) (Table 6) ⟨80JA6364, 80JA6365⟩ exhibits a highly characteristic AA′ BB′ pattern for the methylene hydrogens. The methylene hydrogen suffers considerable deshielding ⟨71CRV109⟩. The spectrum exhibits the following signals: δ 5.03 (1H, s), δ 3.08 (6H, AA′, J_{AB} = 10.9 Hz, $J_{AA'} = J_{AB'}$ = 5.9 Hz), and δ 2.80 (6H, BB′, $J_{BB'}$ = 6.1 Hz). The dication (**69**) showed the methine hydrogen at δ 6.51 and a methyl singlet for 6H at δ 2.96. Coupling constants obtained from computer simulation of the pattern are fully consistent with the expected highly eclipsed conformation.



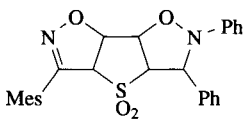
(**69**)

The symmetrical structure of (**38**) (Table 4) was evident from the coupling constant values of various protons. A multiplet at δ 6.65 to δ 7.62 corresponds to aromatic protons and three different signals at δ 4.12 (q), δ 5.20 (d), and δ 5.27 (d) clearly stand for the proton pairs H_{3a} and H_{4a}, H_3 and H_5, H_{7a} and H_{7b}, respectively. These signals show up coupling constant values $J_{H7a-H4a} = J_{H7b-H3a}$ = 5.7 Hz and $J_{H3a-H3} = J_{H4a-H5}$ = 3 Hz ⟨81JOC3502⟩. It is also worthwhile to note the ^{1}H NMR spectra of compounds (**70**) and (**71**) ⟨81JOC3502⟩.

The asymmetric structure of (**33**; Ar = Ph) (Table 4) is fully supported by its ^{1}H NMR spectral pattern wherein all the ring protons are distinguishable ⟨78T3545⟩. The *anti*-stereochemistry has been established by the lack of appreciable coupling (< 1 Hz) in (**33**) between the adjacent protons on the side joining the two heterocyclic rings ⟨76JOC3349⟩. The ^{1}H NMR spectrum of (**72**) closely corresponds to that of the phenyl derivative of (**33**) ⟨78T3545⟩. In (**73**) the C-5 isoxazolonic protons absorb at low field (δ 6.54) as a doublet due to the deshielding effect of oxygen and sulfur, whereas the doublet of the other isoxazolonic proton at C-4 appears at a higher field (δ 4.22) with J = 7.4 Hz which is in the usually expected range reported for C-4 isoxazolonic protons ⟨77JCS(P2)706⟩. In

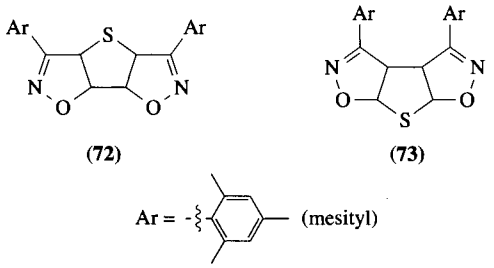


(**70**) Mes = mesityl
δ 6.67–6.92 (4H,s)
δ 5.70 (1H,d, $J_{H7b-H9a}$ = 8 Hz)
δ 4.95 (1H,d, $J_{H9a-H7b}$ = 8 Hz)
δ 2.38 (6H,s)
δ 2.25 (3H,s)



(**71**) Mes = mesityl
δ 6.77–8.30 (12H,m)
δ 5.56 (1H,d, $J_{H7a-H4a}$ = 6.3 Hz)
δ 5.20 (1H,d, J_{H4a-H5} = 2.4 Hz)
δ 5.00 (1H,d, $J_{H9a-H7b}$ = 9 Hz)
δ 4.06 (1H,dd, $J_{H4a-H7a}$ = 6.3 Hz, J_{H5-H4a} = 2.4 Hz)

the symmetrical structures (**72**) and (**73**) an *anti*-stereochemistry is suggested by analogy with (**33**; Ar = mesityl).



(**72**) (**73**)

Ar = (mesityl)

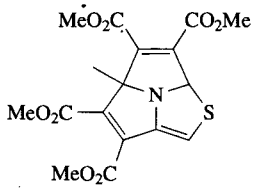
The *spiro*-heterocyclic compound (**58**) (Table 9) displays the following ^{1}H NMR characteristics ⟨80CJC1645⟩:

(i) OH group: δ 5.85 (1H, disappeared on deuteration);
(ii) pair of methylene protons: δ 3.36 (1H, d, J = 14 Hz), δ 2.15 (1H, d, J = 14 Hz);
(iii) five downfield methyl groups: δ 2.36 (6H, s), δ 2.31 (3H, s), δ 2.15 (3H, s), δ 2.04 (3H, s);
(iv) two upfield methyl groups: δ 1.56 (3H, s), δ 1.47 (3H, s).

The ^{1}H NMR data turned out to be insufficient for arriving conclusively at the correct structure. The unequivocal proof for the structure of compound (**58**) was finally achieved with the help of x-ray crystallography.

Compound (**42**) (Table 5), described as one of the bimanes, shows a ^{1}H NMR spectrum at room temperature having a single signal for CH_2. This is most likely due to the equilibration of the hydrogen by flipping of the bimane ring. The coalescence temperature of the 3,7-dimethyl derivative (**42**; R = Me) is 205 K and that for the 3,7-dichloro compound (**42**; R = Cl) is below 181 K. Through the simulation of NMR spectra at different temperatures the rate constant (6–8 × 10^5 sec^{-1}) and activation energy (11 ± 1 Kcal $mole^{-1}$) have been found for the 3,7-dimethyl bimane derivative ⟨90JA7315⟩.

In the thiacyclazine derivative (**74**), the chemical shift of the methyl group of the Δ^3-pyrroline moiety can be safely taken as a diagnostic value occurring at δ 1.67 instead of in the range δ 2.2 to 2.6 which is generally observed for pyrrole methyl groups ⟨80JOC5396⟩.



(**74**)

Though ^{1}H NMR spectroscopy is almost routinely applied on three heterocyclic ring fused (5 : 5 : 5) systems, use of ^{13}C NMR is not so routine. Some ^{13}C NMR data have been compiled in order to get an insight into this area.

Table 10 Carbon-13 NMR spectral data for (**47a–d**).

Structure	R^1	R^2	*2-c*	*2a-c*	*4-c*	*4a-c*	*6a-c*	*Carbonyl*
(**47a**)	CO_2Me	CO_2Me	107.8s	170.7s	155.0s	73.3d	86.7s	162.3s 165.0s
(**47b**)	COPh	COPh	108.3s	172.6s	156.6s	75.4d	89.3s	192.6s 194.7s
(**47c**)	H	CO_2Me	107.2s	171.1s	155.5s	72.7d	86.0s	162.8s
(**47d**)	H	COPh	108.0s	171.8s	155.8s	73.2d	87.8s	192.2s

Carbon-13 NMR spectral data for compound (**47**) (Table 6) is reported in Table 10 ⟨83CL763⟩.

Tricyclic trisaminomethane (**45**) (Table 6) had two absorption signals in the ^{13}C NMR spectrum in D_2O solvent, at δ 93.2 and δ 41.9. It should be emphasized that the dication (**69**) in D_2O solvent showed the following signals in its ^{13}C NMR spectrum: δ 106.8 (C_1), 53.9 (C_2), 52.2 (C_3), 41.9 (C_4), and 41.5 (C_5), which indicates that tricyclic integrity is common to (**45**) and (**69**) ⟨80JA6364⟩.

The ^{13}C NMR spectral data confirms the structures (**38**), (**70**) and (**71**) ⟨81JOC3502⟩. The ^{13}C chemical shifts of the tertiary carbon atoms located on the thiophene-1,1-dioxide moiety are noteworthy (Table 11).

Table 11 Significant ^{13}C NMR signals for heterocycles (**38**), (**70**), and (**71**).

Structure	C_α	C_β	$C_{\beta'}$	$C_\beta - C_\alpha$
(**38**)	75.92	78.70	70.68	2.78
(**70**)	74.37	85.52	152.79	11.15
(**71**)	74.10	84.56	152.93	10.46
	76.14	79.83	70.23	3.69

Among these heterocycles (**38**), (**70**) and (**71**) the higher-field carbon signals are assigned to the one located at the position α to the SO_2 group. The results of the substituent increment generally observed in the tetrahydrothiophene series ⟨79CJC131⟩ indicate that this signal at higher field is due to the shielding effect offered by the heterocyclic oxygen atom. Nevertheless crystal structure analysis has been essential for the elucidation of the complete stereostructure of these heterocycles.

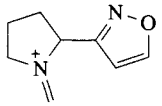
Carbon-13 NMR spectroscopy has been successfully used in order to establish the correct structure for (**35**) (Table 4) ⟨81KGS694⟩.

8.35.3.3 ESR Spectroscopy

A detailed study was carried out on the radical anion derived from (**10c**) (Table 2) in connection with the conformational analysis of heteroaromatic carbonyl compounds. Notably different ESR signals could be observed originating from distinct rotational isomers. Unfortunately no information on the interconversion of the rotamers of (**10c**) could be definitely derived since these radicals were highly unstable at the temperature necessary for interconversion ⟨74JCS(P2)562⟩.

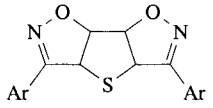
8.35.3.4 Mass Spectroscopy

This technique is almost routinely applied for unambiguous characterization of this class of heterocycles. Thus the base peak for the compound (**19**) (Table 2) is the $(M-1)^+$ peak due to the formation of aromatic species (**75**) ⟨91OMS(26)667⟩.



(**75**)

The mass spectral fragmentation for (**33**) (Table 4) and (**33a**) revealed some common features, for example, a peak of low intensity at m/z 313 and an intense peak at m/z 229, which were ascribed to the ions $(M\text{-}ArCNO)^+$ and $(ArCNO)^+$ arising from a retro cycloaddition-type fragmentation. Peaks at m/z 329$(M\text{-}ArCN)^+$ and 213$(ArCN)^+$ were also present to a major extent in the case of (**33**) (Table 4) ⟨77JCS(P2)706⟩. Both these fragmentation patterns have been reported for 3-aryl-2-isoxazolines ⟨73G223, 74T3765⟩. Other notable fragments of compound (**33**) are m/z 546(5%), 544(10), 542(7), 258(42) and 178(100) and those of (**33a**) are 546(7%), 544(15), 542(11), 329(2), 258(100), and 178(72).



(**33b**)

High resolution mass spectral data have been reported for compounds (**68a**) and (**68b**) ⟨90H(31)603⟩: (**68a**), ms m/z 285(M^+, 11%), 157(100); hrms m/z 285.0583 (calculated for $C_{14}H_{11}N_3O_2S$: 285.0572); (**68b**), ms m/z 465(M^+, 100), 324(69); hrms m/z 465.1499 (calculated for $C_{28}H_{23}N_3O_2S$: 465.1511).

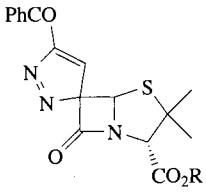
8.35.3.5 Photoelectron Spectroscopy

The photoelectron spectrum of compound (**50**) (Table 7) has been reported in which a single broad peak was observed centered at -1.38×10^{-18} J. This was attributed to the transitions from the energetically very similar molecular orbitals formed from the interacting sulfur and nitrogen lone pairs. If the nitrogen and sulfur lone pairs were completely localized and noninteracting, two sharp peaks would have been expected, one at ca. -1.39×10^{-18} J for a transition from the sulfur orbitals and another at ca. -1.43×10^{-18} J for a transition from the nitrogen orbitals ⟨77JA3226⟩. The proximity of these expected peaks may alone account for the broadness of the observed transition.

8.35.3.6 X-ray Studies

X-ray crystallographic studies are mainly carried out on type three heterocyclic ring systems fused (5 : 5 : 5) where the assignment of the correct structure could not be unequivocally settled through the application of standard spectroscopic techniques. Thus the structure of the compound (**50**) (Table 7) prepared by Craig *et al.* ⟨55JA1283⟩ could only be assigned with full certainty after a considerable period of time by x-ray crystal structure determination ⟨84JCS(D)2073⟩. The study revealed a general flattening of (**50**) with the nitrogen atom being pulled slightly into the plane defined by the three sulfur atoms. The crystals are rhombohedral having space group R3c with $a = 7.721(2)$ Å, $\alpha = 105.14(2)°$ and $Z = 2$. The structure was solved by direct methods and refined to a final $R^1 = 0.024$ ($R^2 = 0.041$) for 649 unique reflections.

The absence of a β-lactam moiety in the product formulated as (**76**; $R = CH_2CCl_3$), obtained from the reaction between propiolophenone and trichloroethyl 6-diazopenicillinate, could be unambiguously settled as (**22**) through x-ray crystallographic analysis ⟨82TL2813⟩. The crystals of the ester turn out to be trigonal having space group $P3_1$ with $a = 10.751(3)$ Å, $c = 16.586(4)$ Å and $z = 3$. The structure analysis actually used 1353 independent reflections with $I > 26(I)$ and refinement of all nonhydrogen atoms with anisotropic vibration parameters converged at $R^1 = 0.085$ and $R^2 = 0.092$.



(**76**) $R = CH_2CCl_3$

In order to analyze the structure of (**68b**) in detail a single-crystal x-ray analysis was carried out ⟨90H(31)603⟩.

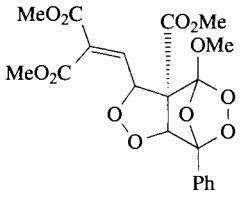
Only crystallographic analysis on (**38**) (Table 4) could reveal its stereostructure unequivocally as *anti* ⟨81JOC3502⟩ with oxygen atoms bonded to the carbon atoms 7a and 7b in positions *β* to the SO_2 group. The dihedral angle turns out to be $H_3C_3C_{3a}H_{3a} = 104.8°$ indicating H_3 and H_{3a} to be *trans* to each other which supports the coupling constant value ($J_{H3-H3a} = 3$ Hz) in the ^{1}H NMR spectrum (*vide supra*). Further the dihedral angle $H_{3a}C_{3a}C_{7b}H_{7b} = 28.1°$ points out H_{3a} and H_{7b} to be *cis* disposed ($J_{H3a-H7b} = 5$–6 Hz) and the dihedral angle $H_{7a}C_{7a}C_{7b}H_{7b} = 82.5°$ corroborates the coupling constant $J_{H7a-H7b} = 0$ Hz indicating the two oxazolidine rings in (**38**) to be *anti* to each other.

As has already been emphasized, only x-ray analysis could unequivocally establish the structure of the *spiro*-heterocycle (**58**) (Table 9) ⟨80CJC1645⟩ as (2*R*,3a′*R*,5*R*,6a′*R*)3,3a′,4,4′-tetraacetyl-5-hydroxy-5,5′,6′-trimethylspiro[furan-2(5*H*),2′(3′*H*)-furo(2,3-*b*)furan]. Automatic centrosymmetric direct methods were applied to solve the structure. The study clearly delineates the spiran system (**58**) between a furan ring and a *cis*-fused furo[2,3-*b*]furan system. The study further reveals that in (**58**) the rings A and C are essentially planar, whereas obvious puckering in ring B is present with the 3′-carbon atom being projected (0.50 Å) out of the plane of the four other atoms.

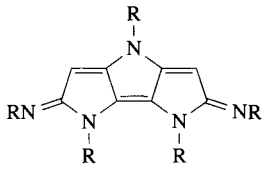
An x-ray study of (**60**) (Table 9), which has C_2 symmetry, established it as tricyclic [1,4 : 2,5 : 3,6]-trianhydro-D-mannitol where the rings are half-chair with atoms C-3 and C-4 as much as 0.54 Å on either side of the plane formed by the rest of that ring ⟨75AX(B)552⟩.

The correct structural assignment of tricyclic biperoxide (**77**) was settled through x-ray analysis ⟨89CC1608⟩. The structures of bimanes (**42**; R = Me or Cl) (Table 5) were also settled by x-ray studies ⟨90JA7315⟩.

The structure of the dipyrrolopyrrole (**78**) was settled unambiguously by applying x-ray crystallography ⟨94IC1539⟩.



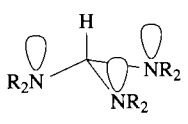
(**77**)



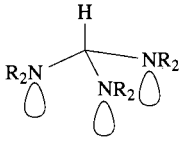
(**78**) R = *p*-tolyl

8.35.4 THERMODYNAMIC ASPECTS

The orthoamide (**45**) (Table 6) most plausibly adopts a conformation in which the lone pairs are *syn*-periplanar or nearly *syn*-periplanar to the central carbon–hydrogen bond as it shows pronounced deshielding of the methine hydrogen in the ^{1}H NMR spectrum and absence of Bohlmann bands in the IR spectrum ⟨71CRV109⟩. Thus the orthoamide (**45**) adopts conformation (**45a**) in which the central carbon–hydrogen bond is *syn*-periplanar to the adjacent lone pairs and not the conformation (**45b**) in which the carbon–hydrogen bond is *anti*-periplanar. Thus there is a dramatic anomeric effect of the nitrogen lone pairs. This conformational preference of (**45**) leads to its obvious inertness for reaction with mercuric acetate even in boiling ethanol. The complex, which may form at the initial stage of the reaction, must respond very slowly in the *syn*-elimination of mercury and acetic acid ⟨58JA371⟩.



(**45a**)

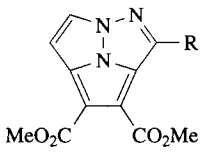


(**45b**)

In assessing the aromaticity of various cyclazines, 1,6a-diaza[2.2.2]cyclazines (**46**) (Table 6) turns out to be diatropic in nature from a comparison of the chemical shifts of the protons H-5 and H-6.

In (**46**) these two protons appear at δ 5.42 to δ 6.62, whereas in (**79**), obtained through ddq dehydrogenation of (**46**), these protons are shifted to downfield at δ 7.08 to δ 8.02 ⟨78AHC(22)321⟩.

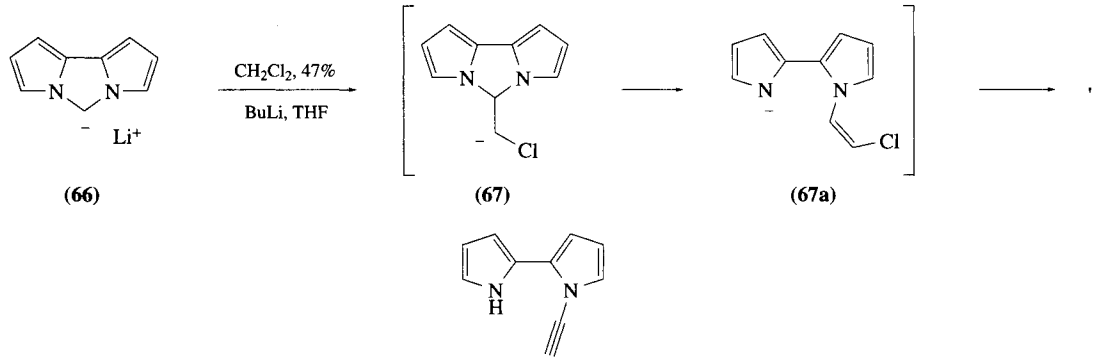
It has been claimed that the anion (**66**), generated from (**1**) (Table 1) by the treatment of methyllithium in THF, records Hückel aromaticity although there is no possibility to give singly charged resonance structures through charge delocalization ⟨80HCA1190⟩.



(**79**)

8.35.5 REACTIVITY OF FULLY CONJUGATED AND NONCONJUGATED RINGS

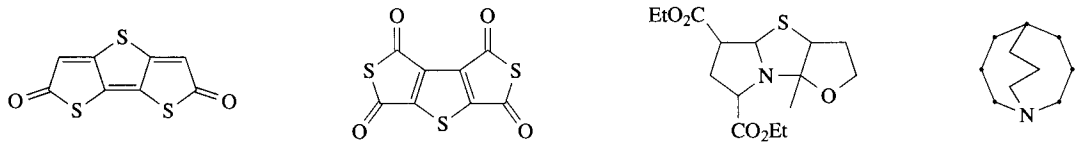
The reaction of dipyrrolo[1,2*c*:2′,1′*e*] imidazolyl anion, as the lithium salt (**66**) of compound (**1**) (Table 1) with chlorocarbene in THF, generated from the reaction between CH_2Cl_2 and BuLi, ultimately afforded the acetylenic compound (**80**) ⟨83T2065⟩. This is probably formed following eliminative ring fission of chlorocarbanion intermediate (**67**) which is generated by trapping of the intermediate chlorocarbene from (**66**). The intermediate (**67**) can eliminate either of the enantiotopic pyrryl moieties leading selectively to the (Z)-β-chlorovinyl derivative (**67a**) which subsequently undergoes further modification to ultimately produce the acetylenic product (**80**) (Scheme 1). The reaction has to be carried out in THF as the lithium salt is insoluble in dimethyl as well as diethyl ether; the reaction in either medium affords an intractable mixture of products in low yield.



(**66**) (**67**) (**67a**) (**80**)

Scheme 1

The heterocycle (**10f**) (Table 2) underwent an elimination reaction providing an efficient synthesis of a quinone derivative of (**81**) thieno[3,2-*b*]thieno[2′,3′-*d*]thiophene ⟨91CL1117⟩. Matrix photolysis of (**82**) ⟨91CB2617⟩ offers an attractive method for obtaining heterocumulenes. The transformation to diethylpyrrolo-2,4-dicarboxylate by treating (**83**) with methanesulfonic acid in methanol followed by quenching with triethylamine is noteworthy ⟨81TL2727⟩. A highly interesting compound 1-azabicyclo[3.3.3]undecane (**84**), named maxine, has been prepared in 60% yield by reducing the quaternary ammonium salt (**54**) (Table 8) with metallic sodium in liquid ammonia ⟨72JA7092, 72JA7100⟩.

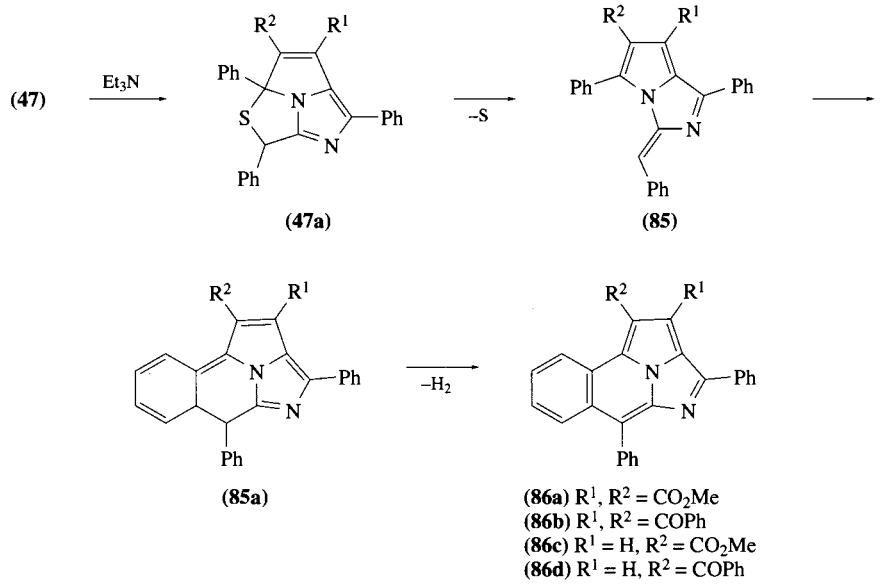


(**81**) (**82**) (**83**) (**84**)

The regio- and periselective [3 + 2] cycloadducts (**47**) (Table 6) obtained from the reaction between acetylenic dipolarophiles and 1,3,6-triphenylimidazo[1,2-*c*]thiazole, acting as a 1,3-dipole or azomethine ylide are thermally unstable as each of these cycloadducts on heating in toluene or

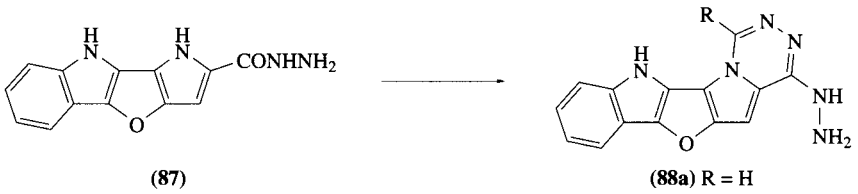
xylene solvent did not isomerize into the thiocarbonyl ylide cycloadducts but underwent decomposition to an intractable and complex mixture of products ⟨83CL763⟩. However, on treatment with an equivalent amount of triethylamine in benzene, (**47**) did follow a clean reaction pathway affording two distinctly different products (**85**) and/or (**86**) depending upon the reaction conditions employed (Scheme 2). Though (**85**) is formed through sulfur elimination, and (**86**) through hydrogen sulfide elimination from (**47**), it has been proved that (**86**) has actually originated from (**85**) as in a separate experiment (**85**) has been quantitatively converted to (**86**). Finally, the formation of (**85**) and (**86**) may be rationalized involving the following sequential steps:

(i) A 1,5-sigmatropic shift induced by triethylamine of H4a of (**47**) to the 2-position forming (**47a**).
(ii) A rare elimination of sulfur leading to the genesis of the isolable intermediate (**85**).
(iii) The phenyl group at the 5-position of (**85**) participates in a 10π cyclization leading to (**85a**).
(iv) Dehydrogenation of (**85a**) affording (**86**).



Scheme 2

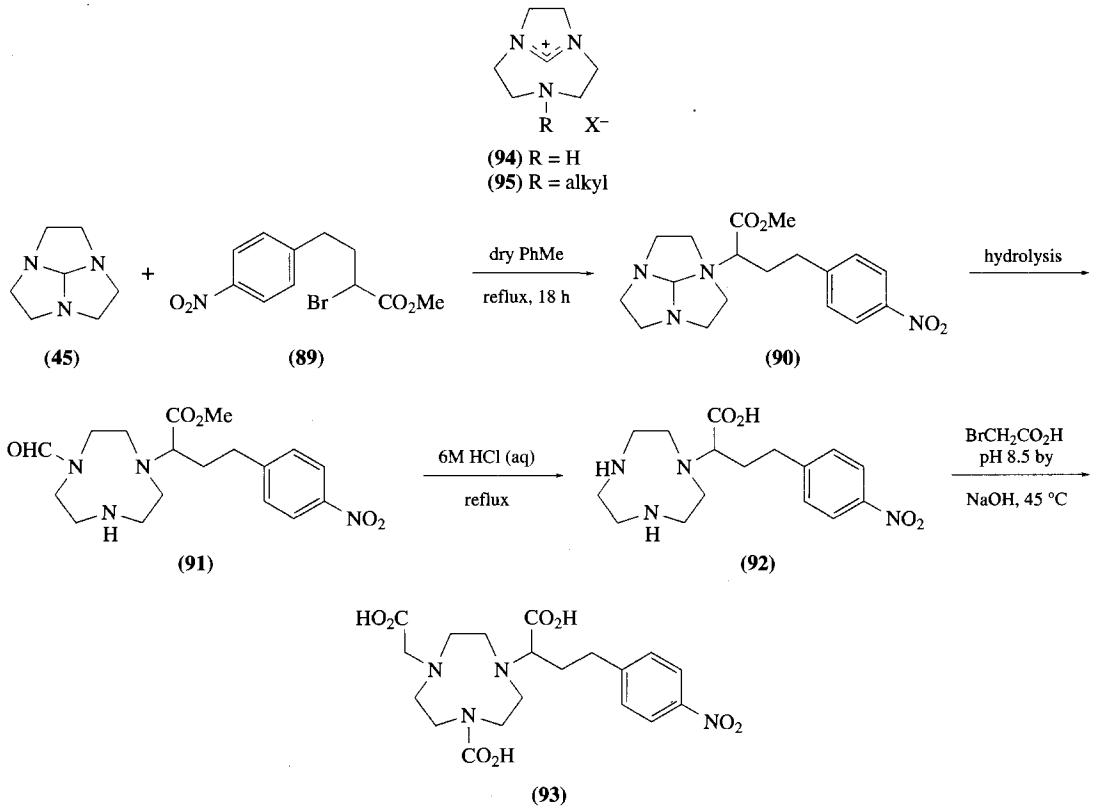
The pyrrolofuroindole (**87**) underwent cyclization with ethyl orthoesters, $RC(OEt_3)$ (R = H, Me) followed by treatment with P_2S_5 and N_2H_4 to afford the triazolotriazinopyrrolofuroindole derivatives (**88**; R = H, Me) (Equation (1)) ⟨84CCC1529⟩.



(1)

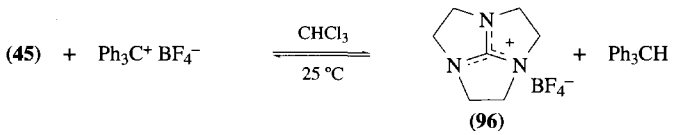
The ring opening of the fused system of three heterocyclic rings (5 : 5 : 5) is also interesting. Thus the report of a direct synthesis of a bifunctional chelating agent, NOTA (**93**) used for radiolabeling proteins, from the easily available orthoamide derivative (**45**) (Table 6) of 1,4,7-triazacyclononane and bromide (**89**) through a ring-opening strategy via (**90**), (**91**), and (**92**), is worth recording ⟨93TL3691⟩. The synthetic protocol delineated in Scheme 3 provides a simple and direct route to an *N*-substituted NOTA, reducing tedious multistep synthesis and replacing preparative HPLC, often required by convenient ion-exchange chromatography.

When (**45**) was allowed to react with either methyl iodide or methyl fluorosulfate, the dication (**69**) was smoothly formed ⟨80JA6364⟩. It is highly unusual that (**69**) is very stable in water and its tricyclic integrity which was present before methylation has been preserved. The high energy demand for the cleavage of one carbon–nitrogen σ-bond in (**69**) leading to an excessively strained formamidinium cation (**94**) is the most plausible reason behind the unusual stability of (**69**).



Scheme 3

Another highly interesting reaction has been recorded for (**45**) involving a net transfer of hydride leading to the formation of (**96**) when a solution of (**45**) in dry $CHCl_3$ is treated with triphenylcarbenium ion tetrafluoroborate (Equation (2)) ⟨80JA6365⟩.



(2)

In the above reduction of $Ph_3\overset{+}{C}$ to Ph_3CH the solvent chloroform has no role as the reaction performed in $CDCl_3$ did not afford any detectable amount of Ph_3CD. Thus the reduction involving the transfer of a proton and two electrons from one molecule to another is a common but puzzling phenomenon.

$$(NR_2)_3CH \rightleftharpoons (NR_2)_3\overset{+}{C} + \overset{+}{H} + 2e^- \tag{3}$$

However, the above reaction may not occur if the amide is preferentially removed.

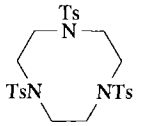
$$(NR_2)_3CH \rightleftharpoons (NR_2)_2\overset{+}{C}H + \bar{N}R_2 \tag{4}$$

Orthoamide (**45**) has been expected to behave differently since the strain incorporated in the bicyclic formamidinium ion (**94**) should prevent transfer of amide, permitting transfer of hydrogen and affording (**96**).

$$(95) \rightleftharpoons (45) + \overset{+}{R} \rightleftharpoons (96) + RH \tag{5}$$

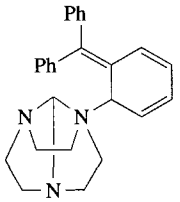
The tetrafluoroborate of (**96**), having D_{3h} symmetry, on treatment with hot NaOH and *p*-TsCl afforded cleanly the monocyclic trisulfonamide (**97**) in 88% yield.

Another important observation is that no Ph_3COH could be detected and only Ph_3CH was recovered in 97% yield when an equimolecular mixture of guanidinium tetrafluoroborate and Ph_3CH in $CHCl_3$ was stirred at 25°C and treated later with water. The observation from this experiment suggests that the equilibrium constant for the transfer of hydrogen in Equation (3) is

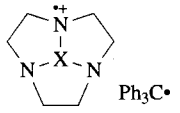


(97)

most probably greater than 100. This transfer may either be direct without the intervention of intermediates or involve the rearrangement of ammonium ion-like compounds (**98**) occurring with the formation of a radical pair (**99**).

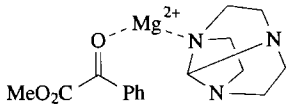


(98)



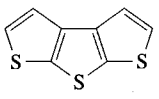
(99)

Since orthoamides could successfully reduce the electrophilic carbenium ion, they may also reduce less active uncharged compounds containing polar multiple bonds. Thus on controlled heating a mixture of equimolar amounts of magnesium perchlorate hemihydrate, orthoamide (**45**), and methyl phenylglyoxalate in carefully dried acetonitrile at 165°C for 12 h, guanidinium perchlorate could be detected. Hydrolysis of the crude product afforded mandelic acid in 45% yield. Several plausible mechanisms provide a role for the magnesium cation involving an intermediate similar to the following ternary complex (**100**) wherein a direct transfer of a proton along with two electrons turns out to be a reality. This observation is extremely important as it establishes that not only 1,4-dihydropyridines, but also orthoamide (**45**) as a simple organic molecule can bring about the transfer of a proton and two electrons efficiently to polar multiple bonds.

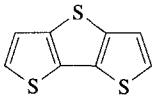


(100)

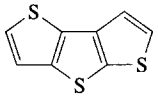
A comprehensive and thorough investigation on electrophilic substitution of dithienothiophene has been successfully carried out ⟨82JCS(P2)301⟩. The reactivities in electrophilic aromatic substitution have been determined through the actual evaluation of partial rate factors for detritiation of dithieno[2,3-*b*:3′, 2′-*d*]thiophen (**101**), dithieno[3,2-*b*:2′, 3′-*d*]thiophen (**102**), and dithieno[2,3-*b*:2′, 3′-*d*]thiophen (**103**). Hückel localization energy calculations turn out to be highly successful in assessing the relative positional reactivities but are actually less good for heterocycles and completely fail to predict with certainty the reactivity of thiophen relative to the thienothiophens.



(101)



(102)



(103)

The thienothiophens (**101**) to (**103**) having specific labeling with tritium were prepared. Their rates of detritiation were measured at 70°C employing either pure CF_3CO_2H or a mixture of $MeCO_2H$ (65%) and CF_3CO_2H (35%). In general a difference in rates of detritiation is observed using the two solvents. This may be attributed to a higher degree of hydrogen bonding in dithi-

enothophens since they incorporate as many as three sulfur atoms. Hence it should be emphasized that it is almost impossible to expect true electrophilic reactivities of compounds (**101**) to (**103**) from the exchange rates observed in 100% CF_3CO_2H due to the presence of such hydrogen bonding. In order to overcome this serious difficulty, a lower acidity, 15% CF_3CO_2H (v/v) in CH_3COOH has been chosen for thienothiophens, where hydrogen bonding is no longer present to a significant extent. The salient features of the results obtained from this systematic study on detritiation are briefly:

(i) The dithienothiophens turn out to be highly reactive toward electrophilic substitution and their reactivity compares well with that of highly reactive aromatics, such as phenols.

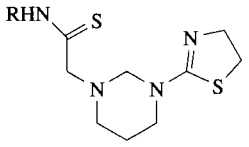
(ii) The electrophilic substitution reactivities observed at the α- and β-positions of dithienothiophens are almost independent of the different structural patterns of various dithienothiophens.

(iii) The positional reactivity order of electrophilic substitution may also be ascertained by Hückel calculations. Thus from the detritiation study the observed order of reactivity, $1 > 5 > 3 > 7 > 6 > 2 > 8 > 4$, turns out to be in remarkably good agreement with the order, $1 > 5 > 3 > 7 > 6 > 4 > 8 > 2$, predicted from Hückel calculations.

(iv) Comparison of the reactivities at like positions from Hückel calculation, and detritiation study shows some small differences in reactivity in a few cases. This may arise due to the small differences in polarizability of the molecules leading to slight changes in the order.

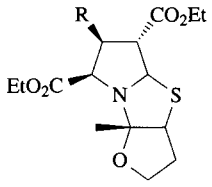
For a new host series, compounds (**10d**) (Table 2) have been utilized to make host–guest (Me_2SO) compounds ⟨92CC1381⟩. The conformation of the host molecule in crystal inclusion compounds turns out to be very dependent on the number of condensed thiophene rings.

Reductive ring opening of tetraazapentalene derivative (**40**) (Table 4) has been successfully carried out by $NaBH_4$ through the release of hypervalent sulfur to give 1,3-disubstituted perhydropyrimidines (**104**) in good yield ⟨90CE145⟩.

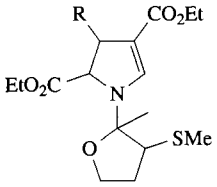


(**104**)

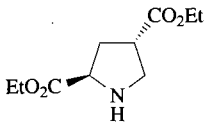
The tricyclic adduct (**15e**; R = CH_2CH_2OBn,Me) closely resembling (**15a**) (Table 2) could be cleaved by *t*-BuOK in *t*-BuOH followed by treatment with MeI to afford dihydropyrroles (**105**; R = CH_2CH_2Bn,Me). The tricyclic adduct (**15e**; R = H) also gave the pyrrolidine derivative (**106**) on treatment with tetrabutyltinhydride followed by acid hydrolysis. The relative stereochemistry of the ethoxycarbonyl functions is not lost during this particular desulfurization procedure ⟨85T3537⟩.



(**15e**)

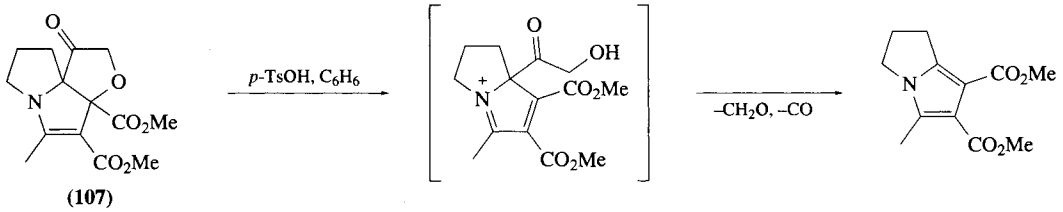


(**105**)



(**106**)

A novel fragmentation of (**107**) has been achieved ⟨92JA593⟩ during chromatography over silica gel or by treating (**107**) with *p*-TsOH in benzene to produce a dihydropyrrolizine diester (Scheme 4).



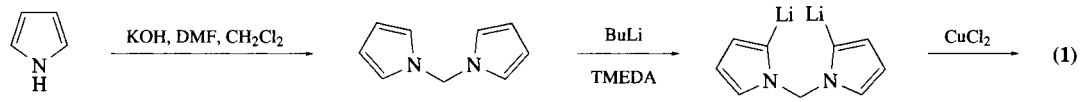
(**107**)

Scheme 4

8.35.6 RING SYNTHESIS AND SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

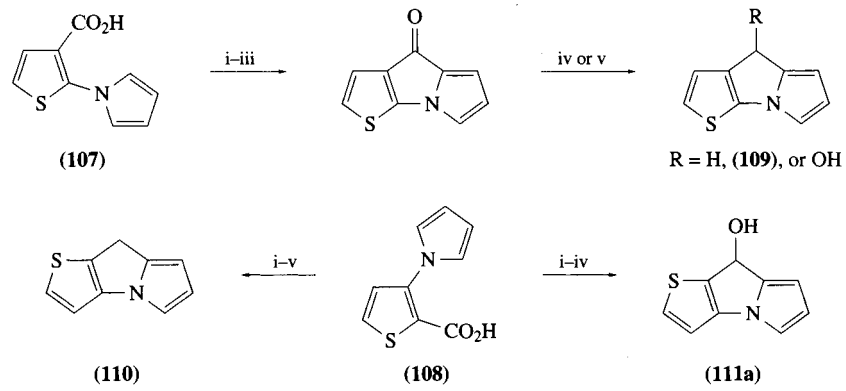
A fairly large number of different methodologies have been applied successfully, mainly since the early 1980s. Because the synthetic methods of this particular class of heterocycles reported in the literature vary widely, it has been considered logical to classify them as shown in Tables 1 to 9 depending on structural patterns along with the number of heteroatoms present. Thus the discussion starts with the synthesis of the linearly fused (5 : 5 : 5) systems with two heteroatoms presented in Table 1, followed by Tables 2–9 respectively.

A very simple and convenient synthesis of dipyrrolo[1,2*c* : 2′,1′*e*]imidazole (**1**) (Table 1) has been accomplished from pyrrole (Scheme 5) ⟨80HCA1190⟩.



Scheme 5

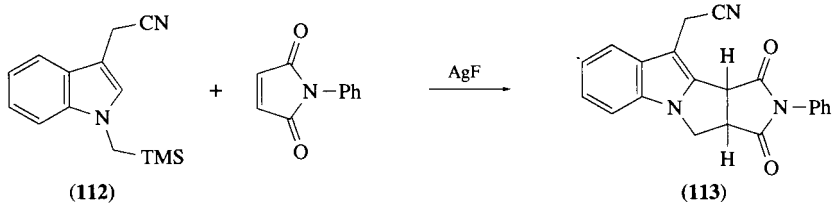
Cyclization of the pyrrolidinocarboxamide derivatives of 2-(1-pyrrolyl)-3-thienyl and 3-(1-pyrrolyl)-2-thienyl carboxylic acids, (**107**) and (**108**) respectively, afforded thieno[2,3-*b*]pyrrolizine (**109**) and thieno[3,2-*b*]pyrrolizine (**110**) through the respective thienopyrrolizine-4-ones as depicted in Scheme 6 ⟨83H(20)477⟩.



i, CH_2N_2, Et_2O, reflux; ii, pyrrole, reflux; iii, $POCl_3$, reflux; iv, $LiAlH_4$ (2 equiv.); v, $LiAlH_4$ (1.75 equiv.), $AlCl_3$ (3.5 equiv.)

Scheme 6

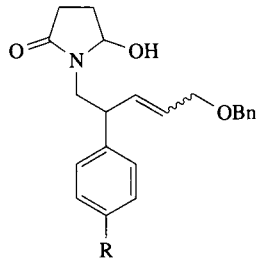
The synthesis of pyrrolo[1,2-*a*]indoles (**113**) has been successfully accomplished in 85% yield through a 1,3-dipolar cycloaddition reaction using *N*-(trimethylsilyl)methyl substituted indoles (**112**) (Equation (6)) ⟨89JOC644⟩.



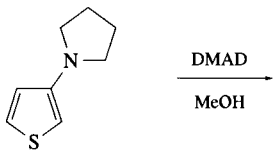
(6)

The building up of the furo[3,4-*a*]pyrrolizine ring system (**6**) (Table 1) has been achieved by cyclization via 2-aza-Cope rearrangement of the *N*-acylium ion generated when the hydroxylactam (**114**) is treated with formic acid ⟨90H(30)501⟩.

The reaction between 3-pyrrolidinothiophene (**115**) as pseudoenamine with DMAD in a polar solvent such as MeOH affords an interesting tricyclic product (**3**) (Table 1) (Equation (7)) ⟨81JOC424⟩.



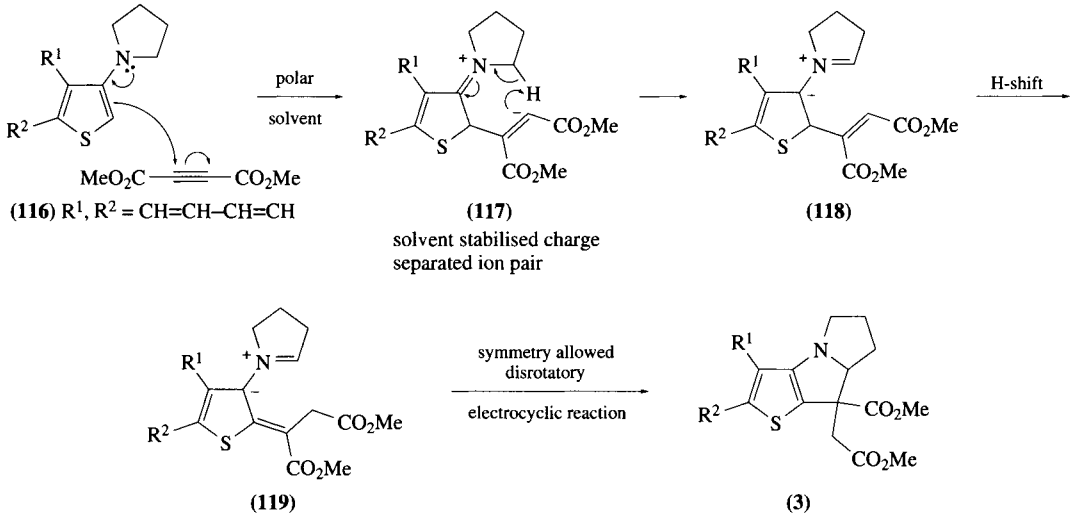
(114) R = H, OMe



(115)

(7)

Similarly, a benzo derivative of compound (**3**) has been prepared from (**116**), and a plausible mechanism has been proposed for this conversion via intermediates (**117**)–(**119**) (Scheme 7). The mechanism has been further examined ⟨83MI 835-01⟩.



(116) R^1, R^2 = CH=CH–CH=CH

(117) solvent stabilised charge separated ion pair

(118)

(119)

(3)

Scheme 7

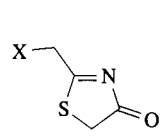
It should be emphasized at this stage that the reaction course follows a completely different pathway if the polar solvent methanol is replaced by a nonpolar one.

The synthesis of various 4-imino and 4-amino derivatives of 4*H*-thieno[2,3-*b*]pyrrolizines (**7b**) (Table 1) and (**7c**) (Table 2) (X = NR, CHNHR) has been reported ⟨85H(23)1471⟩.

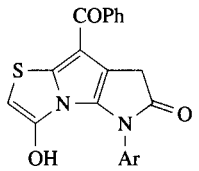
Thermal decomposition of six possible *o*-azidobithienyls has been critically investigated for building up the dithienopyrrole ring system. Thus 4*H*-dithieno[3,2-*b*; 2′,3′-*d*]pyrrole (**10a**) and 4*H*-dithieno[2,3-*b*; 2′,3′-*d*]pyrrole (**18**) (Table 2) were prepared in very good yields from 3-azido-2,2′-bithienyl and 3-azido-2,3′-bithienyl respectively ⟨83JCS(P1)2551⟩. With 2-azido-3,3′-bithienyl and 2-azido-2′,3-bithienyl extrusion of nitrogen occurs at room temperature resulting in ring-opening fragmentation. By contrast 4-azido-3,3′-bithienyl and 4-azido-2′,3-bithienyl are relatively stable and afford polymeric materials on thermal decomposition under drastic conditions.

When 2-substituted-2-thiazolin-4-one derivatives (**120**) were allowed to react with *N*-aryl-

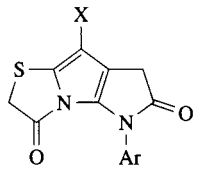
maleimides in refluxing dioxane for 5 h, new pyrrolo[2,3 : 4′,5′]pyrrolo[2,1-*b*]thiazoles (**121a**) and (**121b**) are formed ⟨83H(20)1021⟩.



(120)
X = CN, CO_2Et, COPh

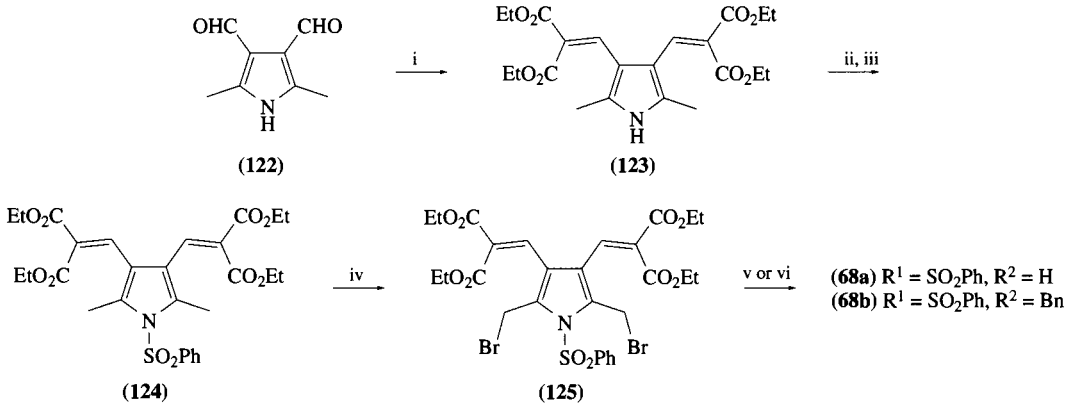


(121a)
Ar = Ph, *p*-tolyl



(121b)
X = CN, Ar = Ph
X = CN, Ar = *p*-tolyl
X = CO_2Et, Ar = Ph
X = CO_2Et, Ar = *p*-tolyl

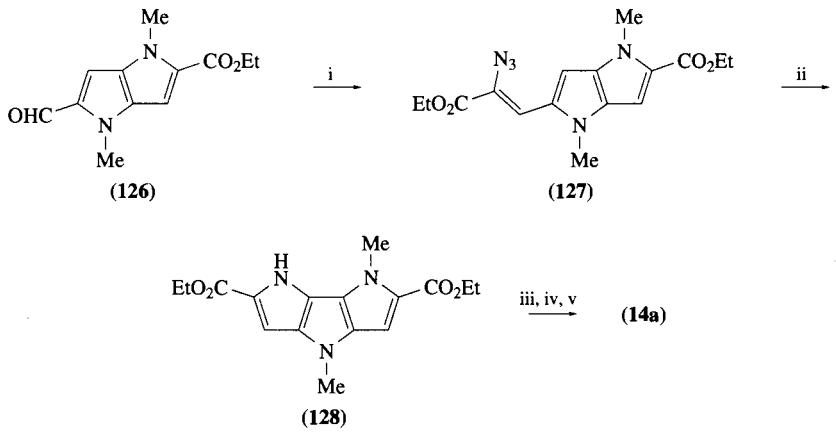
The syntheses of dipyrrolo[3,4-*b* : 3′,4′-*d*]pyrroles (**68a**) and (**68b**) (Table 9) have successfully been achieved starting from the dialdehyde (**122**) via intermediates (**123**)–(**125**) (Scheme 8) ⟨90H(31)603⟩.



i, $CH_2(CO_2Et)_2$, piperidine, benzene, reflux; ii, KH, THF, –78 °C, 30 min; iii, $PhSO_2Cl$, –78 °C to 0 °C; iv, NBS, $(PhCO)_2O_2$, CCl_4, reflux, 2 h; v, 25% NH_3, abs. ethanol 25 °C, 20 h; vi, $PhCH_2NH_2$, 95% EtOH, 18 h

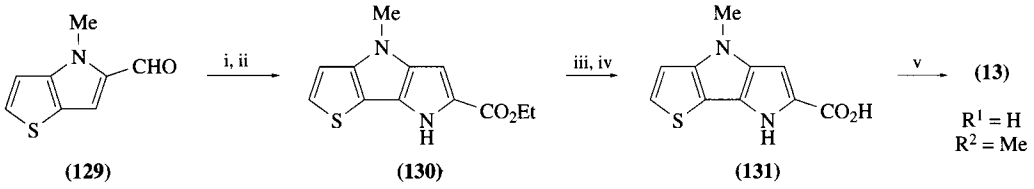
Scheme 8

4,7-Dihydro-1*H*-dipyrrolo[3,2-*b* : 2′,3′-*d*]pyrrole (**14a**) and 4,7-dihydro-4*H*-thieno[3,2-*b*]pyrrolo[2,3-*d*]pyrrole (**13**) (Table 2) have also been elegantly synthesized employing pyrrole annulation techniques on suitable pyrrolopyrrole (**126**) and thienopyrrole (**129**) derivatives as substrates via intermediates (**127**), (**128**) and (**130**), (**131**) respectively (Schemes 9 and 10) ⟨89TL1655⟩.



i, $N_3CH_2CO_2Et$; ii, pyrolysis; iii, *N*-methylation; iv, HO^-; v, H^+

Scheme 9



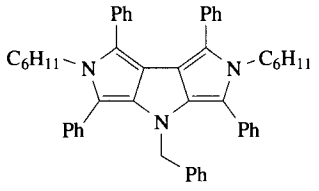
(129) (130) (131)

i, $N_3CH_2CO_2Et$; ii, pyrolysis (pyrrole-annelation); iii, *N*-methylation; iv, hydrolysis; v, Δ, quinoline, Cu powder

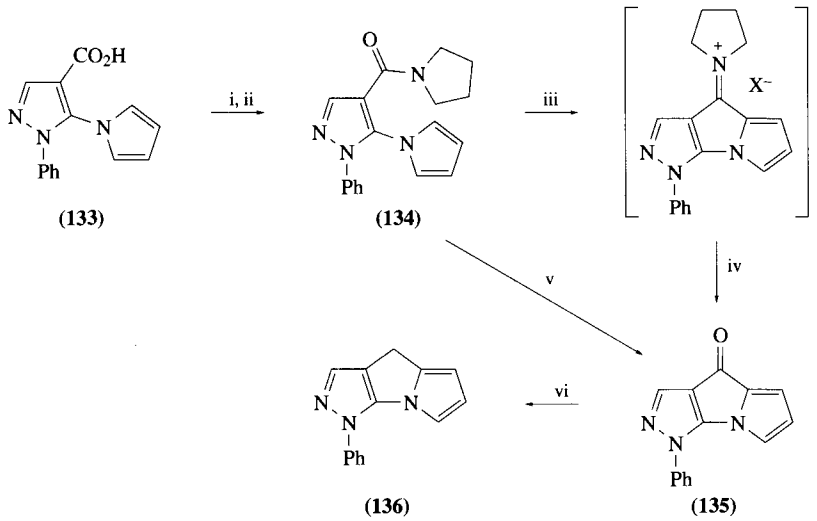
Scheme 10

Following a very simple preparative method, tetraphenyldipyrrolo[3,4-*b*:3′,4′-*d*]pyrrole (**132**) could be obtained in 87% yield from *N*-benzyl-2,3,4,5-tetrabenzoylpyrrolidine by allowing it to react with cyclohexylamine in methanol at room temperature ⟨72JCS(P1)1459⟩.

The synthesis of 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**136**) and 2-phenyl-2*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**143**) has been accomplished via the respective keto derivatives (**135**) and (**142**) starting with 1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic acid (**133**) and ethyl-3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (**137**) respectively (Schemes 11 and 12) ⟨90JHC1805⟩.



(132)

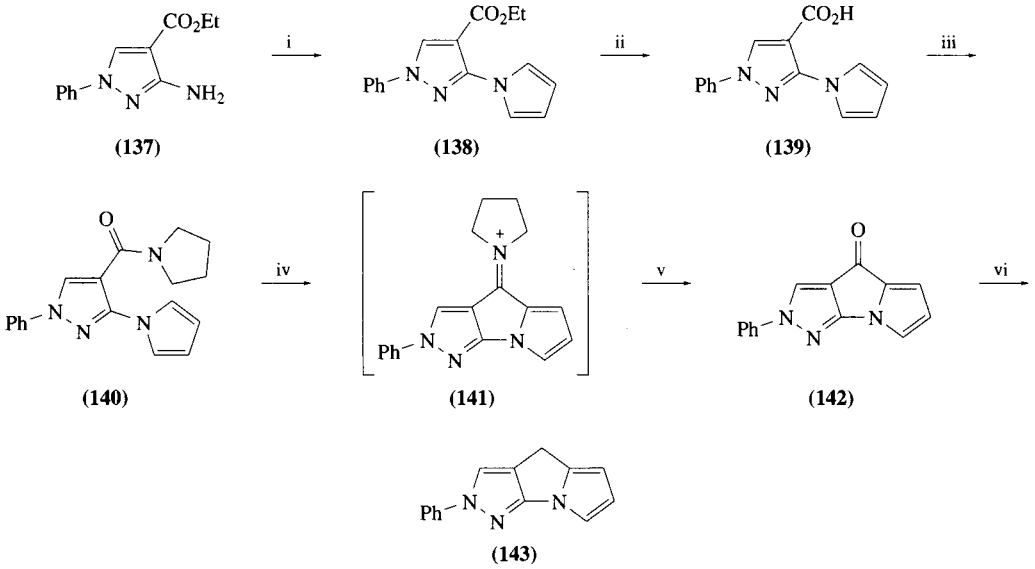


(133) (134) (136) (135)

i, $SOCl_2$; ii, pyrrolidine; iii, $POCl_3$, reflux, (Bischler–Napieralski reaction); iv, aq. NaOH; v, $AlCl_3$ (Friedel-Craft cyclization); vi, $LiAlH_4/AlCl_3$

Scheme 11

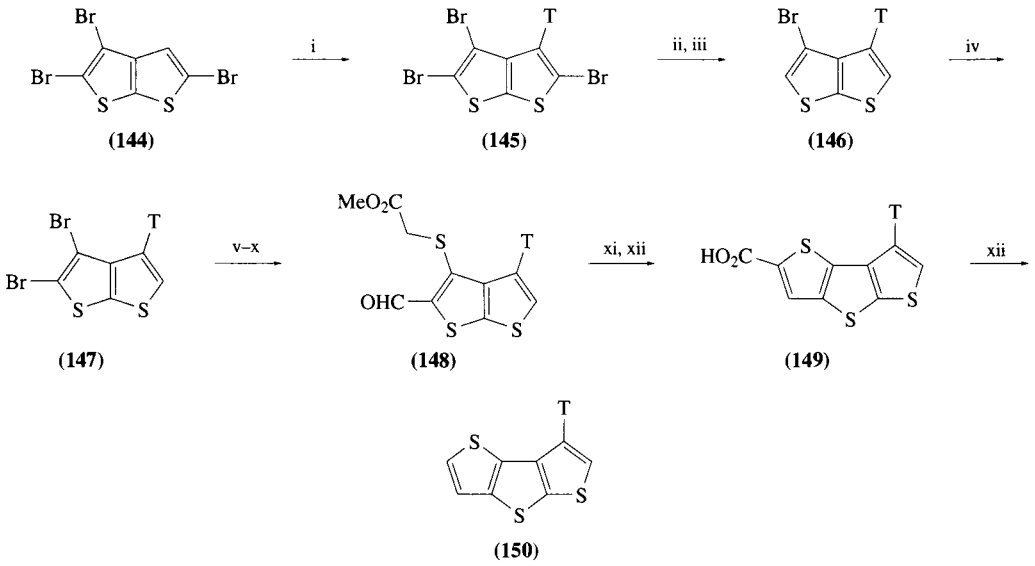
While carrying out an investigation on electrophilic aromatic substitution on various dithienothiophens through their partial rate factors for detritiation, the preparation of the labeled dithienothiophens [7-3*H*]dithieno[2,3-*b*:2′,3′-*d*]thiophen (**150**) from (**144**), via intermediates (**145**)–(**149**), and [2-3*H*]dithieno[2,3-*b*:2′,3′-*d*]thiophen (**157**) from (**151**), via intermediates (**152**)–(**156**), has been achieved (Schemes 13 and 14) ⟨82JCS(P2)301⟩.



(137) **(138)** **(139)** **(140)** **(141)** **(142)** **(143)**

i, MeO⟨O⟩OMe , glacial AcOH; ii, KOH (hydrolysis); iii, ⟨NH⟩ *N*-(dimethylaminopropyl)-*N'*-ethyl carbodiimide; iv, $POCl_3$; v, KOH; vi, $LiAlH_4/AlCl_3$

Scheme 12

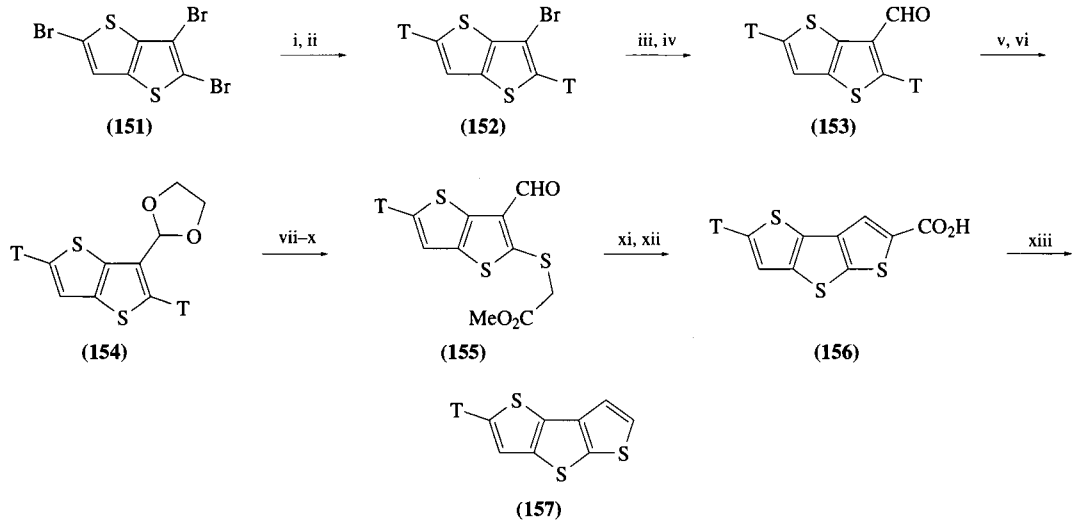


(144) **(145)** **(146)** **(147)** **(148)** **(149)** **(150)**

i, CF_3CO_2H–T_2O; ii, Mg–Et_2O; iii, H^+; iv, NBS–AcOH; v, Bu^nLi; vi, DMF; vii, Bu^nLi; viii, S; i. $ClCH_2CO_2Me$; ix, H^+; x, NaOEt; xi, H^+; xii, heat, Cu

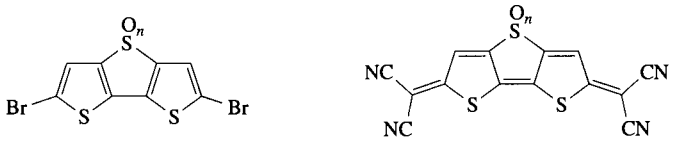
Scheme 13

Cyclocondensation of dibromodithienothiophen (**158**; $n = 0$) with tetracyanoethylene oxide afforded bis(dicyanomethylene)dihydrodithienothiophen (**159**; $n = 0$) which formed charge-transfer complexes with tetrathiafulvene or tetrathiadecalin as well as highly conducting complexes as sodium and tetrabutylammonium salts ⟨87CL2339⟩. The corresponding sulfone (**159**; $n = 2$) has also been prepared from (**158**; $n = 2$) by the action of either tetracyanoethylene oxide or a Pd(0)-catalyzed substitution ⟨89BCJ1547⟩.

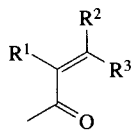


i, Mg–Et_2O; ii, T_2O; iii, Bu^nLi; iv, DMF; v, $HO(CH)_2OH$; vi, H^+; vii, Bu^nLi; viii, S; ix, $ClCH_2CO_2Me$; x, H^+; xi, NaOEt; xii, H^+; xiii, heat, Cu

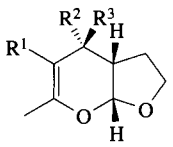
Scheme 14



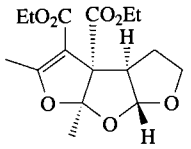
Synthesis of furanofurans has been achieved by the rearrangement of 4-acetylpyrans. Thus the hetero Diels–Alder reaction between 1-oxabutadienes (**160**)–(**162**) bearing electron-withdrawing groups with 2,3-dihydrofuran afforded 4*H*-4a,5,6,6a-tetrahydrofuro[2,3-*b*]pyrans (**163**) and (**164**) which have been successfully rearranged to difuro[2,3-*b*:3′,4′-*d*]furans (**11**) and (**165**) ⟨92T5883⟩.



(**160**) $R^1 = R^2 = R^3 = Ac$
(**161**) $R^1 = R^2 = H$, $R^3 = Ac$
(**162**) $R^1 = R^3 = CO_2Et$, $R^2 = Ac$



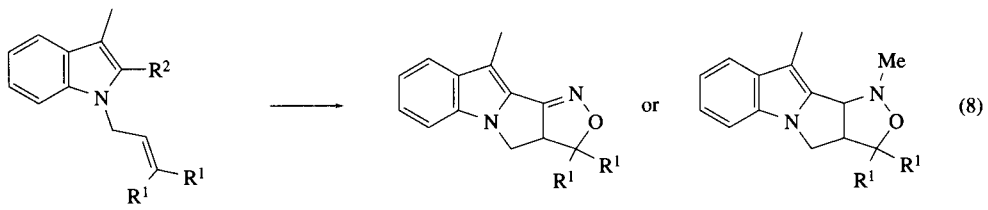
(**163**) $R^1 = R^2 = R^3 = Ac$
(**164**) $R^1 = R^2 = CO_2Et$, $R^3 = Ac$



(**165**)

A synthesis of the 2,4-dioxa-10-azatricyclo[6,3,0,$0^{3,7}$]undecane ring system (**17**) (Table 2) has been achieved through a photocycloaddition reaction of 4-ethoxycarbonyl-5-phenyl-1*H*-pyrrole-2,3-dione with a dihydrofuran ⟨87CPB4730⟩.

Another route involving intramolecular cycloaddition of nitrone and nitrile oxide functionalities of the indole derivative (**166**) gave a novel class of mitomycin analogues which are dihydro- and tetrahydroisooxazolo[3′,4′ : 3,4]pyrrolo[1,2-*a*]indole (**167**) and (**168**) (Equation (8)) ⟨89TL1421⟩.



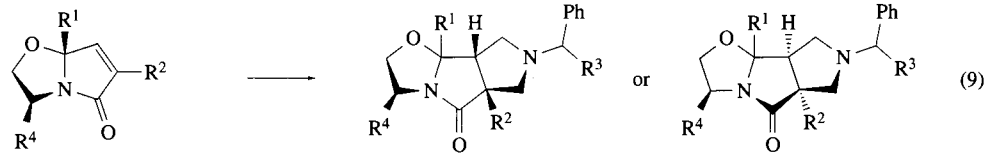
(**166**) R^1 = H, Me
R^2 = CH=N(O)Me or CHO

(**167**) R^1 = H, Me

(**168**) R^1 = H, Me

(8)

The synthesis of the lactams (**169**) and (**170**) involving diastereoselection during 1,3-dipolar cycloaddition of suitable chiral and achiral azomethine ylides constitutes a highly promising methodology (Equation (9)) ⟨92TL3575⟩. The interaction of the chiral unsaturated bicyclic lactams (**171**) with the respective azomethine ylides from $R^3CHPhN(CH_2OMe)CH_2SiMe_3$ (R^3 = H, Me; *R* or *S* enantiomer) has been described in terms of steric factors. Thus the directional mode of cycloaddition has been found to be dependent upon the steric requirement of the angular substituent R^1 in (**171**). A predominantly α-approach of the 1,3-dipole was observed for R^1 = Me,Ph to afford (**169**) and a β-approach for R^1 = H to give (**170**).



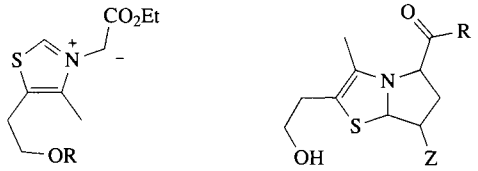
(9)

(**171**)
R^1 = Me, R^2 = CO_2Me
R^4 = Pr^i

(**169**)

(**170**)

The thiazolium ylide (**172**) obtained from the 5-hydroxyethyl-4-methylthiazole derivative reacts with a suitable alkene CH_2CHR to afford ultimately (**15a**) (Table 2) ⟨81TL2727⟩. If the alkene CH_2CHR is replaced by α,β-unsaturated esters or nitriles a fused thiazoline (**173**) can be isolated. Surprisingly (**173**) cyclizes to give (**15b**) (Table 2) when it is purified by chromatography over silica gel.

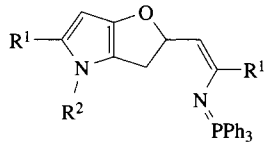


(**172a**) R = H
(**172b**) R = Me, Et

(**173**) Z = CO_2Et, CN

The same thiazolium ylide (**172**) was utilized for the synthesis of other compounds (**15**) (Table 2) through 1,3-dipolar cycloaddition reactions exploiting assorted dipolarophiles (e.g., MeCOCHCHMe, MeCOCHCHPh, CH_2CHCO_2Et) followed by silica gel-assisted cyclization ⟨85T3537⟩. Other thiazolium ylides (**172b**) were also used for the preparation of this type of heterocycle.

The preparation of furodipyrroles (**12**; R^1 = CO_2Et, R^2 = Me, $PhCH_2$) (Table 2) has been accomplished from the appropriate iminophosphoranes (**174**) which were in turn obtained from the reaction between suitable ethyl azidoheteroacrylates and triphenylphosphine with phenylisocyanate ⟨92M807⟩.



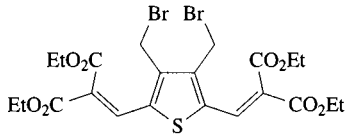
(**174**)

In a novel reaction of 1,4-diaza-1,3-dienes, with RNCHCHNR in the presence of $FeCl_2$, the product obtained was the dipyrrolopyrrole (**78**; R = *p*-tolyl) which is plausibly formed following a series of metal-mediated condensations of the diazadiene ⟨94IC1539⟩.

An efficient method has appeared for the elaboration of the thieno[2,3-*c*:4,5-*c*′]dipyrrole ring system (**16**) (Table 2) ⟨93T6831⟩. Thus the reaction of the thiophene derivative (**175**) with sodium azide followed by treatment with triphenylphosphine and water affords (**16**; R = H). On the other hand (**175**) may react with aniline or benzylamine to produce (**16**; R = Ph, CH_2Ph).

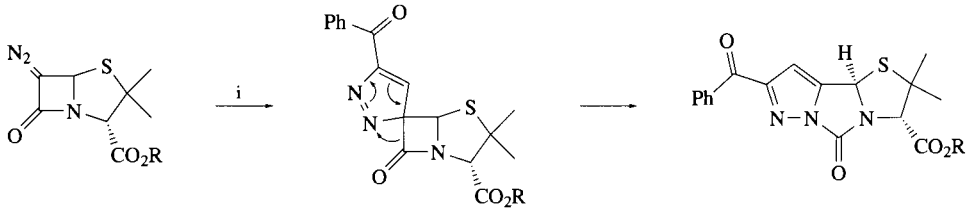
Other preparations of various dipyrrolopyrroles in the literature are also worthy of note ⟨88JAP(K)284178, 89JAP(K)172387⟩.

An unusual synthesis of (**22**) (Table 3) has been accomplished following a new β-lactam expansion



(175)

reaction of a *spiro*-penicillinic acid (**76**), formed as an intermediate ⟨82TL2813⟩. Thus treating trichloroethyl 6-diazopenicillinate (**176**) with β-phenylsulphinylpropenophenone in the dark at room temperature for 2 days afforded a product thought to be (**76**; R = CH_2CCl_3), shown to be the adduct minus one mole of phenylsulfinic acid. An identical product was obtained directly by addition of the diazoester (**176**; R = CH_2CCl_3) to propiolophenone. The corresponding benzhydryl ester thought to be (**76**; R = $CHPh_2$) was prepared, since attempts to remove the trichloroethyl protecting group in (**76**; R = CH_2CCl_3) failed. Removal of the benzhydryl protecting group in (**76**; R = $CHPh_2$) afforded the corresponding acid which was found to be completely inert in both β-lactamase and antimicrobial assays indicating a non-β-lactam structure for (**76**). X-ray crystallographic analysis finally assigned the correct structure as (**22**). Hence in this reaction the anticipated acyl migration in (**76**) has actually occurred to nitrogen before β-lactam ring opening, leading to the fused pyrazole (**22**) as depicted in Scheme 15. Most likely acyl migration could not be prevented as the geometrical constraints offered by the *spiro*-azetidinone are insufficient. The plausible intermediate (**76**) has never been isolated.

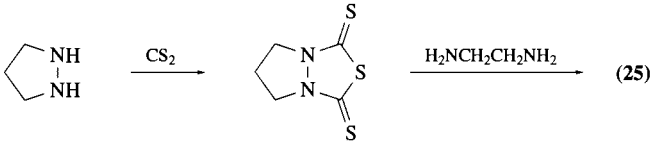


(176) (76) (22)

i, PhCOCH=CHS(O)Ph (*E*) or PhCOC≡CH

Scheme 15

A synthesis of (**25**) (Table 3) has been reported from pyrazolidine (**177**) through the intermediacy of 1,3-dithioxo-6,7-dihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole (**178**) (Scheme 16) ⟨92PHA416⟩.

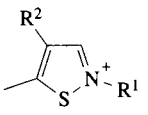


(177) (178) (25)

Scheme 16

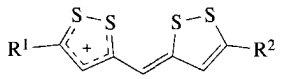
Thieno[3′,4′-4,5]imidazo[2,1-*b*]thiazoles (**26**) (Table 3) have been successfully prepared ⟨90EVP358116⟩.

Through dimerization of easily available 5-methylisothiazolium salts, (**179**; R^1 = Ph, substituted Ph, Pr, Me, CH_2Ph; R^2 = Me, Et, Pr, Ph) by bases such as secondary amines, the unexpected formation of thiophen-annulated 6aλ^4-thia-1,6-diazapentalens (**24**) (Table 3) could be established ⟨92JPR25⟩.



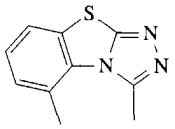
(179)

The red colored condensed ring trithiapentalenes (**23**) (Table 3) have been successfully obtained in general by pyridine-induced deprotonation of the cations containing four sulfur atoms in line (**180**) which are obtained by reacting a 3-methylthio-1,2-dithiolylium cation with the conjugate base of a 3-alkyl-1,2-dithiolylium cation ⟨80AHC(27)151, 80AHC(27)177⟩.



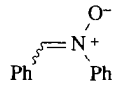
(**180**)

The synthesis of (**27**) (Table 3) has been accomplished using (**181**) as a starting material ⟨92MI 835-01⟩.

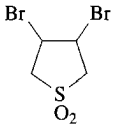


(**181**)

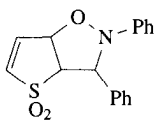
The diadduct (**38**) (Table 4) was obtained by using a large excess (5 equivalents) of the nitrone (**182**) which was heated with the dibromo derivative (**183**) in the presence of pyridine or triethylamine in refluxing chloroform or benzene for 48 h ⟨81JOC3502⟩. During this reaction (**184**) could also be isolated. When a solution of (**184**) and mesitonitrile oxide (**185**) in $CHCl_3$ was heated for 3 days, (**71**) could be isolated.



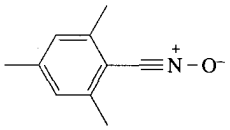
(**182**)



(**183**)



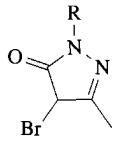
(**184**)



(**185**)

Along with another product, the diadduct (**70**) can be obtained by heating under reflux a benzene or chloroform solution of a mixture of (**183**) and (**185**) along with pyridine or triethylamine for 3 days ⟨81JOC3502⟩.

Pyrazoloimidazolothiazole (**36**; R = H, Ph) (Table 4) has been prepared using bromomethylpyrazolones (**186**; R = H, Ph) and 2-thiol-1-imidazoline ⟨90JIC610⟩.

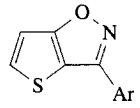


(**186**)

During a detailed study on the selectivity in cycloaddition of benzo- and mesitonitrile oxide to thiophen, the heterocycles formed as cycloadducts (**33**; Ar = phenyl, mesityl), (**72**), and (**73**; Ar = mesityl) could be prepared ⟨78T3545⟩. Thus using thiophen as a solvent with the slow *in situ* generation of benzonitrile oxide, (**33**; Ar = phenyl) can be obtained as a 2:1 adduct as well as the dimerization products of benzonitrile oxide and a 3:1 adduct. The more stable mesitonitrile oxide, kept in thiophen at room temperature for seven minutes afforded the cycloadducts (**33**; Ar = mesityl) along with the symmetrical biadducts (**72**) and (**73**). Extensive spectroscopic studies on the cycloadducts (**33**), (**72**), and (**73**) adduced sufficient evidence to solve unequivocally the stereochemical features (see Section 8.35.3).

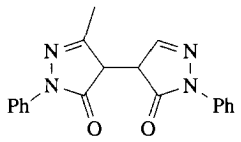
The compounds (**33**) and (**72**), where Ar is 3,5-dichloro-2,4,6-trimethylphenyl, were also prepared ⟨77JCS(P2)706⟩. Thus boiling a solution of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide in thiophen

for 48 h afforded the biadduct (**33**) along with the monoadduct (**187**) ⟨67JCS867⟩. Both (**33**) and (**72**) may be obtained by refluxing the monoadduct (**187**) with the nitrile oxide in benzene for 48 h.



(187)

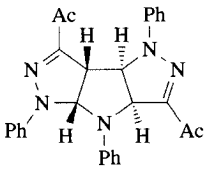
The preparation of (**37**; R = C(CHO)=CHNMe$_2$) (Table 4) has been elegantly demonstrated by applying the Vilsmeier–Haack reaction on the bipyrazoledinone (**188**) followed by cyclization ⟨92BCJ1652⟩. Treatment of (**37**) with other secondary amines, such as piperidine, or morpholine, replaces the dimethylamino group. Alternatively, (**37**) on treatment with NH_2OH, N_2H_4, or $PhNHNH_2$ afforded new derivatives of (**37**) wherein R is 4-isoxazolyl, 4-pyrazolyl, or 1-phenyl-4-pyrazolyl, respectively.



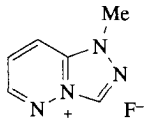
(188)

The cycloaddition reaction of 1-methylpyrrole with nitrileimine (AcC≡$\overset{+}{N}\overset{-}{N}$Ph) afforded (**34**) (Table 4) along with another cycloadduct (**189**) ⟨72TL4703⟩. The tricyclic product (**31**) (Table 4) was formed by hydrazinolysis of the fluoride salt (**190**) ⟨74MI 835-01⟩.

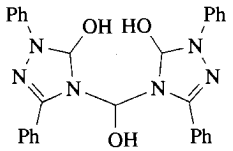
A preparative link has been established between compound (**35**) (Table 4) and (**191**) involving dehydration accompanied by oxidation ⟨81KGS694⟩. A cycloaddition reaction involving benzonitrile oxide and isoxazolone derivative (**192**) afforded (**32**) (Table 4) besides other products ⟨83JCR(S)172⟩.



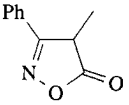
(189)



(190)

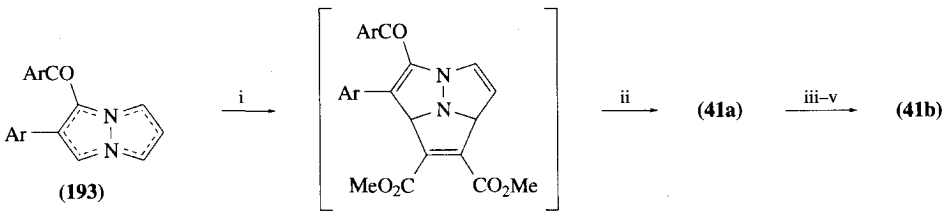


(191)



(192)

Through an unusual [8 + 2] cycloaddition of 4,8-diazapentalene (**193**; Ar = Ph) with DMAD under dehydrogenating conditions, Boekelheide and Fedoruk synthesized the cyclazine (**41a**) (Table 5) (Scheme 17) ⟨66PNA(55)1385⟩. A simple course of reactions converts (**41a**) to (**41b**) (Table 5).

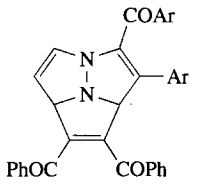


i, DMAD; ii, Pd/C; iii, hydrolysis; iv, Δ (–CO_2); v, KOH in EtOH

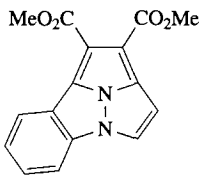
Scheme 17

Diazapentalenes (**193**; Ar = Ph, *p*-chlorophenyl) have also been utilized for reaction with PhCOC≡CCOPh to prepare other cyclazines (**194**; Ar = Ph, *p*-chlorophenyl) ⟨90CE1841⟩. The diazacyclazine (**195**) could be prepared by allowing suitable pyrazolo[1,2-*a*]indazoles to react with

DMAD ⟨88H(27)1207⟩. Exploiting an identical strategy, compound (**44**) (Table 5) has also been obtained.

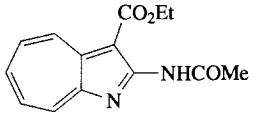


(**194**)

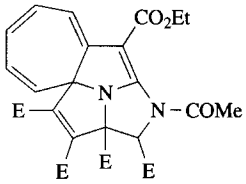


(**195**)

In another cycloaddition, 2-acylamino-3-ethoxycarbonyl-1-azaazulene (**196**) reacts with DMAD in refluxing MeCN to produce the diazapentaleno[1,6-*aj*]azaazulene-1,2,2a,3,5-pentacarboxylate ester (**197**) ⟨92BCJ1784⟩.

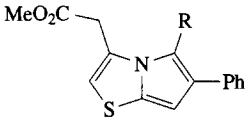


(**196**)



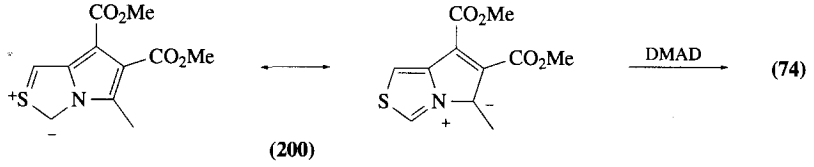
(**197**) E = CO_2Me

The preparation of 1-thia[2.2.2]cyclazine (**43**) (Table 5) has been accomplished from the pyrrolothiazole (**198**) through its formylation to (**199**) followed by cyclization ⟨75USP3920672, 77USP4033978⟩.



(**198**) R = H
(**199**) R = CHO

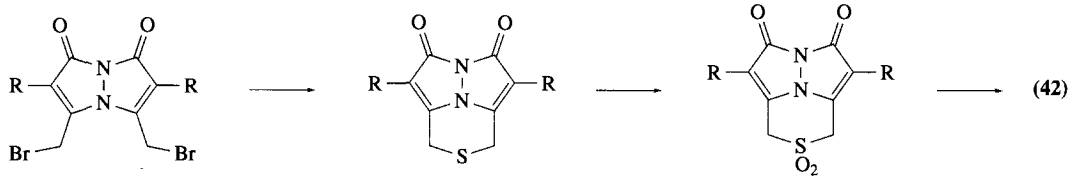
Thiacyclazine derivative (**74**) has been prepared through a 1,3-dipolar cycloaddition reaction from pyrrolothiazole (**200**) and DMAD (Scheme 18).



(**200**)

Scheme 18

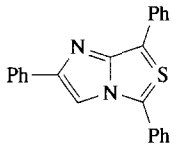
The bimanes (**42**; R = Me, Cl), 3,7-dimethyl- and 3,7-dichloro-4,6-(1′,2′-dimethylene)-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione (Table 5), have been prepared from (**201**; R = Me, Cl) via (**202**; R = Me, Cl), which was oxidized to sulfone (**203**; R = Me, Cl). Thermolysis of the latter at 525 °C afforded (**42**) through the extrusion of SO_2 (Scheme 19) ⟨90JA7315⟩.



(**201**) (**202**) (**203**)

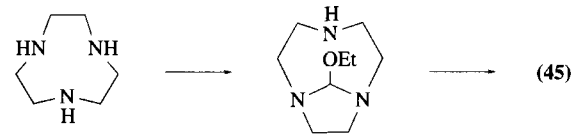
Scheme 19

Two types of masked 1,3-dipole, an azomethine ylide and a thiocarbonyl ylide, are present in 1,3,6-triphenylimidazo[1,2-*c*]thia^{4}zole (**204**). Acetylenic dipolarophiles produced regio- and periselective [3 + 2] cycloadducts (**47**) (Table 6) by reaction with the azomethine ylide 1,3-dipole of (**204**) ⟨83CL763⟩. Thus DMAD or benzoylacetylene in dry benzene at room temperature react with (**204**) to afford (**47a**; $R^1,R^2 = CO_2Me$) and (**47b**; $R^1 = H$, $R^2 = COPh$) respectively. Dibenzoylacetylene and methyl propiolate react with (**204**) in refluxing benzene to give (**47c**; $R^1,R^2 = COPh$) and (**47d**; $R^1 = H$, $R^2 = CO_2Me$) respectively.



(**204**)

In a proposed preparation of tricyclic trisaminomethanes (**45**) (Table 6) the reaction of uncatalyzed exchange between ethyl orthoformate $HC(OEt)_3$ and the macrocyclic triamine 1,4,7-triazacyclononane (**205**) was initially unsuccessful. However the exchange reaction proceeded smoothly when the more reactive dimethylformamide dimethylacetal $HC(OMe)_2NMe_2$ was substituted for $HC(OEt)_3$ to afford (**45**) in 88% yield ⟨80JA6364⟩; a stoichiometric amount of reactants either neat or in the presence of inert solvent at 120 °C were used for performing the reaction. When (**45**) was treated with either MeI or methyl fluorosulfate, the dication (**69**) was formed. Compound (**45**) was reported to be prepared in 84% yield by the reaction of (**205**) with $HC(OEt)_3$ in THF in the presence of *p*-TsOH at 135 °C for 60 h ⟨80JA6365⟩. Most plausibly, such drastic conditions are needed because of the involvement of two unfavorable steps: the formation of a strained formamidinium ion (**95**) as intermediate or the direct displacement of ethanol from the ester aminal intermediate (**206**) (Scheme 20).

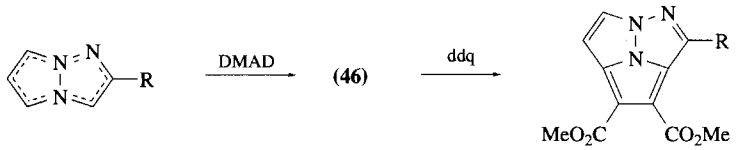


(**205**) (**206**) (**45**)

Scheme 20

The formation of (**49**) (Table 6) may be considered as new evidence for the presence of a *spiro*-indolenine intermediate in the Pictet–Spengler reaction of N^b-hydroxytryptamine ⟨88CC463⟩. Thus *N*-substituted N^b-hydroxytryptamines with cysteinals afforded only (**49**; R = Me, CH_2OMe). In similar reactions with N^b-hydroxytryptamines, (**49**; R = H) was formed along with β-carboline derivatives.

The synthesis of (**46**) (Table 6) has been achieved by exploiting the high reactivity of the azomethine ylide functionality of 1,4,8-triazapentalenes (**207**) towards DMAD ⟨78TL1291⟩. The cycloaddition will occur at the azomethinimine ylide function of (**207**) when the reaction at the azomethine ylide moiety of (**207**) is deliberately hindered, for example, by benzocondensation. On treatment with ddq, (**46**) finally affords (**208**) (Scheme 21).

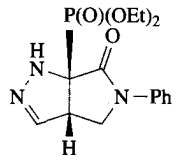


(**207**) (**46**) (**208**)

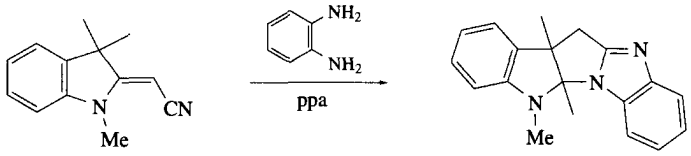
Scheme 21

The preparation of the annulated γ-lactam (**48**) (Table 6) has been described from (**209**) which in turn has been obtained from *N*-allyldiazoacetamides containing a phosphinyl group at the α-position through intramolecular 1,3-cycloaddition followed by a 1,3-hydrogen shift ⟨93BCJ1496⟩. Treatment of 1,3,3-trimethyl-2-cyanomethyleneindole (**210**) with *o*-phenylenediamine in phosphoric

acid results in formation of indolopyrrolobenzimidazole (**211**) via Plancher rearrangement (Equation (10)). The corresponding quaternary ammonium compound is obtained by treating (**211**) with MeI ⟨92KGS513⟩.



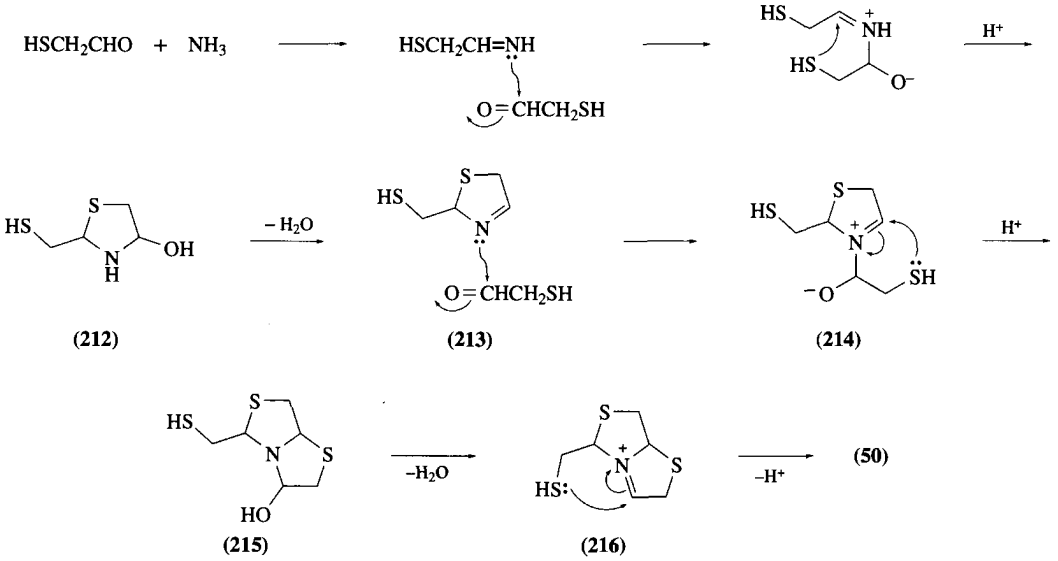
(**209**)



(10)

(**210**) (**211**)

Though the correct structure of 2,2a,4,4a,6,6a-hexahydro-1,3,5-trithia-7-azacyclopenta[*cd*]pentalene (**50**) (Table 7) has been established ⟨84JCS(D)2073⟩, its successful preparation was achieved much earlier by Craig *et al.* who obtained it as a by-product in the reaction of dithiocarbamate with chloroacetaldehyde hydrate and assigned a wrong structure for it ⟨55JA1283⟩. A relatively unambiguous route was subsequently worked out for its preparation from the reaction between ammonia and thiolacetaldehyde ⟨60M473⟩. A plausible mechanism has been suggested for the formation of (**50**) via intermediates (**212**)–(**216**) (Scheme 22) ⟨67JOC3685⟩.



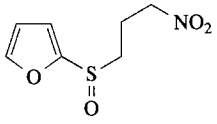
(**212**) (**213**) (**214**)

(**215**) (**216**)

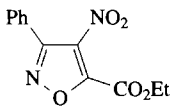
Scheme 22

The compound (**51**) (Table 7) has been prepared recording regio- and stereoselectivity of intramolecular nitrile oxide cycloaddition using furan (**217**) ⟨89TL5013⟩. By exploiting the efficient 1,3-dipolar cycloadditions of ethyl 4-nitro-3-phenylisoxazole-5-carboxylate (**218**) with excess of diazomethane, compounds (**52**) and (**53**) (Table 7) could be prepared ⟨89JOC706⟩. A cyclocondensation reaction of HCOCR=CMeSCN with ring-substituted anilines followed by treatment with a secondary amine gave the heterocycles (**219**) ⟨88ZC287⟩.

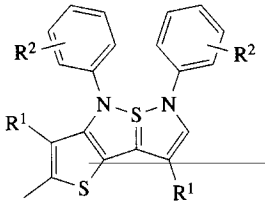
The quaternary azapropellane (**54**) (Table 8) has long been known ⟨54CCC298⟩. The synthesis of dicationic quarternary salts of triaza- and oxadiazapropellanes (**56**) (Table 8) has also been carried out ⟨87G451⟩. Compound (**55**) has been converted into a potential bifunctional mimic of trans-



(217)



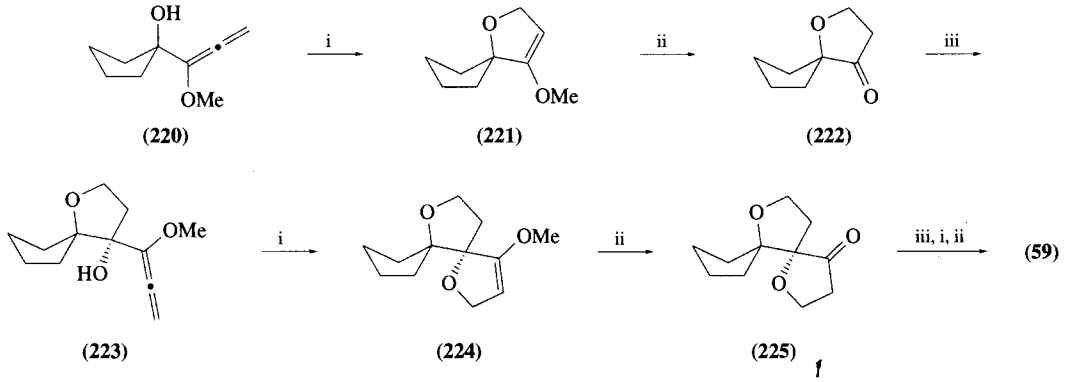
(218)



(219) R^1 = H, alkyl, aryl, alkylaryl
R^2 = H, OH, NO_2, halo, MeCO, alkyl, alkoxy, aryloxy

aminases by attaching dimethyltriazatricycloundecane (**55**; R = H) (Table 8) to a pyridoxamine nucleus via an all-carbon chain ⟨92ACS60⟩.

Compound (**59**) (Table 9) has been prepared elegantly by utilizing the allenic ether (**220**) as a starting material via intermediates (**221**)–(**225**) (Scheme 23) ⟨B-81MI 835-01⟩. One can in principle continue this reiterative reaction by repeating the steps (c),(a) and (b) sequentially on to the ketone functionality to generate a further *spiro*-ketone moiety.



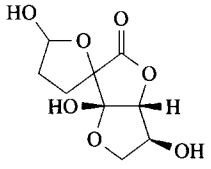
(220) (221) (222) (223) (224) (225) (59)

i, KOBu^t, HOBu^t, dicyclohexane-18-crown-6; ii, H_3O^+; iii, α-lithio-α-methoxyallene

Scheme 23

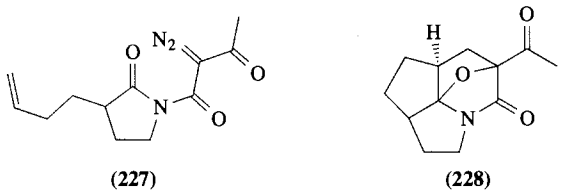
The *spiro*-heterocycles (**57**) (Table 9) were also formed during the synthesis of (**34**) (Table 4) ⟨78JHC293⟩ and (**189**) ⟨72TL4703⟩.

Preparation of the *spiro*-lactol (**226**) has been elegantly accomplished by Michael addition of ascorbic acid to acraldehyde in aqueous solution ⟨87JCR(S)277⟩.



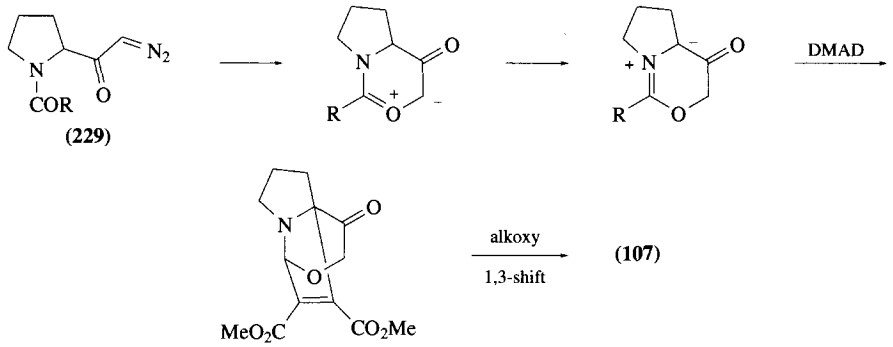
(226)

Rhodium(II) acetate in benzene catalyzes the decomposition of the diazoamide containing a tethered π-system (**227**) to form the 1,3-dipole of an isomunchnone which subsequently undergoes intramolecular dipolar cycloaddition to afford the cycloadduct (**228**) in high yield ⟨92TL4731⟩.



(227) (228)

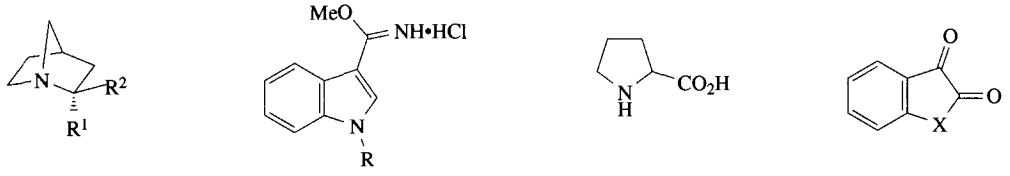
Tricyclic dihydropyrrolizidines such as (**107**) were obtained from the reaction between a dipolarophile and an azomethine ylide intermediate derived from *N*-acyl-2-(1-diazoacetyl)pyrrolidines (**229**; R = Me, OMe, Ph, $CH_2CH(CH_2)_3$) on treatment with a catalytic quantity of a Rh(II) carboxylate in the form of Rh_2OAc_4. Most plausibly the generation of the expected carbonyl ylide dipole by the internal cyclization of the ketocarbenoid on to the oxygen atom of the amide group occurs at the initial stage of the reaction followed by isomerization to an azomethine ylide which accepts the dipolarophile DMAD to afford an adduct which undergoes alkoxy 1,3-shift to generate the tricyclic dihydropyrrolizidine ring system (**107**) ⟨92JA593⟩. This mechanism of formation of (**107**) has been established by NMR spectroscopy (Scheme 24).



Scheme 24

A novel series of *spiro*-fused indolyloxazolines and the epimer at the *spiro*-carbon (**62**) (Table 9) have been obtained by exploiting the addition of diastereomeric azabicyclic amino-alcohols (**230**) and (**231**) to an indole imidate (**232**) ⟨90JCS(P1)3183⟩.

Chiral induction in cycloaddition reactions of azomethine ylide has been achieved when the α-amino acid (**233**) reacts with isatin or benzthiophen derivatives (**234**; X = NH, NBu, S) and menthyl acrylate. The course of the reactions involves decarboxylative azomethine ylide formation followed by cycloaddition through an *endo* transition state ultimately affording the cycloadduct (**61**) (Table 9) in 67–82% diastereomeric excess ⟨91TL5417⟩.



(**230**) R^1 = OH, R^2 = CH_2NH_2
(**231**) R^1 = CH_2NH_2, R^2 = OH

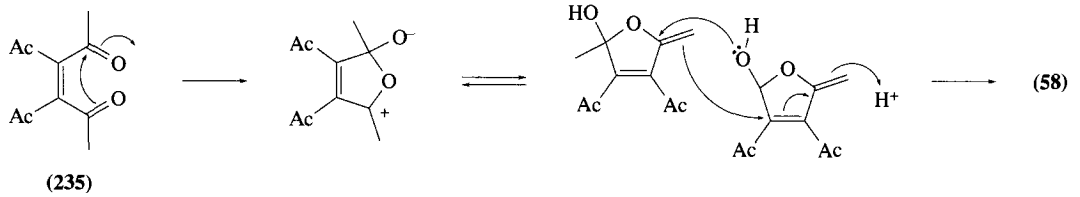
(**232**)

(**233**)

(**234**)

Tetraacetylethylene (**235**), having a conjugated system with a highly activated double bond, undergoes dimerization to compound (**58**) (Table 9) in 80% yield on refluxing in an inert solvent such as benzene for 28 h. A plausible mechanism of the dimerization is shown in Scheme 25 ⟨80CJC1645⟩.

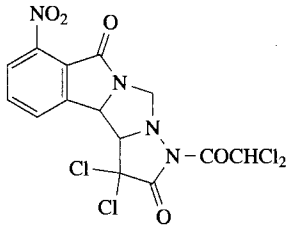
After critical examination of all the synthetic and preparative methods delineated above, it is very



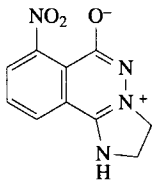
Scheme 25

difficult at this stage to propose effective general synthetic methodologies for the diversified patterns of three heterocyclic ring systems fused (5 : 5 : 5) incorporating heteroatoms in varied classes and numbers. The limited study so far in the literature suggests that the 1,3-dipolar cycloaddition reaction may turn out to be an attractive preparative methodology.

In 1994, the synthesis of an isoindole derivative (**236**) was reported. It was achieved when 2,3-dihydro-7-nitro-1*H*-imidazo[2.1-α]phthalazin-4-ium-6-olate (**237**) underwent a backbone rearrangement on treatment with dichloacetic anhydride ⟨94H(38)1453⟩.



(**236**)



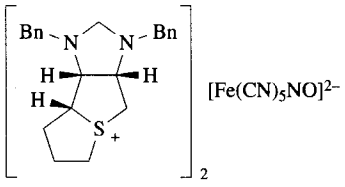
(**237**)

8.35.7 IMPORTANT COMPOUNDS AND APPLICATIONS

The number of compounds reported since the mid-1980s is limited. Hence the appearance of important new compounds with their applications is also expected to be restricted. Only a few of the compounds which appeared in the literature are documented in this section.

Compound (**14a**; R = alkyl, arylalkyl) (Table 2) is useful as an intermediate for agrochemicals, pharmaceuticals and electronic materials. The polymeric form is used as a support electrolyte ⟨89JAP(K)172387⟩.

Compound (**37**) (Table 4) has been screened for antibacterial and antifungal activities. (+)-Bis(trimethaphan)nitroprusside (**238**) was found to be a very effective antihypertensive agent and vasodilator ⟨83GEP(O)3301134⟩.



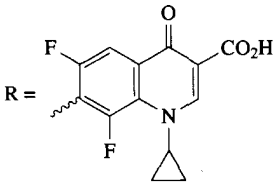
(**238**)

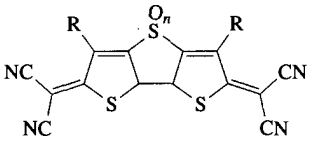
The heterocycles (**15c**) (Table 2) have been described as inotropic excitatory amino-acid receptor agonists ⟨94EUP600741⟩. Compound (**4**) (Table 1), having R = quinolone derivatives, is reported to be a bactericide ⟨92GEP(O)4032562⟩.

A polymeric dye with structure (**30**) (Table 3) has been found to be an optical sensitizer ⟨76AHC(19)123⟩. Thienopyrrolopyrroles (**13**) (Table 2) are considered as intermediates for agrochemicals, drugs, and conductor materials ⟨89JAP(K)6786⟩.

The bifunctional chelating agent NOTA (**93**), easily prepared from compound (**45**) (Table 6), is well known for its use in radiolabeling proteins ⟨93TL3691⟩. This chelating agent finds potential use for the identification of proteins for therapeutic applications in general and radioimmuno diagnosis in particular. The successful use of this bifunctional chelating agent is due to its capability of maintaining a stable complex *in vivo* and its possession of a functional group which can be used for protein modification without deleterious effect.

The heterocycles (**13**) and (**14a**) (Table 2) find much application in electrochemical polymerization to prepare electroconductive polymers ⟨89TL1655⟩. The conductive complexes (**239**), named 2,6-bis(dicyanomethylene)-2,6-dihydrodithieno[3,2-*b*: 2′,3′-*d*]thiophene, have been described as potential electron acceptors ⟨89BCJ1547⟩.





(239a) R = H, n = 0, 2
(239b) R = Br, n = 0

Indole oxazolines (**62**) (Table 9) are novel 5-HT_3 antagonists ⟨90JCS(P1)3183⟩.

ACKNOWLEDGMENT

We are grateful to Dr. A. J. Boulton for helpful discussions. We also thank Mr. A. K. Kundu, P. Chatterjee, and G. H. Jana for help during the preparation of the manuscript.

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8.36
Three Heterocyclic Rings Fused (5 : 6 : 5)

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8.36.1 INTRODUCTION AND OVERVIEW

8.36.1.1 Historical Preface

Different aspects of the chemistry of tricyclic-fused heterocycles (5:6:5) have been described throughout the seven volumes of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (See Table 1). The present attempt to summarize in a single chapter the most relevant aspects of the structure, the physical properties, the chemical behaviour, and the synthesis of these fused heterocycles, covering the literature published since 1982, has required a great effort of abridgement on account of the variety of structural arrays and the complexity of ring assemblies characteristic of these fused systems. Publication in the field has increased enormously. *Chemical Abstracts* has registered 326 entries (some of them with more than 50 references) under the ring system (5,5,6) for the period 1982–1986 (CA, 11th Coll. Vol.), and this number increases to 406 entries for the period 1987–1991 (CA, 12th Coll. Vol). Most of the systems registered deal with fused-heterocyclic systems; therefore, it is essential to systematize the different modes of assembly of the known tricyclic fused-heterocycles.

In order to facilitate comparisons between different rings systems, the base components indene, indacene, pentalene, and naphthalene have been chosen for the design of the carbocyclic pattern of the tricyclic assembly (Table 2). Of these broad classes of structures, [*f*]annelated- (**1**), [*e*]annelated- (**5**), [*a*]annelated- (**2**), and [*c*,*d*]annelated-indenes (**6**) have been the most completely explored, less being known of (1,4)-methano-naphthalenes (**7**), while [*c*]annelated- (**3**), [*d*]annelated-indenes (**4**), and tricyclo[4.2.1.$1^{2,5}$]decanes (**12**) have been the least extensively investigated. The bridged systems (**8**–**10**) and the (3a,6a)-butano-pentalenes (**11**) have been scarcely mentioned, if at all, in CHEC-I.

8.36.1.2 Reviews

Without doubt, the most important contribution to the knowledge of fused heterocycles from the synthetic point of view is due to work carried out by Ellis ⟨87HC(47)1, 92HC(47)1⟩. This important overview summarizes a compendium of methods, classified according to the functional groups which interact to form the new ring for the synthesis of a heterocyclic ring that is fused to another ring. The reagents, solvents, catalysts, and percentage yields for one or more derivations are shown for each type of cyclization. The information presented in the first volume ⟨87HC(47)1⟩ is concisely presented in over two thousand equations. Official names for ring systems are given to facilitate searching and more than two thousand references cited. The 1992 book ⟨92HC(47)1⟩, completes the

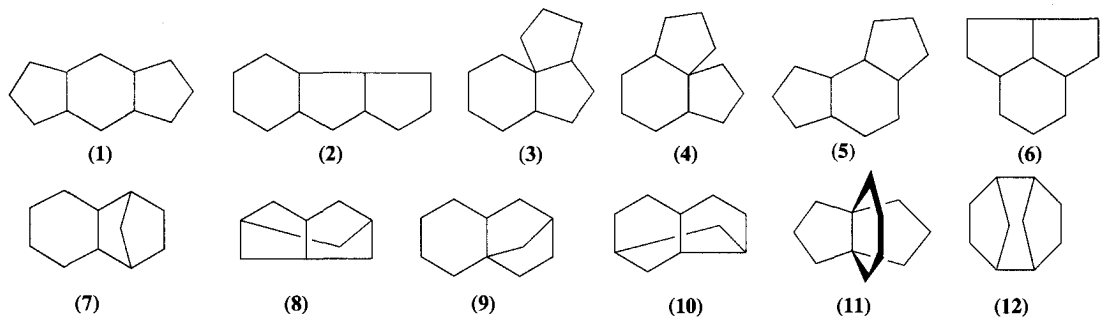
Table 1 Coverage of tricyclic heterocycles in CHEC-I.

Tricyclic assembly	*Structural features*	*Location in CHEC-I* (Vol. Nos)
1. *Ortho*-fused systems	1.1. Heteroindenes fused with five-membered heterocyclic rings.	
	1.1.1. Annelated indoles	1, 4, 5 and 7
	1.1.2. Annelated isoindoles	1, 4, 6 and 7
	1.1.3. Annelated indazoles	5 and 6
	1.1.4. Annelated purines	5
	1.2. Six-membered heterocycles fused with two five-membered heterocyclic rings	
	1.2.1. Condensed azines: pyridines, pyridazines, pyrimidines, pyrazines, triazines, tetrazines, thiazines, oxathiazines	2 and 3
	1.2.2. Condensed polyoxa, polythia and polyaza systems: [1,3]dioxins, [1,4]dioxins, [1,4]dithiins	3 and 4
	1.3. Benzoderivatives of five-membered heterocycles fused with five-membered heterocyclic rings	4
	1.3.1. Condensed benzofurans, benzothiophenes and benzopyrroles	5 and 6
	1.3.2. Condensed benzoxazoles, benzothiazoles, benzoselenazoles, benzotellurazoles and related systems	
2. *Ortho*- and *peri*-fused systems	2.1. Heteropentalene derivatives	4 and 6
	2.2. [2.2.3] Cyclazines, aza[2.2.3]cyclazines and diaza[2.2.3]cyclazines	4
3. Bridged naphthalenes	3.1. 1,4-Methano-naphthalene and related systems	3 and 4
4. Fused-heterocycles containing less common elements	4.1. Fused-three heterocyclic rings containing B, Si, Ge, Sn Pb, halogens, Se, Te or P	1

Table 2 Three heterocyclic rings fused (5 : 5 : 6)—types of hydrocarbon ring assembly.

Tricyclic systems		*Structure*	*Type of ring assembly*[a]
a. *Ortho*-fused indenes	a.1 linear systems	**(1)**	[*f*]-Annelated (*s*-indacene) (32)
		(2)	[*a*]-Annelated (58)
	a.2 angular systems	**(3)**	[*c*]-Annelated (1)
		(4)	[*d*]-Annelated (1)
		(5)	[*e*]-Annelated (*as*-indacene) (54)
b. *Ortho*- and *peri*-fused indenes		**(6)**	[*c,d*]-Annelated (23)
c. Bridged systems		**(7)**	1,4-Methano-naphthalene and related systems (16)
		(8)	2,5-Methano-pentalene and related systems (0).
		(9)	2,4a-Methano-naphthalene and related systems (0)
		(10)	1,6-Methano-indene and related systems (0)
		(11)	(3a, 6a)-butano-pentalene (0)
		(12)	tricyclo[4.2.1.$1^{2,5}$]decane (1)

[a]Numerals in parentheses indicate the number of different triheterocyclic structures appearing in CHEC-I belonging to each of the ring assemblies ⟨84CHEC-I(8)1011⟩.



information since 1987 and incorporates an improved general index which includes all examples of reacting groups.

Since CHEC-I appeared in 1984, several reviews on specific fused (5,5,6) heterocycles have been published. A review on pyrrolo[1,2-*a*]indoles has appeared in which the different synthetic approaches leading to this particular heterocyclic assembly have been systematized ⟨86RTC199⟩. Special interest of the authors in the five most important strategies leading to the pyrrolo[1,2-*a*]indole skeleton has been shown, of which the greater part is related to the synthesis of the *mitomycins*, alkaloid-type antibiotics with antitumor activity. The literature cited covered the period from 1978 to the end of 1985.

A review has appeared in which Italian authors describe the synthesis, reactivity, spectroscopic properties, and biological activities of thiazolobenzimidazoles ⟨88H(27)1975⟩. Special attention has been given to the synthetic approaches to four main assemblies of this tricyclic heterocyclic system.

The synthesis of [2.2.3]cyclazines, aza[2.2.3]cyclazines and their derivatives has also been covered. The attention of the reviewers has been focused on the study of the developments in the synthesis of several benzocyclazines and azacyclazines by the [8 + 2] cycloaddition reaction of the dimethyl acetylene dicarboxylate with various types of indolizines. The synthesis of indolizines, imidazo[1,2-*a*]pyridines, and related compounds, which are key intermediates for the synthesis of cyclazines, is also described ⟨88H(27)2251⟩.

A contribution to the synthesis of angular benzodipyrazoles and several related systems with different central rings has appeared ⟨91H(32)41⟩. The synthesis and mechanistic aspects of different approaches to these tricyclic systems have been discussed.

An excellent account of isobenzofurans and their derivatives, which covers the period 1980–87, has also appeared ⟨88T2093⟩. According to the authors, this work does not purport to be an exhaustive account, but rather a subjective look at the chemistry of isobenzofurans, somewhat biased towards the synthetic utility of these compounds.

A review on the chemistry of fused aromatic heterocyclic systems containing the furan ring fused with five- or six-membered rings and their condensed derivatives has been published ⟨90CCC597⟩. The authors focus their attention on the substitution, addition, and cycloaddition reactions of condensed furo[3,2-*b*]pyrroles.

An overview on condensed 1,2,4-triazolo[3,4-*z*]heterocycles has appeared in which the synthesis of numerous condensed tricyclic systems has been reported ⟨90AHC(49)277⟩.

8.36.2 THEORETICAL METHODS

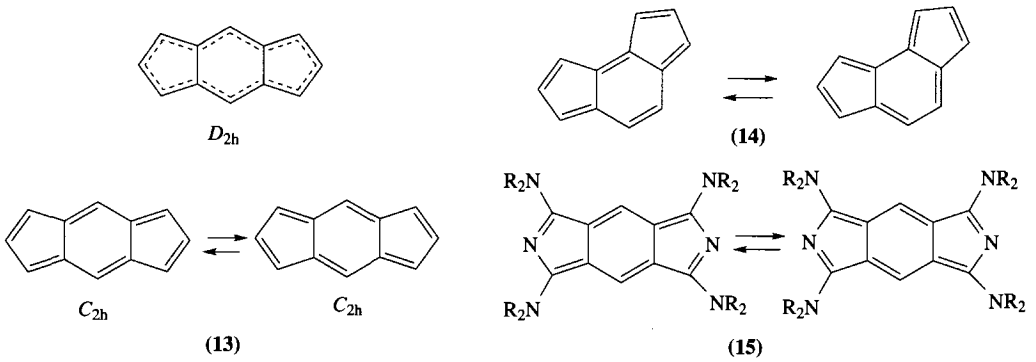
8.36.2.1 *Ab Initio* MO Methods

The main part of the theoretical work found in the literature on tricyclic fused (5,5,6) heterocycles deals with ortho-fused systems related to *s*-indacene. Non-benzenoid, polycyclic-conjugated, π-electron systems such as *s*-indacene (**13**) ⟨63AG1041, 71PAC1, 92JPC3674⟩, *as*-indacene (**14**), and 1,3,5,7-tetraamino-2,6-diaza-*s*-indacene (**15**) ⟨87AG(E)1037⟩ have focused the attention of numerous groups of theoretical chemists and have promoted an intensive literature aimed at answering the issue of the double-bond localization.

s-Indacene is a planar, conjugated, tricyclic-fused hydrocarbon with 12 π electrons which can be considered as a [12]annulene perturbed by two σ-bonds or as a hydrocarbon obtained by the fusion of two fulvenes. Pioneering work on HMO calculations about the structure of *s*-indacene ⟨64T2119⟩ found the localized structure (**13**, C_{2h}) to be more stable than the delocalized one (**13**, D_{2h}). This conclusion was in good agreement with the results obtained by semiempirical studies ⟨86AG(E)630⟩ and has been supported by Hartree–Fock (HF) MO calculations ⟨93JPC1286⟩. Nevertheless, *s*-indacene is extremely reactive and decomposes instantaneously, and hence structural confirmation by x-ray diffraction has not been possible.

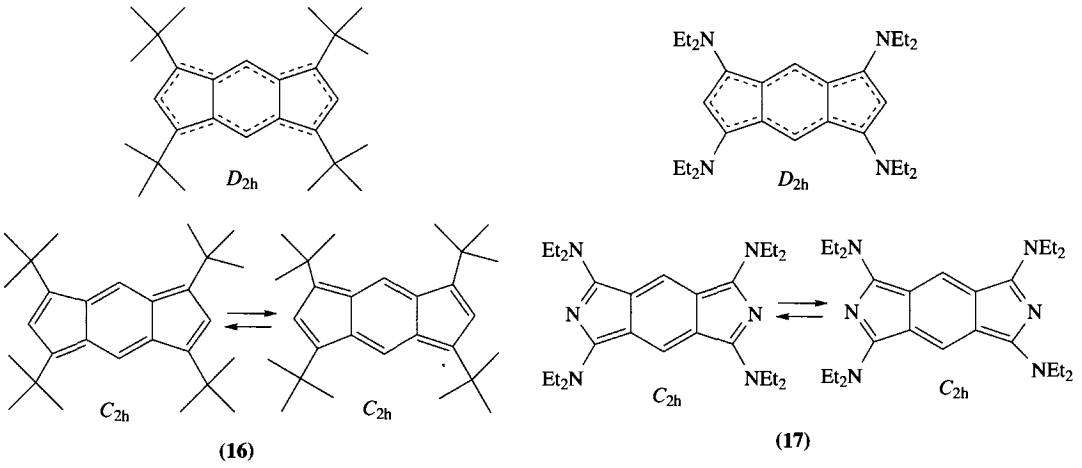
An important extension of the problem has been introduced; namely, the influence that substitution on *s*-indacene positions may exert on the extent and the direction of double-bond localization ⟨64AG(E)165, 86AG(E)630⟩. The NMR data obtained for 1,3,5,7-tetra-*t*-butyl-*s*-indacene (**16**) can only be explained by a very low energy barrier between the two degenerate C_{2h} valence isomers or by a completely delocalized π electron system. According to the x-ray analysis it has been concluded that (**16**) has a carbon skeleton with D_{2h} symmetry ⟨86AG(E)630⟩. This structural assignment has been subsequently confirmed in the literature ⟨88AG(E)387⟩.

HMO theory has been used to establish a qualitative rationalization of the substituent effect on



the localization in the above-mentioned systems ⟨87AG(E)360⟩. It has been shown that (**16**) should have a stronger tendency towards delocalization than *s*-indacene (**13**).

The use of conventional *ab initio* methods with the inclusion of correlation effects, and methods based on density functional theory, in which electron correlation is contained implicitly, converged to give the same answer concerning the structure of *s*-indacene ⟨94AG(E)1192⟩. It has been concluded that the equilibrium structure of *s*-indacene has D_{2h} symmetry and a completely delocalized 12 π electron system, despite its formal classification as a $4n$ π antiaromatic system. According to Koch *et al.*, the x-ray structure of 1,3,5,7-tetra-*t*-butyl-*s*-indacene (**16**) corresponds to the ground state structure of this molecule, and the high reactivity of *s*-indacene can be explained by its diradical character.



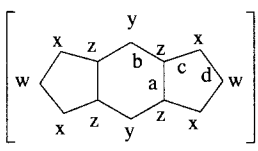
Knowledge of the problem has been extended to the 2,6-diaza-*s*-indacenes ⟨87AG(E)1037, 88AG(E)1437⟩; however, further investigation into this interesting topic is necessary in order to clarify whether 1,3,5,7-tetrakis(diethylamino)-2,6-diaza-*s*-indacene (**17**) has a delocalized structure (D_{2h}) or whether a very rapid valence isomerization between two localized structures takes place (C_{2h}).

8.36.2.2 Semiempirical Methods

MNDO calculations have been carried out on several conjugated bicyclic and tricyclic hydrocarbons; among them, pentalene, heptalene, *s*-indacene, and some of their derivatives have been studied ⟨84T4455⟩.

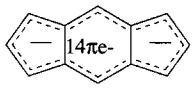
CNDO and *ab initio* calculations were in accordance with the NMR spectra obtained for the dianion of *s*-indacene (**18**), and according to these theoretical studies the negative charge was localized primarily on the centres marked x and to lesser extent at those marked y. MNDO

calculations were optimized to D_{2h} symmetry and provided values for the bond orders and charges as shown in (**18**).

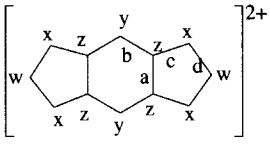


a, 1.183; b, 1.342
c, 1.211; d, 1.405

w,-0.092; x, -0.309
y,-0.116; z, -0.059

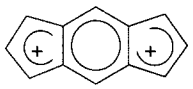


(**18**)



a, 1.347; b, 1.378
c, 0.988; d, 1.439

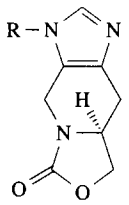
w, -0.196; x, +0.339
y, +0.145; z, -0.121



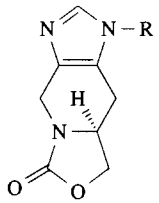
(**19**)

The dication of *s*-indacene (**19**), however, provided a 10 π-electron periphery; free optimization gave D_{2h} symmetry and bond orders and charges as shown. A quite different electronic structure has been obtained in this case from that in the dianion. Whereas the latter has a peripheral delocalized π-electron system, the cation appears to have a 6 π-electron system in the central ring with allyllic 2 π-electron systems in the outer rings. Charge is largely concentrated on the end atoms of the allyl systems; however, there is little interaction between the three delocalized systems ⟨84T4455⟩.

Semiempirical quantum mechanical MNDO calculations ⟨77JA4899, 77JA4907⟩ of conformationally constrained (+)-pilocarpine analogues (**21**) and (**22**) predicted global minimum energy conformations for both isomers ⟨93BCJ191⟩. Since the tricyclic intermediate (**20**) underwent a regioselective alkylation (**21** : **22** = 3 : 1) by treatment with iodomethane under basic conditions, it has been assumed that the electrophilic attack at N(1) is favored because the differentiation between the two faces of the substrate is possible thanks to the formation of an aggregated transition state.

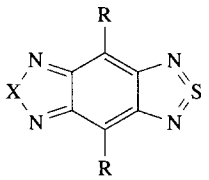


(**20**): R= H
(**21**): R= Me

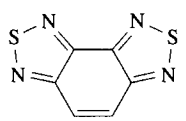


(**22**): R= Me

The HOMO and LUMO coefficients and the charge distribution of benzobisthiadiazole (**23**) have been calculated by the MNDO-PM3 method in order to rationalize the high electron affinity developed by the benzobisthiadiazoles (**24**) and (**25**) and the selenium analogues (**26**) and (**27**) in comparison with the weaker electron-acceptor properties exhibited by the Kekulé-type isomer (**28**). The high electron affinity of compounds (**24**)–(**27**) is attributable to the 14π electron system containing a tetravalent sulfur atom, which generates more stable Kekulé-type thiadiazole moieties upon accepting an electron ⟨94AG(E)1977⟩.

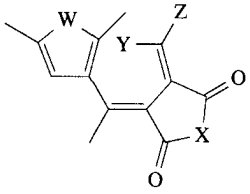


(**23**): R= H; X= S
(**24**): R= Br; X= S
(**25**): R= Ph; X= S
(**26**): R= Br; X= Se
(**27**): R= Ph; X= Se

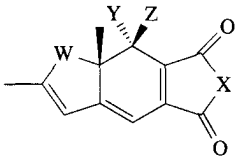


(**28**)

MNDO calculations have been used to get further insight into radical ion electrocyclization on triene-like substrates of the type (**29**) to the tricyclic fused systems (**30**) ⟨84JA7626⟩.



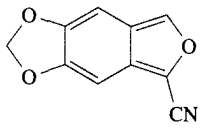
(**29**)



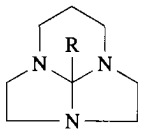
(**30**)

Remarkably good agreement is found on comparing results obtained from MNDO calculations on 5,6-(methylenedioxy)benzo[*c*]furan (**31**) with the lengths and angles obtained by x-ray diffraction ⟨86JOC3973⟩.

On the basis of empirical force field calculations (MM2) the detailed conformational analysis of tricyclic orthoacetamides (**32**) and orthopropionamides (**33**) has been presented ⟨81TL4365⟩.



(**31**)



(**32**): R= Me
(**33**): R= Et

8.36.3 EXPERIMENTAL METHODS

Although the spectroscopic data used in the structural elucidation of fused tricyclic systems have been the subject of comment in this series before, the vast amount of information has been spread along the eight volumes of CHEC-I. The present study attempts to cover the most outstanding aspects of the topic appearing in the literature since 1982 and has been organized by modes of assembly of the tricyclic fused systems.

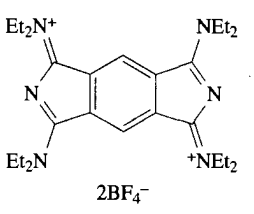
8.36.3.1 *Ortho*-fused Systems

8.36.3.1.1 Benzo[1,2-c:4,5-c']dipyrroles (2,6-diaza-s-indacenes)

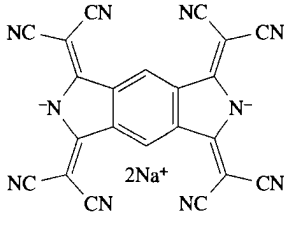
Benzodipyrroles have been covered in CHEC-I in the comments made on the reactivity of pyrroles and their benzoderivatives ⟨84CHEC-I(4)231, 84CHEC-I(4)286, 84CHEC-I(4)311⟩.

(i) Proton NMR, UV, VIS spectroscopy

Table 3 lists selected data (^{1}H NMR, UV/Vis.) of 1,3,5,7-tetrakis(diethylamino)-2,6-diaza-*s*-indacene (**17**, C_{2h}) and related 2,6-diaza-*s*-indacenes (**34**)–(**35**) ⟨87AG(E)1037⟩.



(**34**)



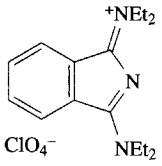
(**35**)

Table 3 Spectroscopic data of 2,6-diaza-*s*-indacenes.

Compd.	*m.p* (°C)	*UV/Vis.* λ_{max} (logε)	^1H *NMR*, δ (ppm)
(**17**)	>120	(hexane): 223, 260, 295, 306, 327, 343, 395, 609; (benzene): 313, 334, 376, 614	(THF-d_8): δ: 1.00 (t, 24H, CH_2CH_3); 2.55 (q, 16H, CH_2CH_3); 7.66 (s, 2H, H-4, H-8).
(**34**)	276	(CH_2Cl_2): 260 (4.66), 269 (4.66), 326 (4.20), 352 (4.13), 420 (3.99), 434 (3.99), 440 (3.99)	(CD_3CN): δ: 1.45 (t, 12H, CH_2CH_3); 1.53 (t, 12H, CH_2CH_3); 4.00 (q, 8H, CH_2CH_3); 4.10 (q, 8H, CH_2CH_3); 8.05 (s, 2H, H-4, H-8).
(**35**)	>350	(DMF): 347 (sh), 362, (4.76), 394 (4.50), 419 (4.39), 520 (4.51), 543 (4.50)	

Source: 87AG(E)1037.

Three groups of magnetically equivalent protons are present in the ^1H NMR spectrum of the neutral tetramino-diaza-*s*-indacene (**17**). In the dication (**34**), however, two methyl groups and two methylenes are distinguishable; furthermore, the two aryl protons are magnetically equivalent although they appear at a significantly lower field than the aryl protons of (**17**). Additionally, the position of the signals of H(4) and H(8) in the ^1H NMR spectrum of (**34**) (δ : 8.05) differs very little from the position of the signals of H(4) to H(7) in 1,3-bis(diethylamino)isoindolylium perchlorate (**36**) (δ : 7.96). According to this, the interaction of the two azavinamidium moieties in (**34**) appears to be relatively weak.



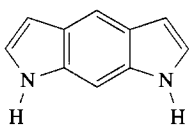
(**36**)

(ii) X-ray

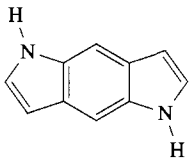
X-ray structural analysis shows (**17**) to be a planar molecule (apart from the methyl groups) with an approximate D_{2h} symmetry. The observed bond lengths are in good agreement with the MNDO calculations and also with the values found in the case of 1,3,5,7-tetra-*t*-butyl-*s*-indacene (**16**) ⟨86AG(E)630, 68T1215⟩.

8.36.3.1.2 Dihydrobenzodipyrroles

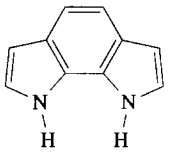
Fully conjugated benzodipyrroles have been reviewed in the CHEC-I ⟨84CHEC-I(4)231, 84CHEC-I(4)286, 84CHEC-I(4)311⟩. Additionally, the physical and selected spectral data concerning several dihydrobenzo[$x_1,y_1 - z : x_2,y_2 - z'$]dipyrroles have appeared ⟨83KGS1086, 84KGS1219, 87CC1176⟩. Table 4 lists selected spectral data of linear and angular systems (**37**)–(**39**).



(**37**)



(**38**)



(**39**)

Table 4 Physical and ^{1}H NMR data of dihydrobenzo[x_1,y_1-*z* : x_2,y_2-*z*]dipyrroles (**37–39**).

Compound	*m.p.* °C	*^{1}H NMR δ* (ppm)
(**37**)	252	DMSO-d_6: 6.35; 7.21; 7.33; 7.62; 10.57
(**38**)	198–203	DMSO-d_6: 6.31; 7.21; 7.41; 10.41
(**39**)	217	DMSO-d_6: 6.42; 7.18; 10.5

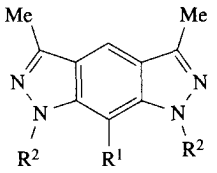
Source: 87CC1176.

8.36.3.1.3 Benzodipyrazoles

The preparation of linear and angular representatives of this series has been described on account of their reported biological activity ⟨88JMC2034, 91H(32)41⟩.

(i) Linear systems

Conventional spectroscopic data (IR, ^{1}H NMR and MS) of benzo[1,2-*c* : 5,4-*c*′]dipyrazoles (**40**)–(**48**) have been published ⟨88JMC2034⟩.



(**40**): $R^1 = R^2 = H$
(**41**): R^1 = Me; R^2 = H
(**42**): R^1 = H; R^2 = Me
(**43**): R^1 = H; R^2 = Et
(**44**): R^1 = H; $R^2 = Pr^n$
(**45**): R^1 = Me; R^2 = Me
(**46**): R^1 = Me; R^2 = Et
(**47**): R^1 = Br; R^2 = H
(**48**): $R^1 = NO_2$; R^2 = H

(ii) Angular systems

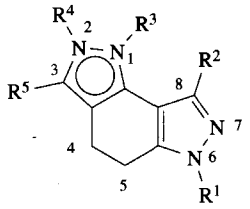
Benzo[1,2-*c* : 3,4-*c*′]dipyrazole derivatives (**49**)–(**77**), benzo[1,2-*c* : 4,3-*c*′]dipyrazoles (**78**)–(**79**), and thiopyrano[3,2-*c* : 5,4-*c*′]dipyrazoles (**80**)–(**84**) have been reviewed ⟨91H(32)41⟩.

Structural assignments of benzo[1,2-*c* : 3,4-*c*′]dipyrazoles (**49**)–(**74**) were made on the basis of ^{1}H NMR parameters and NOE effects ⟨91H(32)41⟩. This is illustrated by the assignment of structures for both (**53**) and (**54**). Chemical shifts for the N(1)—CH_3 and N(6)—CH_3 groups in the ^{1}H NMR(CD_3OD) spectrum of (**53**) were assigned at δ 4.15 ppm and δ 3.95 ppm, respectively, while the N(2)—CH_3 and N(6)—CH_3 of (**54**) were assigned at δ 3.98 ppm and δ 3.93 ppm, respectively. The anisotropy of the N(6), N(7)-pyrazole ring causes the N1—CH_3 group of (**53**) to appear at a significantly lower field than the N2—CH_3 of (**54**).

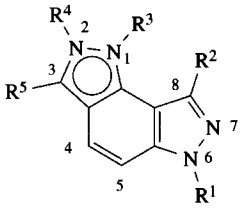
Moreover, when the N(1)—CH_3 of (**53**) was irradiated in an NOE experiment, the C(8)—H signal at δ 8.15 was enhanced, indicating a proximal relationship. No C(8)—H signal enhancement at δ 7.90 was observed when the N(2)—CH_3 signal of (**54**) was irradiated. The structure of the benzopyrazoles (**75–84**) has been supported by ^{1}H NMR and MS data ⟨91H(32)41⟩. The position of the benzyl group on (**83**) was definitely shown to be at C(1) by an NOE study. Irradiation of the benzyl methylene group of (**83**) produced an NOE effect on C(8)—H but no NOE effect on C(3)—H.

8.36.3.1.4 Thiazolobenzimidazoles

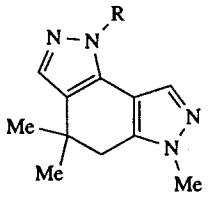
The spectroscopic properties of thiazolo[3,2-*a*]benzimidazoles (**85**), thiazolo[3,4-*a*]benzimidazoles (**86**) and thiazolo[3,2-*c*]benzimidazoles (**87**) have been reviewed ⟨88H(27)1975⟩.



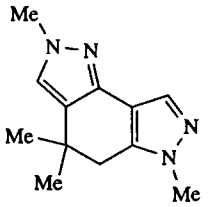
Cmpd.	R^1	R^2	R^3	R^4	R^5
(49)	Me	H	Me	-	H
(50)	Me	H	H	-	H
(51)	Me	H	-	Me	H
(52)	Me	H	H	-	Me
(53)	Me	H	Me	-	Me
(54)	Me	H	-	Me	Me
(55)	H	Me	H	-	H
(56)	Me	Me	H	-	H
(57)	Me	Me	Me	-	H
(58)	H	Me	Me	-	H
(59)	H	Me	H	-	Me
(60)	Bz	H	Me	-	H
(61)	H	H	Me	-	H
(62)	Bz	H	H	-	H
(63)	H	H	H	-	Me
(64)	Bz	H	H	-	Me
(65)	H	H	H	-	Me



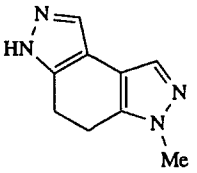
Cmpd.	R^1	R^2	R^3	R^4	R^5
(66)	Me	H	H	-	H
(67)	Me	H	Me	-	H
(68)	Me	H	-	Me	H
(69)	Me	H	H	-	Me
(70)	H	Me	H	-	Me
(71)	H	Me	H	-	H
(72)	H	H	H	-	H
(73)	Me	H	-	Me	Me
(74)	H	H	H	-	Me



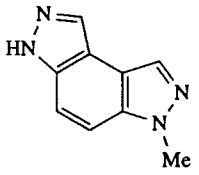
(75): R = H
(76): R = Me



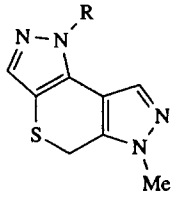
(77)



(78)



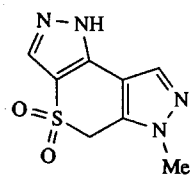
(79)



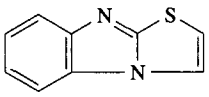
(80): R = H
(81): R = Bz



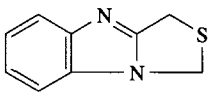
(82): R = H
(83): R = Bz



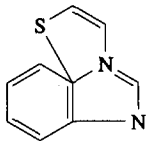
(84)



(85)



(86)



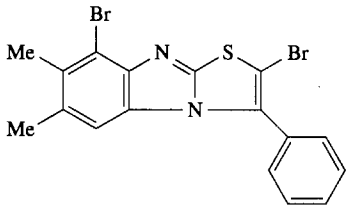
(87)

(i) X-ray

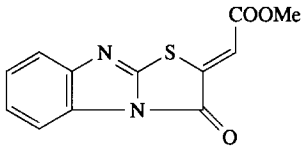
X-ray structural analysis of 2,8-dibromo-6,7-dimethyl-3-phenyl-benz[4,5]imidazo[2,1-*b*]thiazole (**88**) shows that this molecule does not exhibit full planarity ⟨77LA106⟩.

The structural assignment of (*E*)-2-(methoxycarbonylmethylene) benzimidazo[2,1-*b*]-[1,3]thia-

zolidin-3-one (**89**) has been suggested on the basis of the NMR spectra and corroborated by crystal x-ray study ⟨78TL2621⟩.



(**88**)

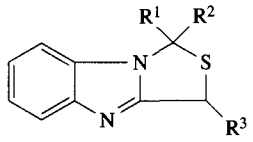


(**89**)

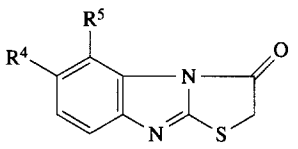
(ii) NMR spectroscopy

The physical characteristics and ^{1}H NMR data of 1*H*, 3*H*-thiazolo[3,4-*a*]benzimidazoles (**90**)–(**98**) have been described ⟨88S244⟩.

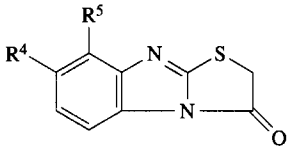
The structural assignment of the two possible isomers of substituted thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (**99**) and (**100**) has been made, first based on NMR spectra ⟨81CPB1876⟩. Furthermore, these derivatives were converted by desulfurization into the corresponding 1-acetylbenzimidazoles for structural determination ⟨82CPB2714⟩.



(**90**): $R^1 = R^2 = R^3 = H$
(**91**): R^1 = Me; $R^2 = R^3 = H$
(**92**): R^1 = Pr^i; $R^2 = R^3 = H$
(**93**): $R^1 = C_6H_{11}$; $R^2 = R^3 = H$
(**94**): R^1 = Ph; $R^2 = R^3 = H$
(**95**): $R^1 = R^2$ = Me; $R^3 = H$
(**96**): $R^1 = R^2$ = Et; $R^3 = H$
(**97**): R^1 = Ph; R^2 = Me; $R^3 = H$
(**98**): $R^1 = R^2 = R^3$ = Me



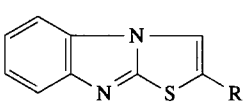
(**99**)



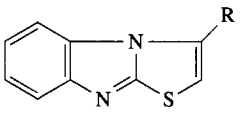
(**100**)

(iii) Mass spectroscopy

Although the mass spectra of thiazoles and imidazoles have been discussed previously in CHEC-I, no survey of thiazolobenzimidazoles has been made. A mass spectral study has been reported in which the fragmentation patterns of this type of compound were analysed and the structures of 2- or 3-substituted thiazolo[3,2-*a*]benzimidazoles (**101**)–(**104**) were confirmed ⟨69JHC797⟩.

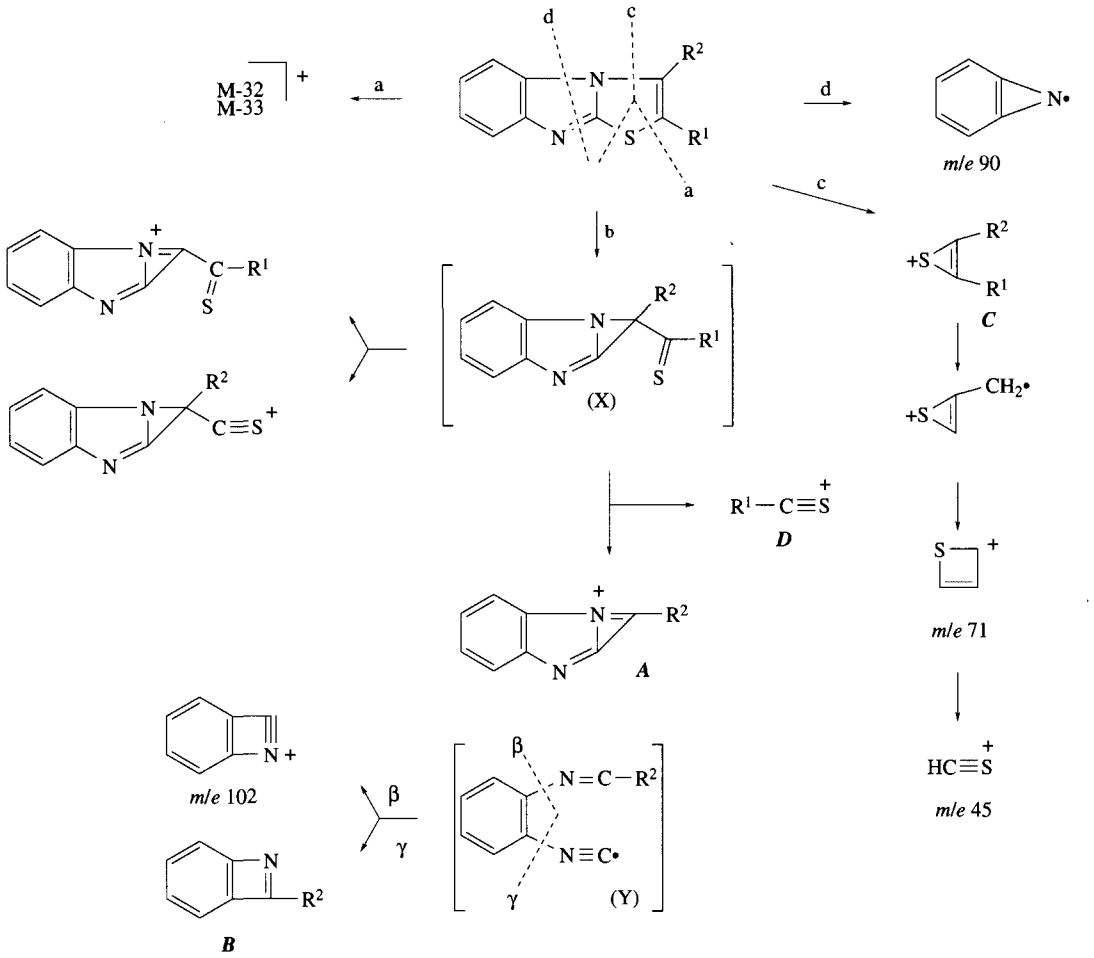


(**101**): R = Me
(**102**): R = Ph



(**103**): R = Me
(**104**): R = Ph

Certain principles may be derived from the fragmentation pattern of the thiazolo[3,2-*a*]benzimidazoles given in Scheme 1. In the thiazolo[3,2-*a*]benzimidazoles, there are four possible directions of cleavage shown by dotted lines a, b, c, and d in Scheme 1. The first pathway (a) shows a M–S and/or M–SH fragmentation to give an ion mass M-32 and/or M-33. The M–H process of 2- and 3-methylthiazolo[3,2-*a*]benzimidazoles (**101**) and (**103**) involves the second pathway (b) through the intermediates (X) and (Y) which undergo preferential cleavage of the C—S bond to yield the ions ***A*** (**101**, *m/e* 129; **103**, *m/e* 143) and ***D*** (**101**, *m/e* 59; **103**, *m/e* 45). These fragmentations and the relative abundances of ions ***A*** and ***D*** can be used to confirm the position of the methyl group of (**101**) and (**103**). The same conclusion is reached in the 2- or 3-phenyl derivatives (**102**) and (**104**). The intermediate (Y) probably undergoes a rupture of the 4—4a or the 8a—9 bond to form two structures: ion *m/e* 102 (4—4a bond rupture) and ion ***B*** (8a—9 bond rupture) (**103**, *m/e* 117; **101**, *m/e* 103). The ion ***C*** (formed through the third mode of cleavage (c) in the case of 2- or 3-methyl compounds was further decomposed to the thietenyl ion (*m/e* 45). The methyl-substituted benzimidazoles (**101**) and (**103**) show the *m/e* 72 peak (2.0% and 1.6%) whereas the phenyl derivatives (**102**) and (**104**) show the *m/e* 134 peak (2.0% and 3.0%). In conclusion, the above-mentioned fragmentations can be used to confirm the structure of the 2- or 3- substituted thiazolo[3,2-*a*]benzimidazoles.



Scheme 1

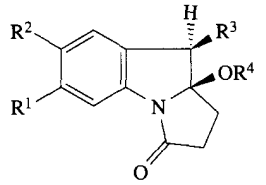
8.36.3.1.5 Annelated indoles

Several aspects of the reactivity of annelated indoles have been discussed in CHEC-I, mainly in Volume 4. However, the spectroscopic properties of these systems have not been previously detailed.

(i) Annelated [a]indoles

An extensive review on the synthesis of pyrrolo[1,2-*a*]indoles has appeared of which the greater part is dedicated to the representatives with the mitosane skeleton ⟨86RTC199⟩.

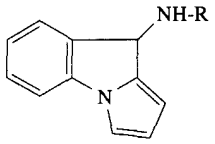
(a) X-ray. The x-ray analysis of rac-(**109**) led to the assignment of the configuration of several mitosane derivatives, (**105**)–(**112**) ⟨85LA1437⟩.



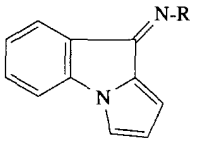
(**105**): R^1 = H; R^2 = H; R^3 = COOMe; R^4 = H
(**106**): R^1 = H; R^2 = H; R^3 = COOMe; R^4 = Me
(**107**): R^1 = Me; R^2 = OMe; R^3 = COOMe; R^4 = H
(**108**): R^1 = H; R^2 = H; R^3 = H; R^4 = Me
(**109**): R^1 = H; R^2 = H; R^3 = CH_2OAc; R^4 = Me
(**110**): R^1 = H; R^2 = H; R^3 = CH_2OAc; R^4 = H
(**111**): R^1 = H; R^2 = H; R^3 = CH_2OCONH_2; R^4 = Me
(**112**): R^1 = Me; R^2 = OMe; R^3 = CH_2OCONH_2; R^4 = Me

(b) ^1H NMR, ^{13}C NMR, IR, UV and mass spectroscopy. Complete ^1H NMR data, including $Eu(fod)_3$-induced chemical shifts, have been obtained to establish the configuration of mitosanes (**105**)–(**112**) ⟨85LA1398, 85LA1413, 85LA1437⟩.

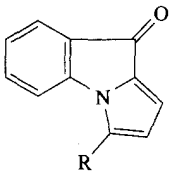
The structures of several 9-amino-9*H*-pyrrolo[1,2-*a*]indoles, (**113**)–(**118**), 9-imino-pyrrolo[1,2-*a*]indoles, (**119**)–(**125**), and pyrroloindolones, (**126**)–(**127**), have been clearly established by ^1H NMR, ^{13}C NMR and IR spectroscopy ⟨85TL2305⟩. Furthermore, the $J(^{13}C–^{13}C)$ coupling constants have been studied in order to ensure that the carbon–carbon sequence is as indicated in (**127**) ⟨86TL3135⟩.



(**113**): R = Me
(**114**): R = Et
(**115**): R = Pr^n
(**116**): R = Bu^n
(**117**): R = C_2H_4OH
(**118**): R = $(CH_2)_3N(Et)_2$



(**119**): R = Me
(**120**): R = Et
(**121**): R = Pr^n
(**122**): R = Bu^n
(**123**): R = C_2H_4OH
(**124**): R = $(CH_2)_3N(Et)_2$
(**125**): R = OH



(**126**): R = H
(**127**): R = Me

The pyrroloindole structures of several 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates, (**128**)–(**134**), are based upon appropriate IR, NMR, UV and mass spectral characteristics ⟨79JOC4742⟩.

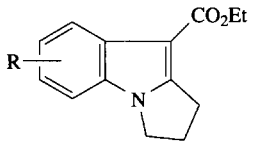
The structures of several 9a-functionalized mitosanes, (**135**)–(**140**), have been supported by IR, UV and ^1H NMR data ⟨79TL2537, 84H(22)541⟩.

Structural assessments of the 2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole ring system (**141**) ⟨83JA2859, 83CC817⟩ and the aziridinomitosenes (**142**)–(**143**) have been primarily based upon the ^1H NMR data ⟨85JOC4515, 83CC1244⟩.

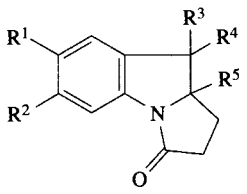
NMR and mass spectroscopic data of several mitomycin C analogues (**144**) ⟨85JOC3791, 85JOC3797⟩ and apomitomycin derivatives (**145**) have provided enough evidence for structural elucidation ⟨80JCS(P1)1607⟩.

(ii) Annelated [b]indoles

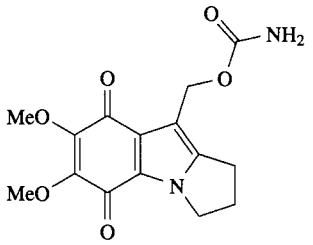
The physical and spectroscopic data of several linear and angular annelated indoles have been described in detail in the period from the mid-1980s to the mid-1990s. The heterocyclic ring system



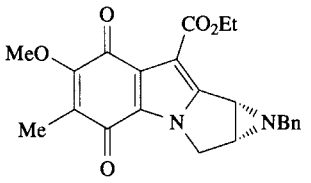
(128): R = H
(129): R = 7-Me
(130): R = 7-Cl
(131): R = 7-OMe
(132): R = 5-OMe
(133): R = 6-Me
(134): R = 8-Me



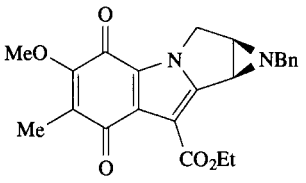
(135): R^1 = H; R^2 = H; R^3 = H; R^4 = H; R^5 = OMe
(136): R^1 = H; R^2 = H; R^3 = CH_2Ac; R^4 = H; R^5 = OMe
(137): R^1 = H; R^2 = H; R^3 = H; R^4 = OH; R^5 = OMe
(138): R^1 = H; R^2 = H; R^3 = CH_2Ac; R^4 = OH; R^5 = OMe
(139): R^1 = NTs; R^2 = Me; R^3 = Me; R^4 = H; R^5 = OH
(140): R^1 = $NSO_2N(Me)_2$; R^2 = Me; R^3 = Me; R^4 = H; R^5 = OH



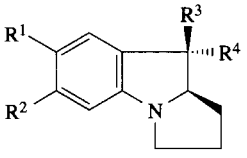
(141)



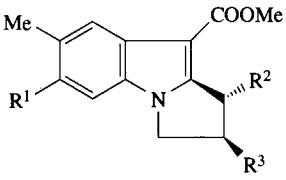
(142)



(143)



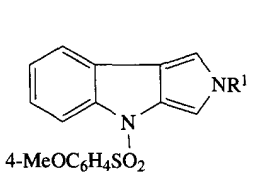
(144)



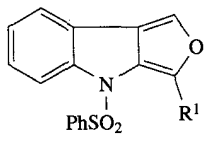
(145)

2,4-dihydropyrrolo[3,4-*b*]indole (**146**)–(**147**) was first described by Welch ⟨76JOC2031⟩, and the spectroscopic properties of the closely related ring systems such as 4*H*-furo[3,4-*b*]indole (**148**)–(**149**) ⟨83TL5435, 84JOC4518⟩, 4*H*-thieno[3,4-*b*]indole (**150**)–(**151**) and 4*H*-selenolo[3,4-*b*]indole (**152**)–(**154**) ⟨82JHC227⟩ appeared later.

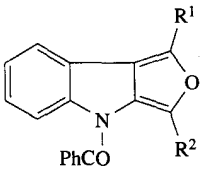
(a) IR, UV, NMR, and mass spectroscopy. The spectroscopic characteristics of several 4*H*-furo[3,2-*b*]indole derivatives have been described ⟨77JHC975, 78JHC123, 79JHC785⟩, and new contributions to the knowledge of this type of system have appeared since the mid-1980s ⟨84JHC709, 84JMC1629, 86JMC2284⟩. Selected IR and UV spectral data has been reported for (**148**) and (**149**)



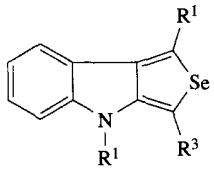
(**146**): R^1 = H
(**147**): R^1 = CO_2Me



(**148**): R^1 = H
(**149**): R^1 = Me



(**150**): R^1 = H; R^2 = Ph
(**151**): R^1 = Ph; R^2 = H



(**152**): R^1 = COPh; R^2 = H; R^3 = Ph
(**153**): R^1 = R^2 = H; R^3 = Ph
(**154**): R^1 = COPh; R^2 = Ph; R^3 = H

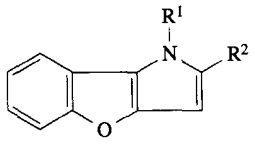
⟨83TL5435, 84JOC4518⟩. In the ^{1}H NMR spectrum of compound (**152**) the proton which is geminal to the selenium atom appears as a strong singlet and a weak doublet centred on the singlet with the splitting constant of 44 Hz (^{77}Se coupling).

8.36.3.1.6 Arylfurocondensed derivatives

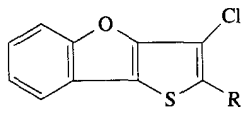
The most recent review from 1990, on the study of condensed furan derivatives provides pertinent information leading to the physical properties of benzofuro[3,2-*b*]pyrroles (**155**)–(**165**), thieno[3,2-*b*]benzo[*b*]furans (**166**)–(**169**) and furo[2′,3′-4,5]pyrrolo[1,2-*d*]1,2,4-triazines (**170**)–(**192**) ⟨90CCC597⟩.

(i) X-ray

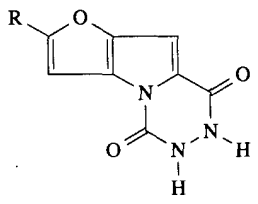
The experimental determination of the geometry of the dioxolobenzo[*c*]furan (**31**) by x-ray crystallographic study has been accomplished. The results indicate that (**31**) is an essentially planar molecule; only the carbon atom of the methylenedioxy group is slightly out of plane, and the bond lengths compare reasonably well with calculated values (MNDO) ⟨86JOC3973⟩.



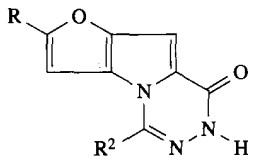
(**155**): R^1 = H; R^2 = CO_2Et
(**156**): R^1 = Me; R^2 = CO_2Et
(**157**): R^1 = Me; R^2 = $CONHNH_2$
(**158**): R^1 = C_2H_4CN; R^2 = CO_2Et
(**159**): R^1 = H; R^2 = CO_2H
(**160**): R^1 = Me; R^2 = CO_2H
(**161**): R^1 = R^2 = H
(**162**): R^1 = Me; R^2 = H
(**163**): R^1 = H; R^2 = Me
(**164**): R^1 = Me; R^2 = CH_2OH
(**165**): R^1 = H; R^2 = $CONHNH_2$



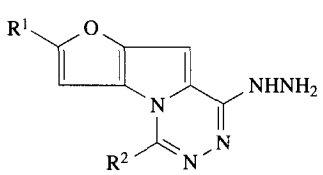
(**166**): R = COCl
(**167**): R = CO_2Et
(**168**): R = CO_2H
(**169**): R = H



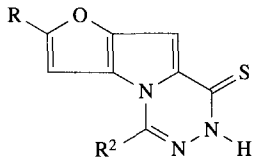
(**170**): R = Ph
(**171**): R = 4-Me-C_6H_4
(**172**): R = 3,4-Cl_2-C_6H_3
(**173**): R^1 = Ph; R^2 = H
(**174**): R^1 = 4-Me-C_6H_4; R^2 = H
(**175**): R^1 = Ph; R^2 = Me
(**176**): R^1 = 4-MeC_6H_4; R^2 = Me



(**177**): R^1 = R^2 = H
(**178**): R^1 = H; R^2 = Me
(**179**): R^1 = 2-NO_2-C_6H_4; R^2 = H
(**180**): R^1 = 2-NO_2-C_6H_4; R^2 = Me



(**181**): R^1 = Ph; R^2 = H
(**182**): R^1 = 4-Me-C_6H_4; R^2 = H
(**183**): R^1 = Ph; R^2 = Me
(**184**): R^1 = 4-MeC_6H_4; R^2 = Me
(**185**): R^1 = R^2 = H
(**186**): R^1 = H; R^2 = Me



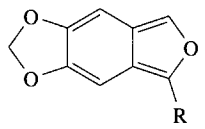
(**187**): R^1 = Ph; R^2 = H
(**188**): R^1 = 4-Me-C_6H_4; R^2 = H
(**189**): R^1 = Ph; R^2 = Me
(**190**): R^1 = 4-MeC_6H_4; R^2 = Me
(**191**): R^1 = 2-NO_2-C_6H_4; R^2 = H
(**192**): R^1 = 2-NO_2-C_6H_4; R^2 = Me

(ii) NMR spectroscopy

NMR analysis of several benzofurol[3,2-*b*]pyrrole derivatives, (**155**)–(**165**), ⟨82CCC3288⟩, thieno[3,2-*b*]benzo[*b*]furans, (**166**)–(**169**), ⟨86CCC1685⟩, furo[2′,3′-4,5]pyrrolo[1,2-*d*]-1,2,4-triazines, (**170**)–(**192**), ⟨83CCC1878, 84CCC1529⟩ and dioxolobenzo[*c*]furans, (**31**) and (**193**)–(**194**) ⟨83CJC1987, 86JOC3973⟩ provided sufficient experimental evidence for the structural elucidation of these tricyclic fused systems.

(iii) Mass spectroscopy

Fragmentation patterns of benzofuro[3,2-*b*]pyrroles (**155**)–(**165**) ⟨82CCC3288⟩ and isobenzofurans (**31**) and (**193**) with the more prominent ions have been described ⟨86JOC3973⟩.



(**31**): R = CN
(**193**): R = CO_2Me
(**194**): R = C_6H_{11}

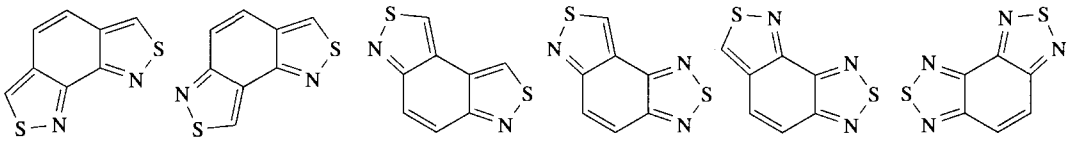
(iv) UV and IR spectroscopy

The most intense band in the electronic spectra of the thieno[3,2-*b*]benzo[*b*]furan (**169**) was found at 289–307 nm. The spectra of the acid chloride (**166**), ester (**167**) and the acid (**168**) showed a bathochromic shift of 25 nm due to the carbonyl groups entering into conjugation with the thieno[3,2-*b*]furan ring ⟨86CCC1685⟩.

Condensed 1,2,4-triazines (**170**)–(**172**) exist, depending on the medium, in two tautomeric forms ⟨83CCC1878⟩; their IR spectra in KBr displayed absorption bands belonging to (C=O), indicating the lactam form. However, the ^{1}H NMR spectra do not show signals of NH groups in hexadeuteriodimethyl sulfoxide. The electronic spectra of the condensed triazines (**170**)–(**192**) were characterized by an intense absorption band (log $\varepsilon = 4.36$–4.83) in the 313–340 nm range and a series of weaker bands at 200–300 nm, corresponding to π–π^* electronic transitions. Spectra of compounds (**181**)–(**192**) were measured in methanol both in neutral and acidic medium; the changes in λ_{max} and in band intensities provide evidence of the tautomerism of these compounds.

8.36.3.1.7 Benzobisisothiazoles, benzobisthiadiazoles, and related systems

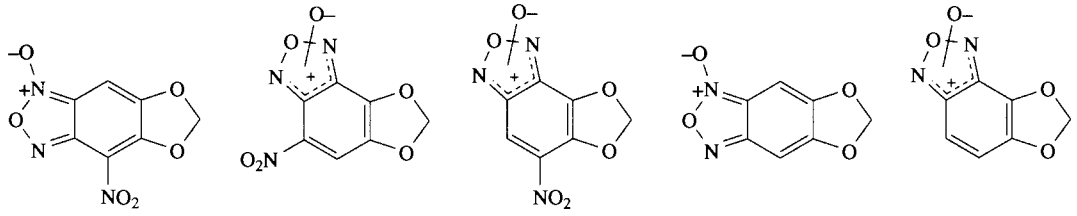
The spectroscopic data (IR, ^{1}H NMR and MS) of benzobisisothiazoles (**195**)–(**197**) ⟨80JHC533⟩, isothiazolo[*c*]-2,1,3-benzothiadiazoles (**198**)–(**199**) ⟨80JHC537⟩ and benzo[1,2-*c*:3,4-*c*′]bis[1,2,5]-thiadiazole (**200**) ⟨75JHC829⟩ have been described.



(195) (196) (197) (198) (199) (200)

8.36.3.1.8 1,2-Methylenedioxy-nitrobenzofuroxans

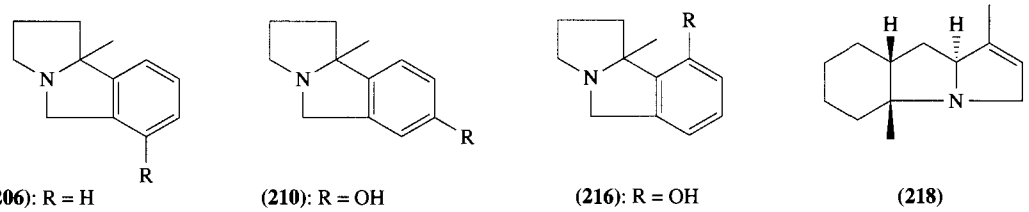
The physical and spectroscopic properties (IR, UV, ^{1}H NMR and MS) of the nitrobenzofuroxans (**201**)–(**203**) and the 1,2-methylenedioxybenzofuroxans (**204**)–(**205**) have been reported ⟨91T7157⟩. Differentiation among the series of isomers (**201**)–(**203**) has been based mainly on ^{1}H NMR and UV data.



(201) (202) (203) (204) (205)

8.36.3.1.9 Benzopyrrolizidines and cyclohexapyrrolizidines

The electron-transfer-induced photocyclization of benzylpyrrolinium salts has been shown to be a reliable method of access to benzopyrrolizidine products. Several representatives of this particular system, (**206**)–(**217**) together with several benzoindolizidines have been fully characterized by spectroscopic methods (IR, UV, ^{1}H NMR, ^{13}C NMR and MS) ⟨90JA3594⟩. X-ray crystallographic study of the picronolate salt of cyclohexapyrrolizidine (**218**) led to the determination of the stereochemical features of this fused pyrrolizidine ⟨78CJC320⟩.



(**206**): R = H
(**207**): R = Me
(**208**): R = CH_2SiMe_3
(**209**): R = $CH_2SiBu^tMe_2$

(**210**): R = OH
(**211**): R = $OSiBu^tMe_2$
(**212**): R = OMe
(**213**): R = Me
(**214**): R = CH_2SiMe_3
(**215**): R = $CH_2SiBu^tMe_2$

(**216**): R = OH
(**217**): R = Me

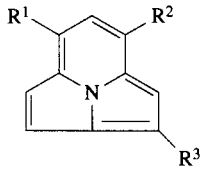
(**218**)

8.36.3.2 *Ortho-* and *Peri-*fused Systems

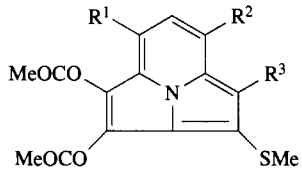
Attention was focused in CHEC-I on these types of fused system ⟨84CHEC-I(4)479, 84CHEC-I(6)973, 84CHEC-I(6)1027, 84CHEC-I(6)1049⟩. Theoretical methods, reports on the synthesis of these compounds, and different aspects of their chemistry have drawn the attention of the reviewers.

8.36.3.2.1 [2.2.3]Cyclazines and aza[2.2.3]cyclazines

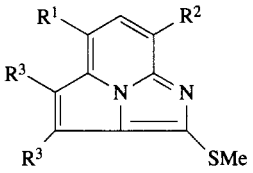
Previous references to cyclazines have been made in CHEC-I ⟨84CHEC-I(4)479⟩. A synthetic survey on [2.2.3]cyclazines (**219**–**227**) and (**237**), 1-aza[2.2.3]cyclazines (**228**)–(**234**) and 5-aza-[2.2.3]cyclazines (**235**)–(**236**) has appeared in which the most significant spectroscopic properties (UV, ^{1}H NMR, and ^{13}C NMR) have been related to structural features ⟨88H(27)2251⟩.



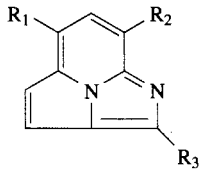
(**219**): $R^1 = R^2 = R^3 = H$
(**220**): $R^1 = H$; $R^2 = Me$; $R^3 = H$
(**221**): $R^1 = R^2 = Me$; $R^3 = H$
(**222**): $R^1 = R^2 = H$; $R^3 = SMe$
(**223**): $R^1 = R^2 = Me$; $R^3 = SMe$



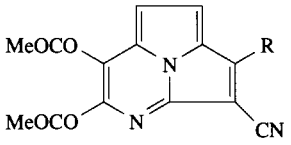
(**224**): $R^1 = R^2 = R^3 = H$
(**225**): $R^1 = H$; $R^2 = Me$; $R^3 = H$
(**226**): $R^1 = R^2 = Me$; $R^3 = H$
(**227**): $R^1 = R^2 = H$; $R^3 = CONH_2$



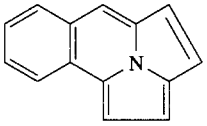
(**228**): $R^1 = R^2 = H$; $R^3 = CO_2Me$
(**229**): $R^1 = R^2 = Me$; $R^3 = CO_2Me$
(**230**): $R^1 = R^2 = Me$; $R^3 = H$



(**231**): $R^1 = R^2 = R^3 = H$
(**232**): $R^1 = R^2 = Me$; $R^3 = H$
(**233**): $R^1 = R^2 = H$; $R^3 = SMe$
(**234**): $R^1 = R^2 = Me$; $R^3 = H$



(**235**): R = SMe
(**236**): $R = NR_2$

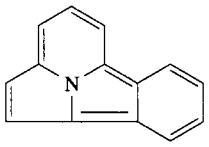


(**237**)

(i) Proton NMR, ^{13}C NMR and UV spectroscopy

It is important to note that the ring proton of [2.2.3]cyclazines (**219**) and (**221**) appears at a lower field than the corresponding ring protons of indolizines since the ring current increases, as is seen in polynuclear aromatic hydrocarbons (PAH). Methyl protons of both methyl and methylthio groups on the cyclazine ring are also shown at lower field, compared with those of the corresponding indolizine derivatives.

The major bands of benzo[*a*][2.2.3]cyclazine (**238**) at λ_{max} 260 nm, 315 nm and 430 nm in the UV spectrum are bathochromically shifted from those of the parent cyclazine (**219**) at λ_{max} 255 nm, 308 nm, and 390 nm, respectively. This may be consistent with the longer conjugated aromatic system in (**238**) ⟨88H(27)2251⟩.



(**238**)

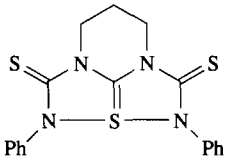
8.36.3.2.2 Fused heteropentalenes

References to ortho- and peri-fused systems other than [2.2.3]cyclazines have been made mainly in Volume 6 of CHEC-I. The spectroscopic properties of two fused-membered heterocyclic rings belonging to classical systems ⟨84CHEC-I(6)973⟩, non-classical systems ⟨84CHEC-I(6)1027⟩, and 1,6,6aλ^4-trithiapentalenes and related systems ⟨84CHEC-I(6)1049⟩ have been studied in detail.

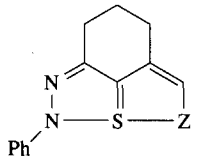
(i) IR, UV ^{19}F NMR and ^1H NMR spectroscopy

The structural assignments of thiatetraazapentalene (**239**) ⟨81T2485⟩, oxathiadiazapentalene (**240**), dithiadiazapentalene (**241**), thiaselenadiazapentalene (**242**), and thiatriazapentalenes (**243**)–(**252**) have been made based on IR, UV, and ^1H NMR spectroscopic data ⟨83JCS(P1)777⟩. ^{19}F NMR spectroscopic data has been used to perform the structural characterization of 10-*S*-5-sul-

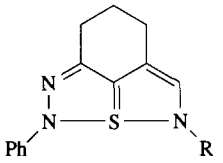
furandioxide salt (**253**), the 10-*S*-4 sulfuranoxide (**254**) ⟨83JA1377⟩, the aryldialkoxybrominanes (**255**)–(**256**) ⟨82JOC1024⟩, the aryldialkoxydifluorperiodinane (**259**), and the aryldialkoxyiodinanes (**257**)–(**258**) ⟨86JA3803⟩.



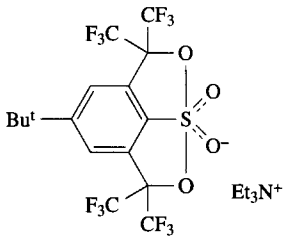
(**239**)



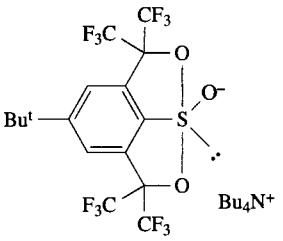
(**240**): Z = O
(**241**): Z = S
(**242**): Z = Se



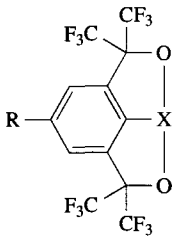
(**243**): R = Ph
(**244**): R = *p*-MeO-C_6H_4
(**245**): R = *p*-NO_2-C_6H_4
(**246**): R = *o*-NO_2-C_6H_4
(**247**): R = 4-Me-2-pyridyl
(**248**): R = Me
(**249**): R = OH
(**250**): R = OMe
(**251**): R = *p*-NO_2-C_6H_4NH
(**252**): R = MeCONH



(**253**)



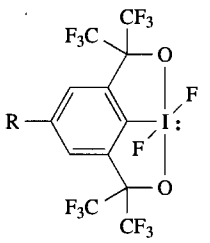
(**254**)



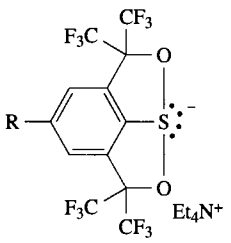
(**255**): R = Me; X = Br
(**256**): R = Bu^t; X = Br
(**257**): R = Me; X = I
(**258**): R = Bu^t; X = I

(ii) X-ray analysis

The x-ray crystallographic structures show the anionic species 10-*S*-5 (**253**), 10-*S*-4 (**254**) and 10-*S*-3 (**260**) to be pseudotrigonal bipyramidal in geometry in the solid state ⟨85JA3209⟩. The complete x-ray crystal structures of brominanes (**255**–**256**) and iodinanes (**257**–**258**) have been described. Both halogenanes are pseudo-trigonal-bipyramidal (Ψ-TBP) species ⟨86JA3803⟩.



(**259**): R = Me

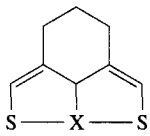


(**260**): R = Bu^t

(iii) ESR spectroscopy and electrochemical properties

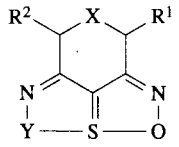
Adduct radicals can be observed by ESR spectroscopy on reaction of some reactive, transient radicals with 1,6,6aλ^4-triheterapentalenes, provided that the atom at position 1 (and/or 6) is sulfur or selenium. The adduct radicals produced by reactions of tri-*n*-butylstannyl radicals with 3,4-

bridged trithiapentalene (**261**) and the dithiaselenapentalene (**262**) have been those most studied ⟨82JCS(P2)431⟩.



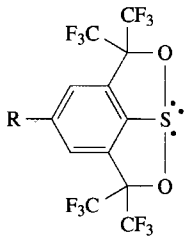
(**261**): X = S
(**262**): X = Se

The electrochemical properties of dioxathiadiazapentalenes (**263–264**) and oxadithiadiazapentalenes (**265–266**) have been analyzed by cyclic voltametry and electron spin resonance ⟨85JCS(P1)833, 85JCS(P2)1797⟩.



(**263**): X = S; Y = O; $R^1 = R^2 = H$
(**264**): X = CMe_2; Y = O; $R^1 = R^2$ = pyr
(**265**): X = S; Y = S; $R^1 = R^2 = H$
(**266**): X = CMe_2; Y = S; R^1 = Ph; $R^2 = H$

Interest in the electronic structure of 9-*S*-3[1] sulfuranyl radicals (**267**) and (**268**) and a S^{IV}-S^{IV} bisulfuranyl species, the dimer of 9-*S*-3[1] sulfuranyl radical (**267**), has led workers to obtain the ESR and electron spin echo envelope modulation (ESEEM) data ⟨86JA3206, 86JA3211⟩.



(**267**): R = Bu[t]
(**268**): R = H

8.36.3.3 Bridged Systems

References to 1,4-bridged naphthalenes, 5,8-bridged benzoaryl systems, and tricyclo[4.2.1.$1^{2,5}$]-decanes are restricted almost exclusively to Volumes 1, 3 and 4 of CHEC-I (see Table 5).

8.36.3.3.1 3a, 6a-butano-heteropentalene derivatives

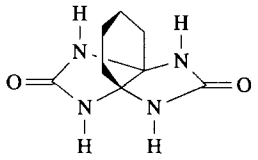
The spectroscopic properties of the bridged glycolurils (**269**) and the bisimidates (**270**) and (**271**) have been reported ⟨87AG(E)1037⟩. X-ray structural analysis of (**271**) afforded insights into the bonding situation in tetrazapropellanes.

8.36.3.3.2 1,4-Epoxynaphthalenes

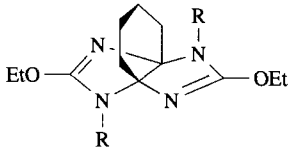
Isobenzofurans generated *in situ* may be trapped by a variety of dienophiles to provide the expected oxo-bicyclo adducts ⟨88T2093⟩.

Table 5 Bridged systems referenced in CHEC-I.

Name	*Vol.*	*Page*	*References in CHEC I*
1,4-Episelenonaphthalene	4	951	76JA867
1,4-Episilanonaphthalene	1	619	64JA1596
1,4-Epithionaphthalene	4	84	76ACS(B)353
1,4-Epoxynaphthalene	1	414	77TL3537
	3	552	71JA2346
	4	66	81AJC1223
	4	97	80TL3663
	4	146	72JCS(CC)347, 76TL2507
	4	628	76JOC3356, 72JA4608
	4	634	76JA6052
	4	683	36JA559
	4	699	56CB1334
Naphthalen-1,4-imine	4	66	81JOC1025
	4	262	81AHC(29)341
	4	351	79T1055
	4	542	71TL3947
1,4-Epoxypyridazino[1,2-a]pyridazine	3	39	77JA8505
	6	829	78CB3037
1,4-Epoxythio-1*H*-2-benzothiin	4	704	81JOC3752
	7	424	69JCS9CC32, 70CJC3704, 72TL4781, 77JOC1910
1,4-Methano-2,3-benzodioxin	4	704	81JOC3752
5,8-2*H*-1-Benzothiin	7	424	69JCS(CC)32, 70CJC3704, 72TL4781, 77JOC1910
5,8-Epoxyisoquinoline	4	982	77TL1741
5,8-Epoxyquinoline	2	364	72JOC3584, 71JCS(C)1227, 70JHC359
5,8-Methano-4,1,2-benzothiazine	3	1076	68CB3567
5,8-Methano-1,2,4-benzotriazine	3	438	30HCA444
5,8-Methano-2*H*-Chromene	3	689	72JCS(CC)388
5,8-Methano-isochromene	1	473	81JCS(P1)146
5,8-Methano-isoquinoline	3	422	69TL5171



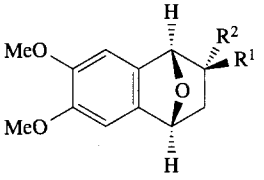
(269)



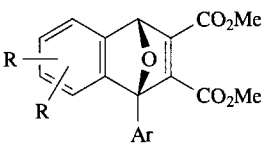
(270): R = H
(271): R = Cl

(i) IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectra

The IR, UV, ^{1}H NMR, ^{13}C NMR, and mass spectra of several benzo[*c*]furan derivatives, **(272–273)**. ⟨83CJC1987⟩, **(274)** ⟨86JOC3973⟩, **(275–279)** ⟨82JOC409⟩ and **(280–281)** ⟨84JCS(P1)859⟩ have been used to elucidate structural features concerning the Diels–Alder reaction of isobenzofurans with dienophiles: the *endo*:*exo* ratios were readily estimated by ^{1}H NMR since the differences between the isomers are typical of all Diels–Alder adducts.

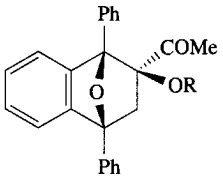


(272): R^1 = CHO; R^2 = H
(273): R^1 = H; R^2 = CHO

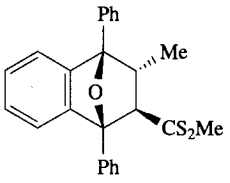


(274)

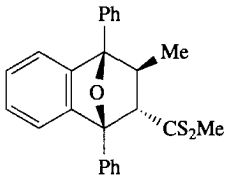
The mass spectra of all adducts were characterized by the presence of a very intense ion corresponding to a retro Diels–Alder fission of the molecular ion. The isobenzofuran ion shows subsequent extrusions of CO, CH_3 and CH_2O ⟨83CJC1987⟩. Adducts of aryl isobenzofurans produce



(275): R = COMe
(276): R = COOEt
(277): R = COCOOMe
(278): R = $COCF_3$
(279): R = $COCCl_3$



(280)

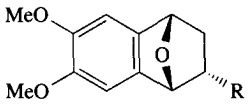


(281)

intense isobenzofuran peaks but very little further fragmentation, except for the loss of a methyl fragment in methoxylated examples. An abundant ion found in all DMAD adducts of aryl isobenzofurans (**274**) corresponds to the acylium ion ($ArCO^+$) ⟨86JOC3973⟩.

(ii) X-ray Analysis

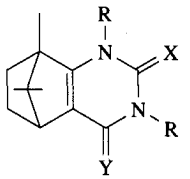
X-ray analysis of 2-*endo*-acetyl and 2-*endo*-carbomethoxy-1,4-epoxy-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalenes (**282**) and (**283**) has been used to establish the stereochemistry of both Diels–Alder adducts ⟨84CJC1099⟩.



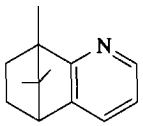
(**282**): R = COMe
(**283**): R = CO_2Me

8.36.3.3.3 5,8-Methanoquinolines and 5,8-methanoquinazolines

Complete spectroscopic methods corresponding to several 5,8-methano-octahydroquinazolinedithiones and diones (**284**)–(**287**) have been reported ⟨81T2451⟩. The circular dichroism spectrum of (+)-5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline (**288**) has been carried out down to 170 nm through the region of the allowed π–π^* transitions.



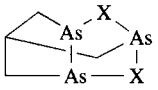
(**284**): R = Me; X = Y = S
(**285**): R = Et; X = Y = S
(**286**): R = Me; X = O; Y = S
(**287**): R = Me; X = Y = O



(**288**)

8.36.3.3.4 Noradamantanes with the heteroelements As, O, S, and Se

Complete spectroscopic data, (IR, ^1H NMR, mass and Raman spectra) have been obtained for a series of noradamantanes with heteroelements arsenic, oxygen, sulfur, and selenium (**289**)–(**291**) ⟨84CB2675⟩.



(289): X = O
(290): X = S
(291): X = Se

8.36.4 THERMODYNAMIC ASPECTS

8.36.4.1 Aromaticity

8.36.4.1.1 Ortho-*fused systems*

(i) S-*Indacenes*

There is a vast amount of information in the literature concerning the theory of double-bond localization, beginning with the work of Longuet-Higgins and Salem ⟨59PRS172, 60PRS445⟩ up to the detailed investigations of Nakajima ⟨64MP149, 86JCS(P2)1731⟩.

Using simple HMO theory, Heilbronner and Yang have given a qualitative rationalization of the substituent effect on the delocalization ⟨87AG(E)369, 87AG(E)360, 89JCE471⟩. They succeeded in explaining why 1,3,5,7-tetra-*t*-butyl-*s*-indacene should have a stronger tendency towards delocalization than *s*-indacene; however, their model provides no answer to the question of whether *s*-indacene prefers a localized or a delocalized structure.

Koch *et al.* have reported high-level quantum chemical calculations on the equilibrium structure of the lowest energy singlet state of *s*-indacene ⟨94AG(E)1192⟩. They made use of two independent theoretical approaches: conventional *ab initio* methods with the inclusion of correlation effects, and methods based on density functional theory, in which electron correlation is implicitly contained in the functional used. At this *ab initio* MO level the delocalized, D_{2h}-symmetric form (**13**, D_{2h}) of *s*-indacene is 3.1 kcal mol^{-1} (13.0 kJ mol^{-1}) more stable than its localized, C_{2h} counterpart. Furthermore, the structural parameters of (**13**, D_{2h}) were compared with the x-ray structure data of 1,3,5,7-tetra-*t*-butyl-*s*-indacene. The agreement between the experimental and computed data was excellent. Since the conventional *ab initio* MO method and the approach based on density functional theory converge to give the same answer concerning the structure of *s*-indacene, the authors conclude that the equilibrium structure of *s*-indacene has D_{2h} symmetry (**13**, D_{2h}) and a completely delocalized 12 π electron system, despite its formal classification as a $4n$ π antiaromatic system.

*(ii) Benzo[1,2-*c*:4,5-*c*′]dipyrroles (2,6-diaza-*s*-indacenes)*

A comparative study of the effect of donor and acceptor substituents in 2,6-diaza-*s*-indacenes has been published by Gompper *et al.* ⟨87AG(E)1037⟩.

X-ray analysis of 1,3,5,7-tetrakis(diethylamino)-2,6-diaza-*s*-indacene (**17**) shows it has a delocalized structure, although it belongs to the Hückel antiarenes. The theoretical predictions on the increasing delocalization and stabilization of *s*-indacene by donor and acceptor groups are also fullfilled in the 2,6-diaza series ⟨88AG(E)1437⟩.

8.36.4.1.2 Ortho- *and* peri-*fused systems*

(i) [2.2.3]Cyclazines

Considerable efforts have been devoted to the investigation of the effect of benzo-fusion on aromatic annulenes ⟨72ACR81, 80IJ294, 82JA2544, 82JA2551, 82JA2571, 84JCS(P1)909⟩.

A review has appeared in which, among others, the question of the effect of benzannelation on [2.2.3]cyclazines has been addressed ⟨88H(27)2251⟩. In general it is shown that the benzannelation toward the macrocyclic compound reduces the diatropicity. The effect of benzannelation on the [2.2.3]cyclazines (**219**) and (**220**) is accompanied by the reduction in diatropicity on benzo[*a*][2.2.3]cyclazine (**238**) as expected. In (**238**), a proton resonates at δ: 7.17 ppm ($J = 3.7$ Hz), which shows

more upfield shift than that of the parent compound (**219**) (δ: 7.40 ppm); the coupling constant of this proton is recognized as of a typical aromatic nature. However, this reduction in diatropicity is less than expected. On the other hand, in the ^{1}H NMR spectrum of benzo[*g*][2.2.3]cyclazine (**237**) the chemical shifts are shown in the range δ: 7.37–8.23 ppm for the peripheral protons of the cyclazine ring and δ: 7.62–8.67 ppm for the benzene ring protons. Thus, owing to the benzo-fusion the peripheral protons display a downfield shift relative to those of the [2.2.3]cyclazine (**219**); the unexpected downfield shift is observed, though very slightly.

The authors conclude that [2.2.3]cyclazine (**219**) is intermediate in aromaticity between the polynuclear aromatic hydrocarbons and peripheral conjugated aromatic compounds involving delocalized 10 π or 14 π electrons. They also state that the resulting [2.2.3]cyclazines and benzo[2.2.3]-cyclazines are strongly diatropic and claim that further theoretical study is required before the details of these novel conjugated systems can be fully understood.

8.36.5 REACTIVITY

The reactivity of fused tricyclic systems has been described throughout the seven volumes of CHEC-I (See Table 1). The aim of the present survey is to offer a summarized outlook into the most outstanding aspects of the reactivity exhibited by some of the most relevant fused tricyclic heterocycles since 1982.

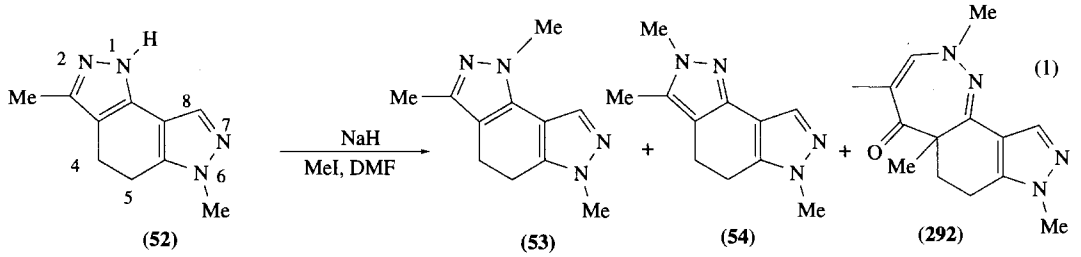
8.36.5.1 *Ortho*-fused Systems

8.36.5.1.1 Benzodipyrroles and benzodipyrazoles

Previous references to these and related systems have been made in Volumes 1,4,5 and 6 of CHEC-I, mainly as part of the reactivity of pyrroles, pyrazoles, and their benzo derivatives. Benzodithiophenes ⟨84CHEC-I(1)113, 84CHEC-I(4)142, 84CHEC-I(4)720, 84CHEC-I(4)749, 84CHEC-I(4)759⟩, benzodifuranes ⟨84CHEC-I(1)294, 84CHEC-I(4)541, 84CHEC-I(4)552, 84CHEC-I(4)593, 84CHEC-I(6)330⟩, and benzimidazoles ⟨84CHEC-I(5)369⟩ have also captured the attention of reviewers.

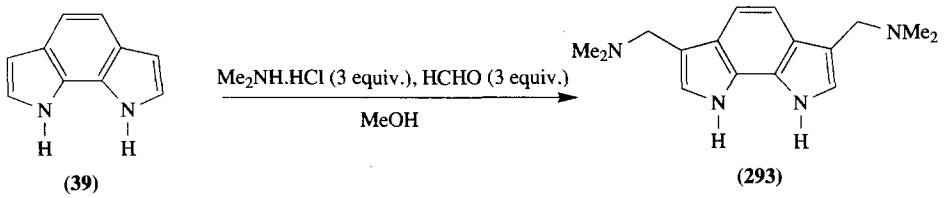
(i) Electrophilic attack at nitrogen

Methylation of tetrahydrobenzodipyrazole (**52**) gave, in addition to monoalkylated products (**53**) (20%) and (**54**) (29%), the condensed 1,2-diazepine (**292**) (5%), which arises from trialkylation and the involvement of solvent as a reactant (Equation (1)) ⟨91H(32)41⟩.



(ii) Electrophilic attack at carbon

By analogy with (**37**) ⟨84KGS1219⟩ and (**38**) ⟨83KGS1086⟩, the β-positions in dihydrobenzo[2,1-*b*:3,4-*b*′]dipyrrole (**39**) are the sites where electrophilic substitutions occur. The benzodipyrrole (**39**) afforded, upon treatment with dimethylamine hydrochloride and formaldehyde in methanol followed by addition of alkali, the Mannich bis-base (**293**) (Equation (2)). Benzodipyrrole (**39**) has been claimed to behave towards electrophilic reagents as a double indole rather than an α,α'-bipyrryl ⟨87CC1176⟩.

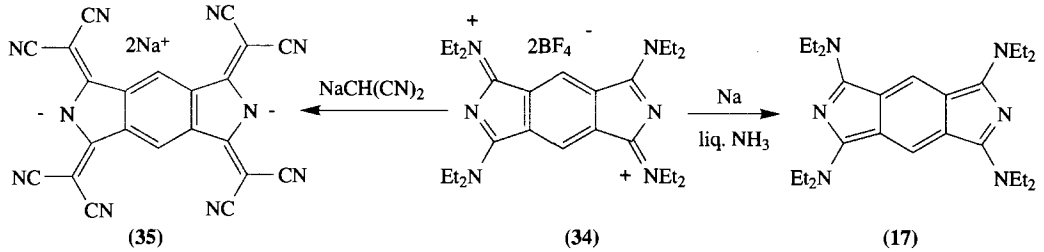


(2)

Electrophilic substitution of benzodipyrazole (**40**) was easily accomplished, since the C(8) position is activated by both N(1) and N(7). Thus, bromination and nitration of (**40**) gave compounds (**47**) and (**48**), respectively (see Section 8.36.3.1.3) ⟨88JMC2034⟩.

(iii) Nucleophilic attack at carbon

The yellow dication salt (**34**) has been used for reactions with nucleophiles; for example, reaction with sodium malononitrile led to the polycyanide (**35**) (Scheme 2).



Scheme 2

(iv) Reactions with radicals and electron-deficient species—reductions and oxidations

By reduction with sodium in liquid ammonia, (**34**) led to 1,3,5,7-tetrakis(diethylamino)-2,6-diaza-*s*-indacene (**17**) ⟨87AG(E)1037⟩.

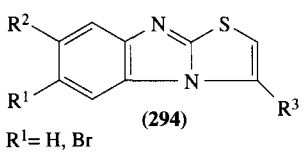
8.36.5.1.2 Thiazolobenzimidazoles

Thiazolo[3,2-*a*]benzimidazoles have been addressed in CHEC-I in the discussion on the reactivity of imidazoles and their benzo derivatives ⟨84CHEC-I(5)131, 84CHEC-I(5)141, 84CHEC-I(5)390, 84CHEC-I(5)419, 84CHEC-I(5)446⟩. Meanwhile, an excellent review has appeared in which the reactivity of the thiazolobenzimidazoles has been covered ⟨88H(27)1975⟩. Thus, only the most outstanding aspects of the chemical behaviour of thiazolobenzimidazoles will be emphasized here.

(i) Reactivity of fully conjugated rings

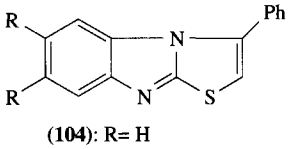
(a) Electrophilic attack at carbon. It has been reported that thiocyanation of thiazolo[3,2-*a*]benzimidazole derivatives (**294**) did not proceed, whereas 2-bromo derivatives can be obtained in good

yields by bromine in $CHCl_3$ solution ⟨72YZ927⟩. Bromination of analogous substrates with NBS led to 2-bromo and 2,8-dibromothiazolo[3,2-*a*]benzimidazoles ⟨77LA106⟩.

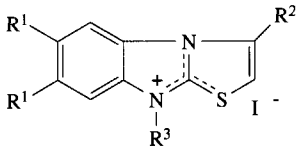


(294)

R^1= H, Br
R^2= H, Me
R^3= Me, Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4



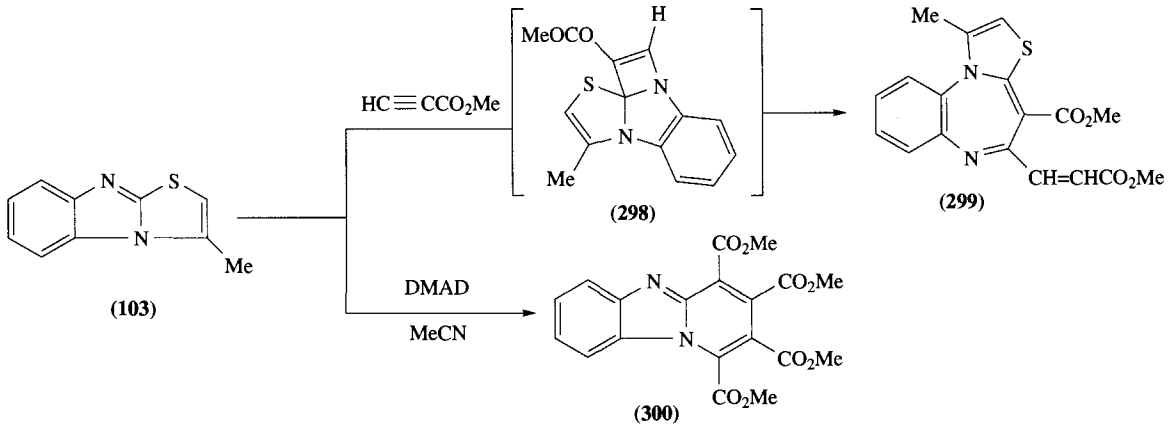
(104): R= H
(295): R= Me



(296): R^1= H; R^2= Ph; R^3= Me
(297): R^1=R^3= Me; R^2= Ph

(b) Electrophilic attack at nitrogen. When the thiazolobenzimidazoles (**104**) and (**295**) were allowed to react with methyl iodide they afforded the benziimidazolium iodides (**296**) and (**297**), respectively ⟨77LA106⟩. Analogous substrates by reaction with a cephem derivative provided the thiazolo[3,2-*a*]benzimidazolium 9-cephem-substituted ⟨87MIP8605184⟩.

(c) Reactions with cyclic transition states. The reaction of (**103**) with methyl propiolate proceeds via a dipolar cycloaddition to form the tetracyclic intermediate (**298**). Further reaction with methyl propiolate accompanied by a ring enlargement leads to the formation of the thiazolo[3,2-*a*][1,5]benzodiazepine (**299**) (Scheme 3). Cycloaddition of 3-methylthiazolo[3,2-*a*]benzimidazole (**103**) with DMAD in acetonitrile gave tetramethyl pyrido[1,2-*a*]benzimidazole-1,2,3,4-tetracarboxylate (**300**) ⟨80CL223, 80BCJ3308⟩.



Scheme 3

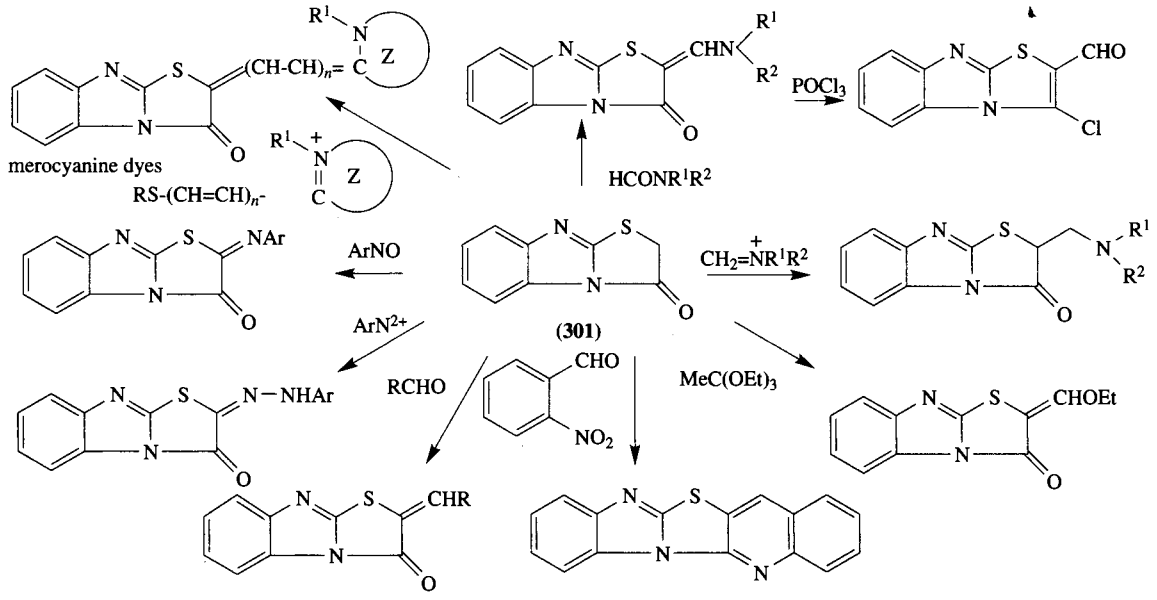
(ii) Reactivity of nonconjugated rings

(a) Electrophilic attack at carbon. The thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (**301**) undergoes nitrosation and diazo coupling reactions, condensation with aldehydes and ketones, iminium ions and related reactions leading to 2-imino-, 2-diazo-, 2-alkylidene-, and dialkylaminomethyl-substituted products ⟨88H(27)1975⟩ (Scheme 4).

(b) Electrophilic attack at sulfur. Oxidation of 2,3-dihydrothiazolo[3,2-*a*]benzimidazoles gave *S*-oxide derivatives ⟨84EUP129409⟩, whereas the oxidation of the analogous 3-hydroxy derivatives afforded thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones ⟨67CJC2903⟩.

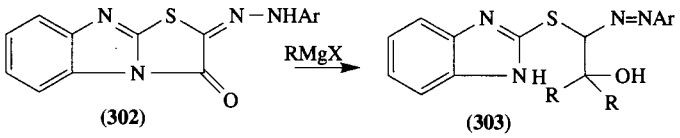
(c) Reactions with radicals and electron-deficient species—reductions and oxidations. The electrochemical reduction and oxidation of a series of 2-arylazothiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones was examined and the products were isolated and identified ⟨83JCS(P2)425, 84MI 836-01⟩. Polarographic reduction and anodic oxidation of some 2-arylidenethiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones were also investigated ⟨83MI 836-01⟩. On the other hand, desulfurization of thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (**99**) and (**100**) was successfully carried out with Raney nickel to give the corresponding acetylbenzimidazoles ⟨82CPB2714⟩.

(d) Nucleophilic attack at carbon. When treated with Grignard reagents, 2-arylazothiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (**302**) underwent opening of the thiazole ring to give 2-(1-arylazo-2,2-

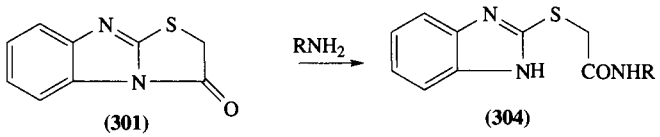


Scheme 4

diaryl-2-hydroxyethylmercapto)benzimidazoles (**303**) (Equation (3)). Additionally, by action of amines on thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (**301**), amides of (2-benzimidazolylthio)acetic acid (**304**) were obtained (Equation (4)) ⟨70LA(740)132⟩.

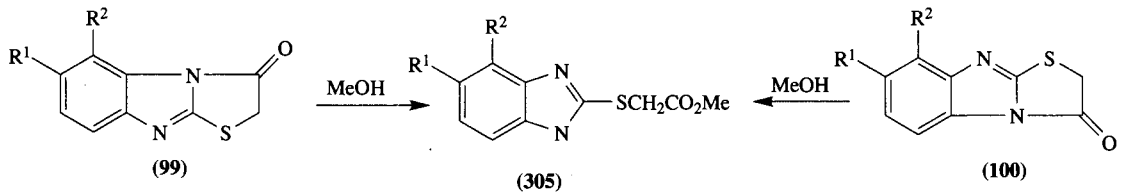


(3)



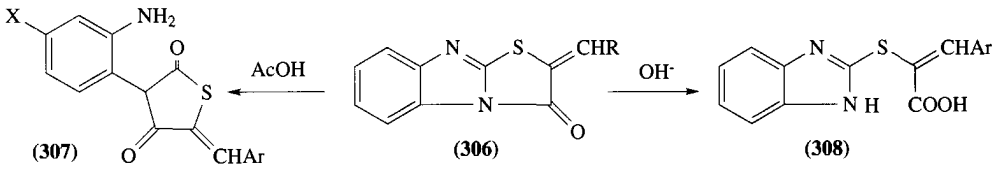
(4)

On treatment with methanol the thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (**99**) and (**100**) readily gave the same benzimidazole derivative (**305**) (Scheme 5) ⟨81CPB1876⟩.



Scheme 5

Degradation of the tricyclic system by hydrolysis of alkylidene derivatives (**306**) both in acetic acid and alkaline medium afforded 5-arylidene derivatives of 3-(*o*-aminophenyl)thiazolidine-2-4-dione (**307**) and α-(2-benzimidazolylthio)-β-arylacrylic acid (**308**), respectively (Scheme 6) ⟨61ZOB1635⟩.



Scheme 6

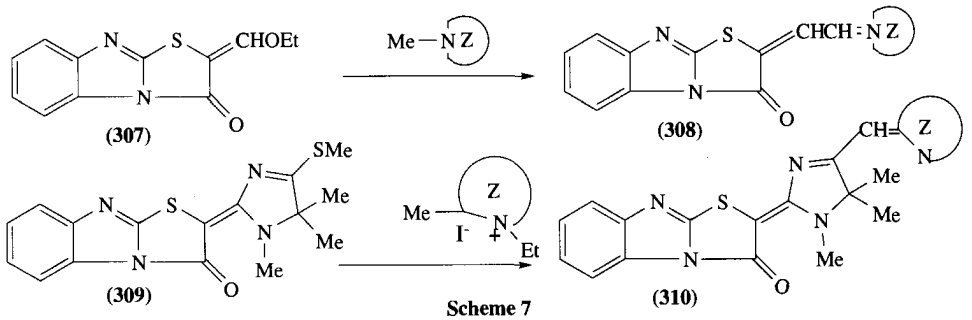
(iii) Reactivity of substituents attached to ring carbon atoms

(a) Reactions with cyclic transition states. Cyclocondensation of some 2-arylidenethiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (**306**, R = Ar) with malononitrile, ethyl cyanoacetate, and cyanoacetamide afforded pyrano and pyrido[2,3 : 4′,5′]thiazolo[3,2-*a*]benzimidazole derivatives ⟨84MI 836-02⟩. Furthermore, the same substrates underwent reaction with diazomethane to give the corresponding α-methyl derivatives ⟨70LA(740)132⟩.

(b) Nucleophilic attack at carbon—carbanions. Grignard reagents added to the exocyclic C=C bond in 2-arylidene derivatives (**306**, R = Ar) to give the corresponding 2-(α-alkyl)- and 2-(αaryl)-benzylthiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones ⟨70LA(740)132⟩.

Another route to merocyanine derivatives (**308**) proceeded via 2-ethoxymethylene-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (**307**) with 1-methyl substituted nitrogen heterocycles (Scheme 7) ⟨56JCS361, 55BRP730489, 56BRP743133, 56BRP749189, 57BRP785939⟩.

It has been reported that the condensation reaction between 2-[(1,5,5-trimethyl-4-methylthio)-3-imidazolyl-2-ylidene]thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (**309**) and the ethiodide of quinaldine or the ethiodide of 2-methylbenzothiazole gave the dye (**310**) ⟨55BRP743792⟩.



Scheme 7

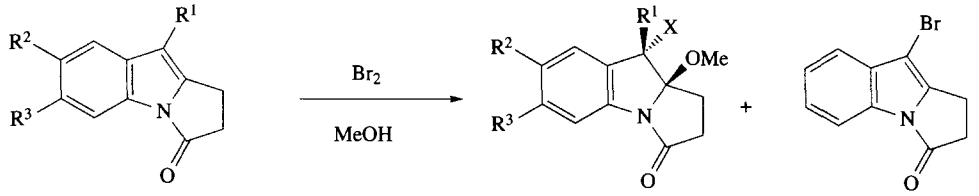
8.36.5.1.3 Annelated[a]indoles

Several aspects of the chemical behaviour of benzopyrroles which are related to the reactivity of annelated [*a*]indoles have been covered in CHEC-I ⟨84CHEC-I(4)223, 84CHEC-I(7)676⟩. A review has appeared on the synthesis of pyrrolo[1,2-*a*]indoles, of which the greater part is related to the synthesis and subsequent modifications of mitomycins and mitomycin analogues ⟨86RTC199⟩.

(i) Pyrrolo[1,2-a]indoles

(a) Electrophilic attack at carbon—halogens. The stereoselective functionalization of the 9a position of various mitosene derivatives has been described ⟨85LA1422⟩. Treatment of (**311**) with bromine in methanol led to racemic (**315**) (78% yield) together with variable amounts of bromopyrrolindole (**316**). Further treatment of (**315**) with tri-*n*-butyltin hydride in refluxing toluene led to

the tertiary methyl ether (**317**) (93% yield) and a small amount of the hydroxy methyl ether (**318**). Similar results were obtained with the acetate (**312**) and the amides (**313**) and (**314**) (Scheme 8).

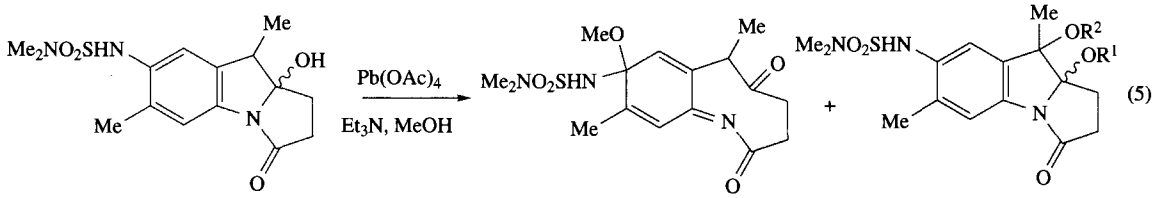


(**311**): R^1= R^2= R^3= H
(**312**): R^1= CH_2OCOMe; R^2= R^3= H
(**313**): R^1= CH_2OCONH_2; R^2= R^3= H
(**314**): R^1= CH_2OCONH_2; R^2= OMe; R^3= Me

(**315**): R^1= R^2= R^3= H; X= Br
(**316**)
(**317**): R^1= R^2= R^3= X= H
(**318**): R^1= R^2= R^3= H; X= OH

Scheme 8

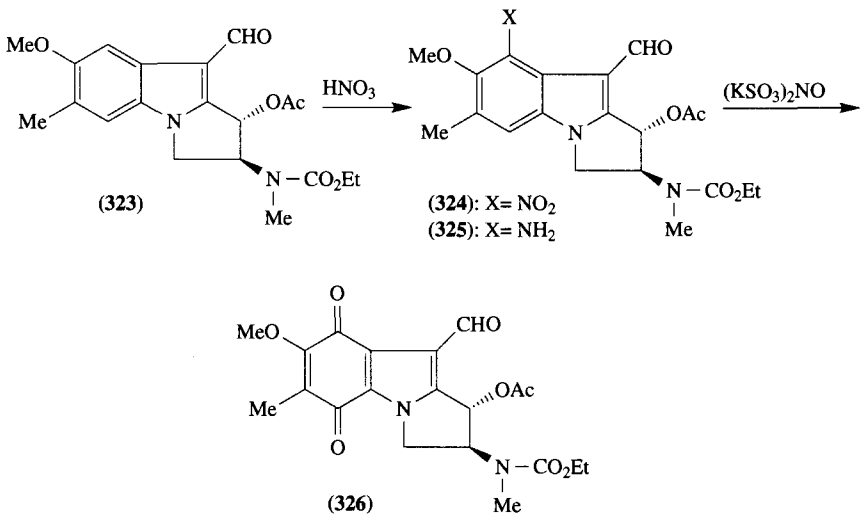
An interesting oxidative ring-opening reaction of mitosane (**319**) led to the eight-membered ring system (**320**). Treatment of the substrate (**319**) with lead tetraacetate in triethylamine/methanol and subsequent reaction with aqueous ethylene glycol afforded the unstable eight-membered compound (**320**) and the monomethoxymitosanes (**321**) and (**322**) (Equation (5)) ⟨79TL2537⟩.



(5)

(**319**)
(**320**)
(**321**): R^1= H; R^2= Me
(**322**): R^1= Me; R^2= H

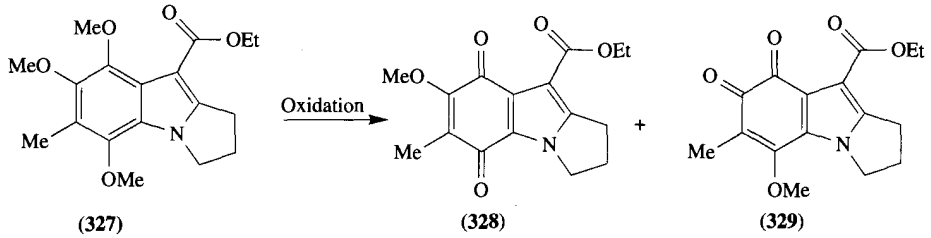
(b) Electrophilic attack at carbon—nitration. Carboxaldehyde (**323**) was converted into nitro compound (**324**) which, by reduction followed by oxidation of the resulting amino compound (**325**), furnished the 5,9-dioxo-pyrrolo[1,2-*a*]indole (**326**) (Scheme 9).



(**323**)
(**324**): X= NO_2
(**325**): X= NH_2
(**326**)

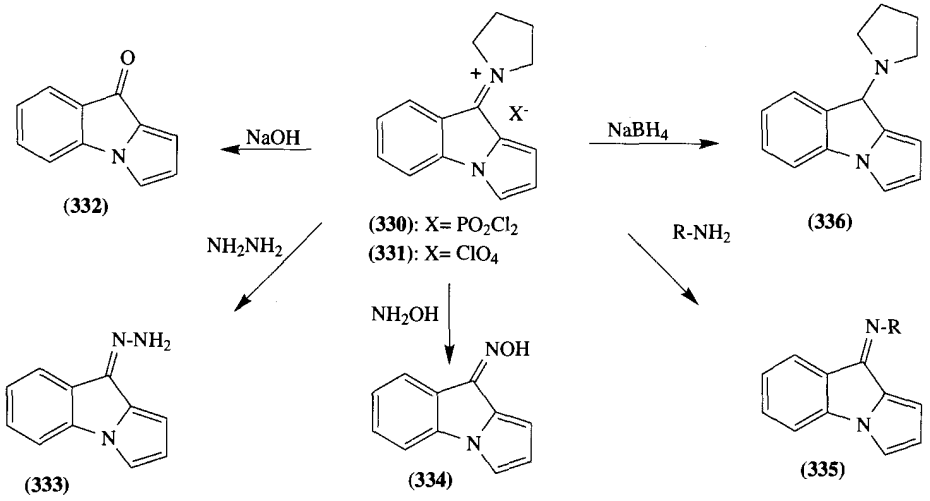
Scheme 9

(c) Electrophilic attack at carbon—oxidation. Oxidative demethylation of trimethoxyarene (**327**) led to isomeric *p*- and *o*-methoxyquinones (**328**) and (**329**). Either *para*quinone (**328**) or *ortho*quinone (**329**) can be obtained as the major isomer, dependent on the choice of oxidant (Equation (6)) ⟨83JA2859⟩.



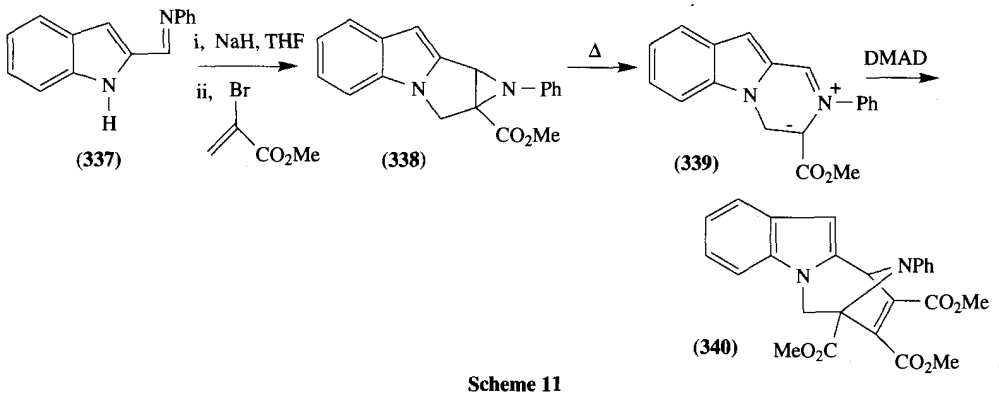
(327) (328) (329) (6)

(d) Nucleophilic attack at carbon. The stable salts (**330**) and (**331**) exhibited a high reactivity towards nucleophilic reagents and led to the indolone (**332**) by treatment with sodium hydroxide, to the hydrazone (**333**) by treatment with hydrazine hydrate and to the oxime (**334**) by reaction with hydroxylamine hydrochloride. Furthermore, the reaction of (**330**) and (**331**) in water with excess of primary aliphatic amines afforded in quantitative yields the *N*-alkyl 9*H*-pyrrolo[1,2-*a*]indole-9-imines (**335**). The reduction of the imminium salt (**330**) with a large excess of sodium borohydride gave the 9-pyrrolidino-9*H*-pyrroloindole (**336**) ⟨85TL2305⟩. All these reactions are shown in Scheme 10.



Scheme 10

(e) Reactions with cyclic transition states. The aziridine (**338**) has been formed in a single step from 2-(*N*-phenylformimidoyl)indole (**337**) by treatment of its sodium salt with methyl 2-bromopropenoate ⟨83CC1244⟩. When this aziridine was heated with DMAD at 110°C in diphenyl ether, it underwent smooth ring opening to the azomethine ylide (**339**) which was trapped by the ethyne to give quantitatively the 1,3-dipolar addition product (**340**) (Scheme 11).



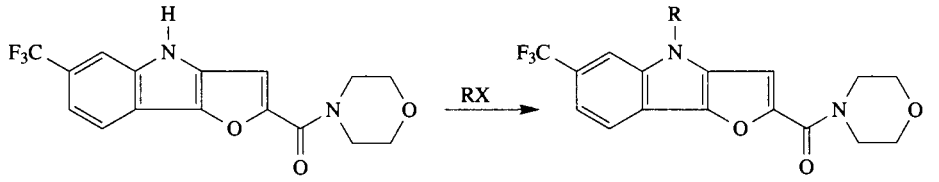
Scheme 11

8.36.5.1.4 Annelated [b]indoles

Several references to pyrrolo-, furo-, thieno-, and cyclopentano-annelated [*b*]indoles have already been made in CHEC-I ⟨84CHEC-I(4)39, 84CHEC-I(4)201, 84CHEC-I(4)599, 84CHEC-I(4)741⟩. Among the different aspects of the reactivity of these systems, the following have been reported.

(i) Electrophilic attack at nitrogen

4-Substituted 2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole derivatives (**341**) have been obtained by the reaction of (**340**) with acyl chlorides, alkyl halides and alkenyl halides under basic conditions (Equation (7)) ⟨86JMC2284⟩.



(340) (341) (7)

(ii) Electrophilic attack at carbon

4*H*- or 4-alkylfuro[3,2-*b*]indole-2-carboxaldehydes (**346–349**) have been obtained by Vilsmeier formylation of the corresponding furo[3,2-*b*]indoles (**342–345**) (Equation (8)) ⟨77JHC975⟩.



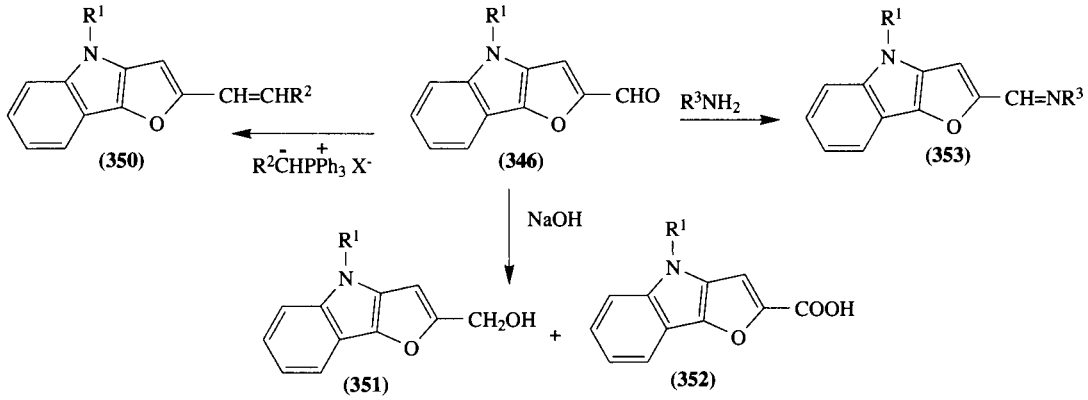
(8)

(**342**): R = H
(**343**): R = Me
(**344**): R = Et
(**345**): R = Pr^n

(**346**): R = H
(**347**): R = Me
(**348**): R = Et
(**349**): R = Pr^n

(iii) Reactivity of substituents attached to ring carbon atoms

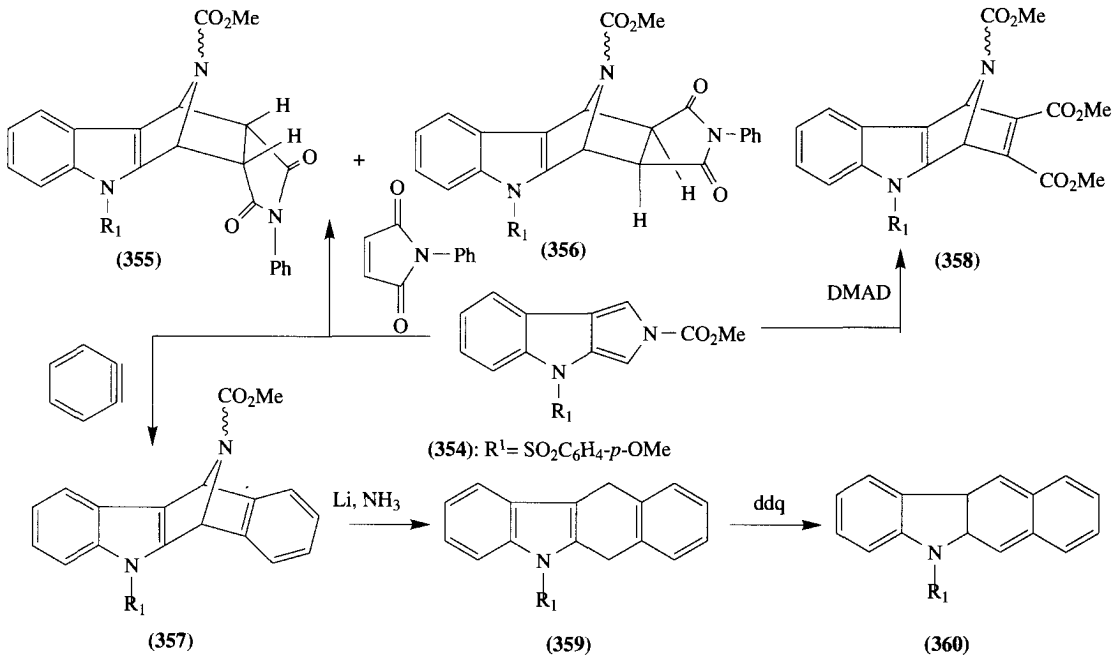
The 4*H*-furo[3,2-*b*]indole-2-carbaldehyde (**346**, R = H) has been submitted to the Cannizzaro, Wittig, and reduction reactions to yield the 2-substituted 4*H*-furo[3,2-*b*]indole derivatives (**350–352**). Schiff bases (**353**) have been obtained by the reaction of 4-ethylfuro[3,2-*b*]indole-2-carbaldehyde (**346**) with amines (Scheme 12) ⟨77JHC975⟩.



Scheme 12

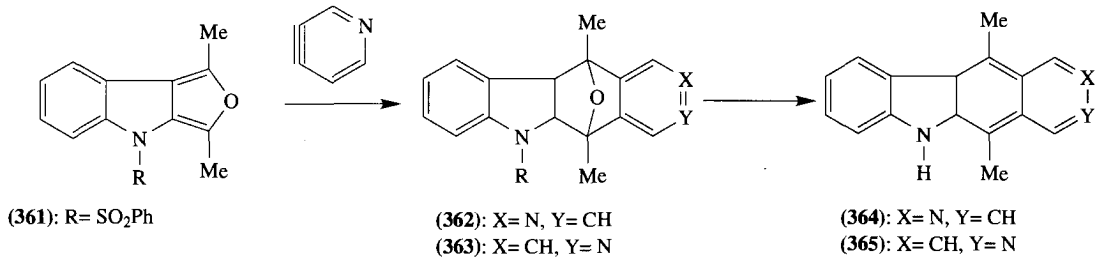
(iv) Reactions with cyclic transition states

The heterocyclic ring system 2,4-dihydropyrrolo[3,4-*b*]indole and the closely related systems such as 4*H*-furo[3,4-*b*]indole, 4*H*-thieno[3,4-*b*]indole and 4*H*-selenolo[3,4-*b*]indole have been of synthetic interest mainly because these systems are stable cyclic analogues of indole-2,3-quinodimethane. The Diels–Alder reaction of the 2,4-dihydropyrrolo[3,4-*b*]indole derivative (**354**) with reactive dienophiles, such as *N*-phenylmaleimide, benzyne, and DMAD, gave the corresponding cycloadducts (**355**), (**356**), (**357**), and (**358**), respectively. The arenimine (**357**) has been treated with lithium/ammonia to afford the dihydrobenzocarbazole (**359**), which has been dehydrogenated by DDQ to give the benzocarbazole (**360**) (Scheme 13) ⟨87JCS(P1)977⟩.



Scheme 13

It has been reported that the furoindole (**361**) underwent Diels–Alder reactions with DMAD, *N*-phenylmaleimide and benzyne to give the expected products ⟨84JOC4518⟩. Treatment of 3-chloro-4-iodo-pyridine with *t*-butyllithium followed by addition of (**361**) led to a mixture of the isomeric Diels–Alder adducts (**362**) and (**363**) in 15% yield. Deoxygenation and desulfonylation of (**362**) and (**363**), gave a readily separable mixture of the pyridocarbazole alkaloids ellipticine (**364**), and isoellipticine (**365**), respectively (Scheme 14) ⟨84JOC4518, 83TL5435⟩.



(**361**): R= SO_2Ph

(**362**): X= N, Y= CH
(**363**): X= CH, Y= N

(**364**): X= N, Y= CH
(**365**): X= CH, Y= N

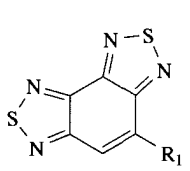
Scheme 14

8.36.5.1.5 Benzo[c]fused bisazoles

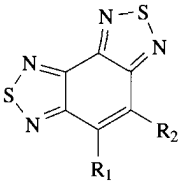
References to similar systems like [1,2,5]thiadiazolo[3,4-*e*]-2,1,3-benzoxadiazole, 6*H*-pyrazolo[4,3-*e*]-2,1,3-benzoxadiazole, benzo[1,2-*d*: 3,4-*d'*]diisoxazole, 6*H*-pyrazolo[3,4-*g*]-1,2-benzisoxazole, 1*H*-pyrazolo[3,4-*g*]-2,1-benzisoxazole have been made ⟨84CHEC-I(6)36, 84CHEC-I(6)115, 84CHEC-I(6)129, 84CHEC-I(6)397, 84CHEC-I(6)402, 84CHEC-I(6)515⟩.

(i) Benzo[1,2-c : 3,4-c']bisthiadiazoles and benzo[1,2-c : 3,4-c']bisselenadiazoles

(a) Electrophilic attack at carbon. Nitration of benzo[1,2-c : 3,4-*c'*]bis[1,2,5]thiadiazole (**200**) with sodium nitrate in sulfuric acid at 100 °C gave 4-nitro-benzo[1,2-*c* : 3,4-*c'*]bis[1,2,5]thiadiazole (**366**) in 90% yield. Nitro compound (**366**) has been readily reduced to 4-amino-benzo[1,2-*c* : 3,4-*c'*]bis[1,-2,5]thiadiazole (**367**) with sodium hydrosulfite in warm water.

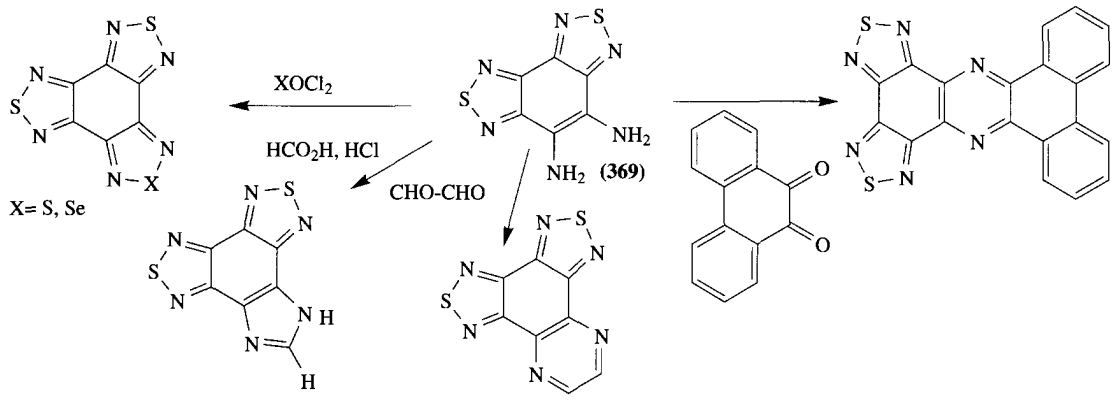


(**200**): R^1= H
(**366**): R^1= NO_2
(**367**): R^1= NH_2



(**368**): R^1= NH_2; R^2= NO_2
(**369**): R^1= NH_2; R^2= NH_2

(b) Nucleophilic attack at carbon. Direct amination of (**366**) with hydroxylamine in methanolic potassium hydroxide at −20 °C gave a nearly quantitative yield of 4-amino-5-nitro-benzo[1,2-*c* : 3,4-*c'*]bis[1,2,5]thiadiazole (**368**) which has been reduced with sodium hydrosulfite in water at 85 °C to give 4,5-diamino-benzo[1,2-*c* : 3,4-*c'*]bis[1,2,5]thiadiazole (**369**). Diamine (**369**) has been transformed into the polycyclic derivatives depicted in Scheme 15 ⟨75JHC829⟩.



Scheme 15

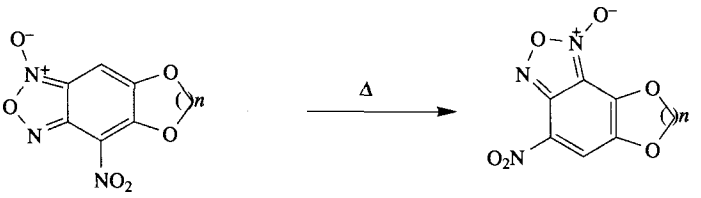
8.36.5.1.6 1,2-Methylenedioxy-nitrobenzofuroxans

The main modes of preparation of benzofuroxans have been previously reviewed ⟨84CHEC-I(6)424⟩. Important aspects such as thermal and photochemical isomerization, ring cleavage, reactions with

electrophiles and nucleophiles, oxidizing and reducing agents, and heterocyclic ring transformations have been discussed.

(i) Thermal rearrangements

Meanwhile, a systematic study aimed at determining the factors operating in the Boulton–Katrizky rearrangement has appeared in which the preparation of six homologous nitrobenzofuroxans has been achieved in order to ascertain the effect of the heterocyclic side ring during the thermal rearrangement. Heating of the furoxans (**370**)–(**372**) in toluene under reflux resulted in their complete and irreversible rearrangement to the isomeric derivatives (**373**)–(**375**) within 10 h, 1 h, and 2 h, respectively (Equation (9)). Surprisingly, attempts to convert (**201**) to (**202**) failed. The isomeric (**202**), however, rearranged smoothly to (**201**). Based on steric repulsions and resonance effects a rational explanation of the thermally promoted transformations has been given ⟨91T7157⟩



(9)

(**201**) $n=1$
(**370**) $n=2$
(**371**) $n=3$
(**372**) $n=5$

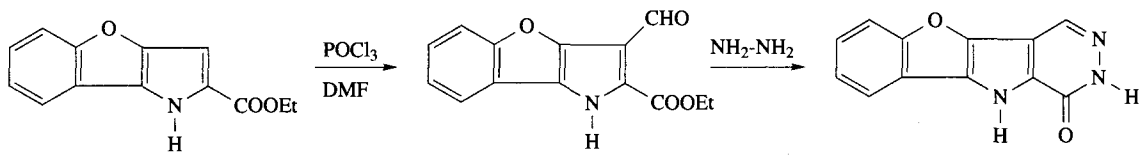
(**202**) $n=1$
(**373**) $n=2$
(**374**) $n=3$
(**375**) $n=5$

8.36.5.1.7 Benzofuran derivatives

Several aspects concerning structural features, the reactivity and applications of condensed benzofurans have been summarized in CHEC-I as part of the study of furans and their benzo derivatives ⟨84CHEC-I(1)294, 84CHEC-I(4)531, 84CHEC-I(4)599, 84CHEC-I(4)657, 84CHEC-I(5)870, 84CHEC-I(6)330⟩. A review has appeared in which the synthesis and reactions of condensed furan derivatives have been covered ⟨90CCC597⟩.

(i) Benzo[b]furo[3,2-b]pyrroles

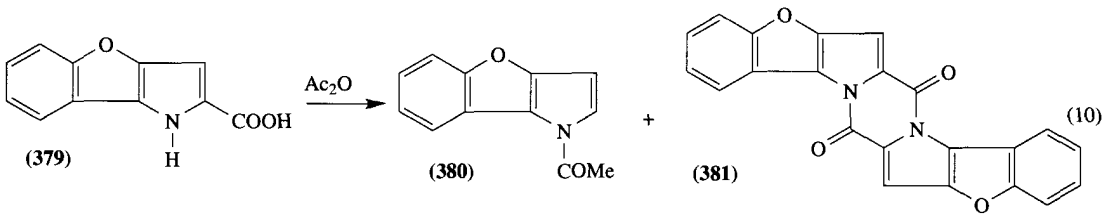
(a) Electrophilic substitution. Formylation of benzo[*b*]furo[3.2-*b*]pyrrole-2-carboxylic acid derivative (**376**) under conditions of the Vilsmeier reaction gave the 3-formylated product (**377**) which has been used as a starting material for the preparation of the new fused heterocycle (**378**) (Scheme 16).



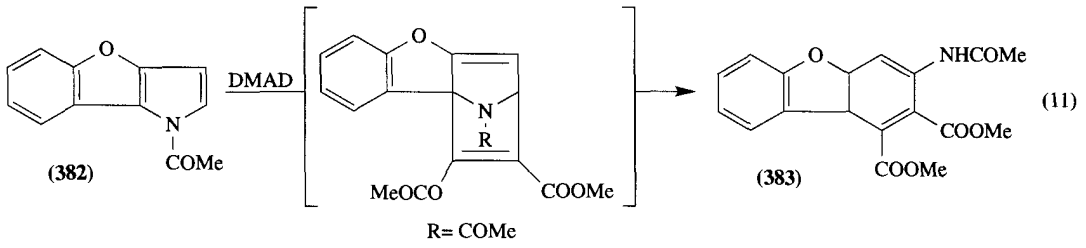
(**376**) (**377**) (**378**)

Scheme 16

(b) Decarboxylation. The acetylative decarboxylation of 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid (**379**) by heating in boiling acetic anhydride has been reported to give, besides 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole (**380**), also the product of the intermolecular dehydration, the pyrazinedione (**381**) (Equation (10)).

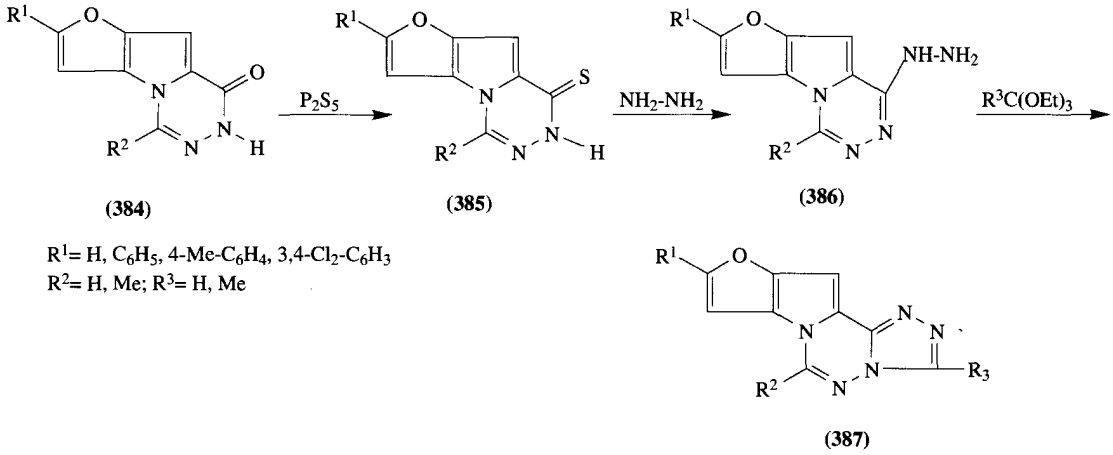


(c) Reactions with cyclic transition states. Concerning the reaction of 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole (**382**) with DMAD, it has been assumed that partial localization of the lone pair at the nitrogen atom due to the mesomeric conjugation of the acetyl group with the π-electron system of the skeleton leads to the enhancement of the diene character of its pyrrole part. This assumption has been confirmed by isolation of (**383**) as a product of the [4 + 2] cycloaddition reaction (Equation (11)).



(ii) Furo[2′,3′ : 4,5]pyrrolo[1,2-d]-1,2,4-triazines

7-R-Furo[2′,3′ : 4,5]pyrrolo[1,2-*d*]-1,2,4-triazine-1-ones (**384**) by reaction with phosphorus pentasulfide gave thiones (**385**) which, by treatment with hydrazine hydrate, yielded the triazines (**386**). Reaction of of the latter compounds with triethyl orthoformate or orthoacetate gave 9-R-furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazines (**387**) and 3- and 6-methyl as well as 3,6-dimethyl derivatives (Scheme 17).



Scheme 17

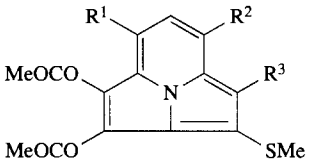
8.36.5.2 *Ortho*-and *Peri*-fused Systems

8.36.5.2.1 [2.2.3]Cyclazines and aza[2.2.3]cyclazines

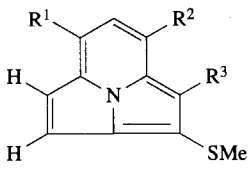
Theoretical methods, preparation, and different aspects of the reactivity of [2.2.3]cyclazines have been previously summarized ⟨84CHEC-I(4)479⟩. Meanwhile, a review has appeared in which, new developments of the synthesis of [2.2.3]cyclazines and aza[2.2.3]cyclazines have been reported ⟨88H(27)2251⟩.

(i) Reactivity of substituents attached at carbon atoms

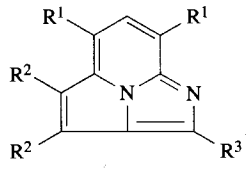
In terms of the chemical reactivity of the substituents attached to carbon atoms a decarboxylation process is mentioned in which the removal of the ester groups of (**388**)–(**391**) smoothly occurred in good yield. Hydrolysis of (**388**)–(**391**) using sodium hydroxide in methanol followed by acidification with 10% hydrogen chloride gave the corresponding diacids. Decarboxylation of the diacids with copper chromate has been conducted in boiling quinoline to afford the corresponding [2.2.3]cyclazines (**392**)–(**395**).



(**388**): R^1= H; R^2= H; R^3= H
(**389**): R^1= H; R^2= Me; R^3= H
(**390**): R^1= R^2= Me; R^3= H
(**391**): R^1= R^1= H; R^2= $CONH_2$



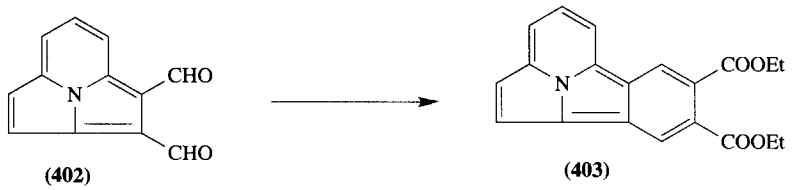
(**392**): R^1= H; R^2= H; R^3= H
(**393**): R^1= H; R^2= Me; R^3= H
(**394**): R^1= R^2= Me; R^3= H
(**395**): R^1= R^2= H; R^3= $CONH_2$



(**396**): R^1= H; R^2= COOMe; R^3= SMe
(**397**): R^1= Me; R^2= COOMe; R^3= SMe
(**398**): R^1= R^2= H; R^3= SMe
(**399**): R^1= Me; R^2= H; R^3= SMe
(**400**): R^1= R^2= R^3= H.
(**401**): R^1= Me; R^2= R^3= H

Analogously, removal of the ester group in aza[2.2.3]cyclazines (**396**)–(**397**) led to decarboxylated aza[2.2.3]cyclazines (**398**)–(**399**) in good yields. The desulfurization of (**398**)–(**399**) with Raney nickel in ethanol solution occurred smoothly to give the desired 1-aza[2.2.3]cyclazines (**400**) and (**401**) in 34% and 85% yields, respectively.

The Wittig reaction of (**402**) with diethyl (diethylphosphinyl) succinate gave diethyl benzo[*a*]-[2.2.3]cyclazine-7,8-dicarboxylate (**403**) in low yield (Equation (12)).



(**402**) (**403**) (12)

8.36.6 SYNTHESIS

A compendium of synthetic methods leading to fused heterocycles has appeared in which an updated knowledge of the synthesis of these systems, classified according to the interacting functional groups, has been reported ⟨87HC(47)1, 92HC(47)1⟩. The attention of this chapter, however, has been focused on the synthesis of particular tricyclic systems. A similar treatment has been followed to that used in CHEC-I, and wherever it has been possible, a critical comparison of the various routes available to particular classes of compounds has also been made.

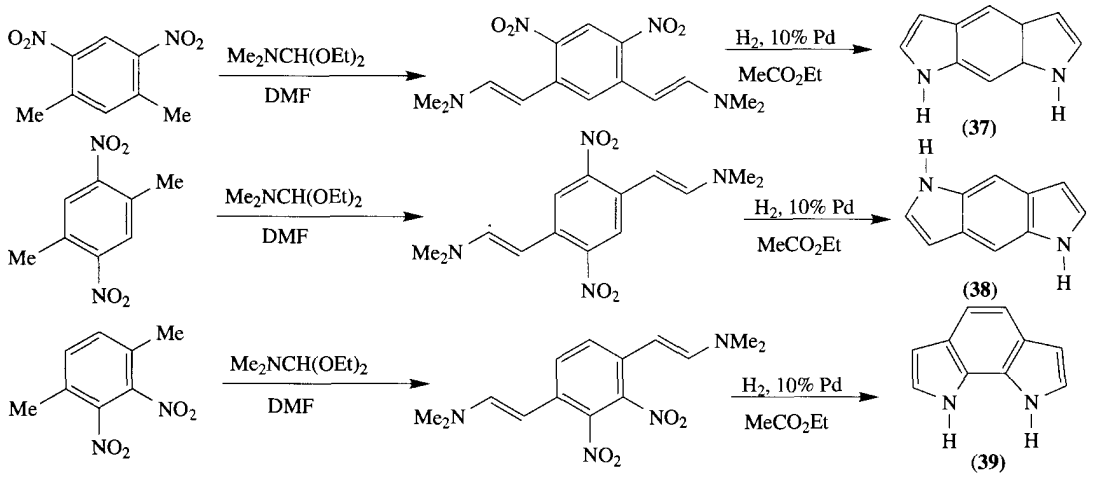
8.36.6.1 *Ortho*-fused Systems

8.36.6.1.1 Benzodipyrroles and benzodipyrazoles

(i) Construction of benzodipyrroles by processes involving the formation of the two pyrrole rings

Double condensation of dimethylformamide diethyl acetal (DMFDEA) with a suitable dinitroxylene, followed by catalytic reduction of the resulting bis-enamine, directly afforded the benzo-

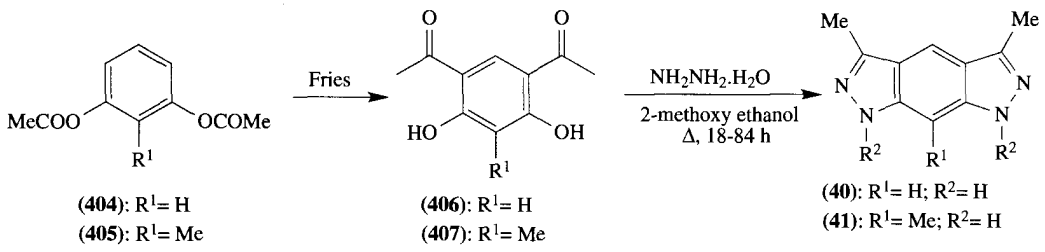
dipyrroles. According to the synthetic sequences depicted in Scheme 18 the dihydrobenzo[1,2-*b*: 5,4-*b'*]-, [1,2-*b*: 4,5-*b'*]-, and [2,1-*b*: 3,4-*b'*]dipyrroles (**37**), (**38**), and (**39**) have been obtained with 60%, 50%, and 70% yields, respectively ⟨87CC1176⟩.



Scheme 18

(ii) Preparation of benzodipyrazoles by simultaneous formation of the two pyrazole rings

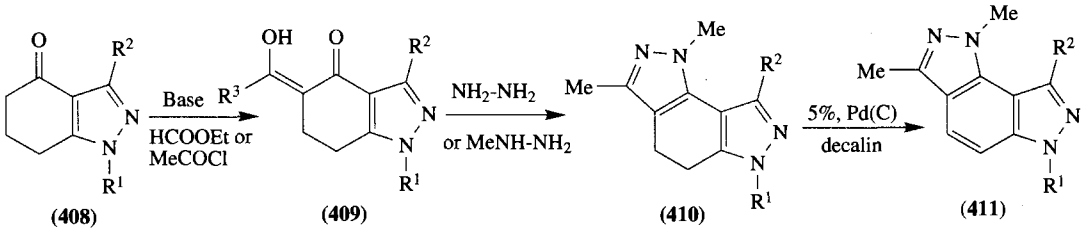
Fries rearrangement of resorcinol diacetate (**404**) with ferric chloride provided 4,6-diacetylresorcinol (**406**). The benzodipyrazole (**40**) has been best prepared from (**406**) by treatment with hydrazine hydrate in 2-methoxyethanol (Scheme 19). The 8-methyl homologue (**41**) of (**40**) has been prepared in similar fashion ⟨88JMC2034⟩.



Scheme 19

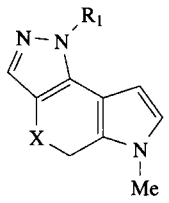
Tetrahydroindazolones (**408**) have been converted to the angular dihydrobenzo[1,2-*c*: 4,3-*c'*]dipyrazoles (**410**) and the corresponding fully unsaturated compounds (**411**) as shown in Scheme 20 ⟨91H(32)41⟩. Treatment of (**408**) with ethyl formate or acetyl chloride in the presence of base gave the β-dicarbonyl derivatives (**409**) which by further treatment with hydrazine or methylhydrazine led to dihydrobenzo[1,2-*c*: 3,4-*c'*]dipyrazoles, e.g., (**410**), and to dehydrobenzo[1,2-*c*: 4,3-*c'*]dipyrazoles, e.g., (**411**), by subsequent dehydrogenation.

Analogously, the preparation of the benzodipyrazoles (**75**)–(**77**) has been successfully achieved from the *gem*-dimethyl indazolone (**412**) and the transformation of the thiopyrano[3,4-*c'*]pyrazole (**413**) into the thiopyranodipyrazoles (**80**) and (**81**) has been possible by application of an analogous synthetic sequence. Furthermore, the oxidation of (**80**) and (**81**) led to the sulfoxides (**82**) and (**83**) and the sulfone (**84**) with acceptable yields (51–93%). The angular 5,6-dihydro-3-methylbenzo[1,2-*c*: 4,3-*c'*]dipyrazole (**78**) has been obtained from the 1,4-cyclohexadione monoethylene ketal by application of a five-step sequence with 20% overall yield. Dehydrogenation of (**78**) with 5% Pd(C) in decalin led to the fully unsaturated benzodipyrazole (**79**) (see Section 8.36.3.14).

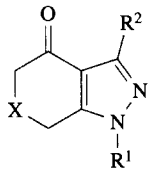


(408) (409) (410) (411)

Scheme 20



(75): X= $C(Me)_2$; R^1= H
(76): X= $C(Me)_2$; R^1=Me
(80): X= S; R^1= H
(81): X= S; R^1= Bn
(82): X= SO; R^1= H
(83): X= SO; R^1= Bn
(84): X= SO_2; R^1= H



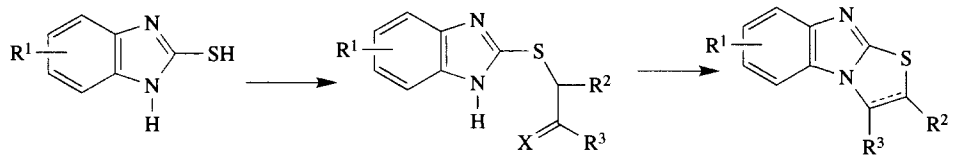
(412): X= $C(Me)_2$
(413): X= S

8.36.6.1.2 Thiazolobenzimidazoles

A review has appeared in which the synthetic approaches to thiazolo[3,2-*a*]benzimidazoles, thiazolo[3,4-*a*]benzimidazoles, and thiazolo[3,2-*c*]benzimidazoles have been summarized ⟨88H(27)1975⟩.

(i) Thiazolo[3,2-a]benzimidazoles

(a) Formation of the thiazole ring from 2-thiobenzimidazoles. The synthesis of thiazolo[3,2-*a*]-benzimidazoles (**416**) has received intensive study, and several approaches have been successful. Among them, those which make use of 2-thiobenzimidazoles as starting materials have been strongly emphasized: reaction of 2-thiobenzimidazoles (**414**) with α-halocarbonyl compounds, with α-haloacetals, with propargyl halides and with 1,2-dihaloethyl derivatives led to 2-thiobenzimidazole derivatives of the type (**415**) before the condensation to the thiazolo[3,2-*a*]benzimidazoles (**416**) occurred (Scheme 21) ⟨88H(27)1975⟩.



(414) (415) (416)

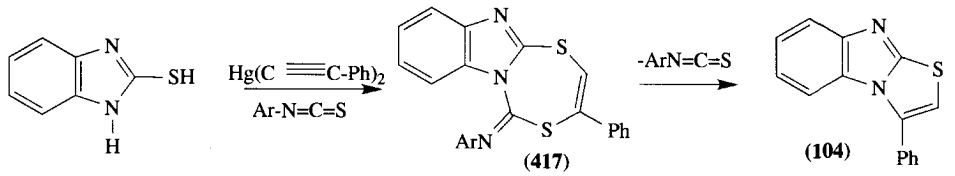
Scheme 21

2,3-Dihydrothiazolo[3,2-*a*]benzimidazoles have been also prepared by cyclization of 1-(β-hydroxyethyl)-2-thiobenzimidazoles with $SOCl_2$ or $POCl_3$ ⟨72KGS177, 72URP355174, 83KGS942⟩.

Reactions of 2-thiobenzimidazoles with $F_3CN{=}CF{-}CF{=}NCF_3$, with hexafluorobut-2-yne, with arylhydrazones derived from ethyl γ-bromo-α,β-dioxobutyrate and with 1-bromo-2,3-epoxy-3-methylbutane have been also discussed ⟨72GEP(O)2062348, 81JCR(S)126, 76UKZ1162⟩.

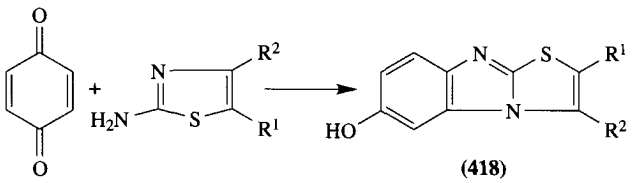
The mechanism of the reaction of 2-thiobenzimidazole with mercury bis(phenylacetylide) and aryl isocyanates has been postulated to involve the formation of the dithiazepine (**417**) and the

successive transformation into (**104**) by elimination of aryl isocyanates (Scheme 22) ⟨75LA79, 77LA106⟩.



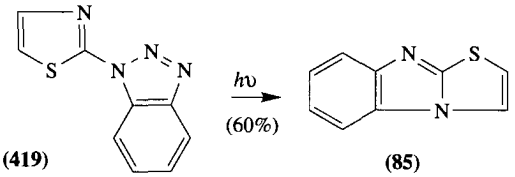
Scheme 22

(b) Formation of the imidazole ring by intramolecular condensation. The reaction of *p*-benzoquinone with 2-aminothiazoles in acetic acid led to 6-hydroxythiazolo[3,2-*a*]benzimidazoles (**418**) (Equation (13)) ⟨57USP2790172, 79BCJ3096, 86IJC(B)1266⟩.



(13)

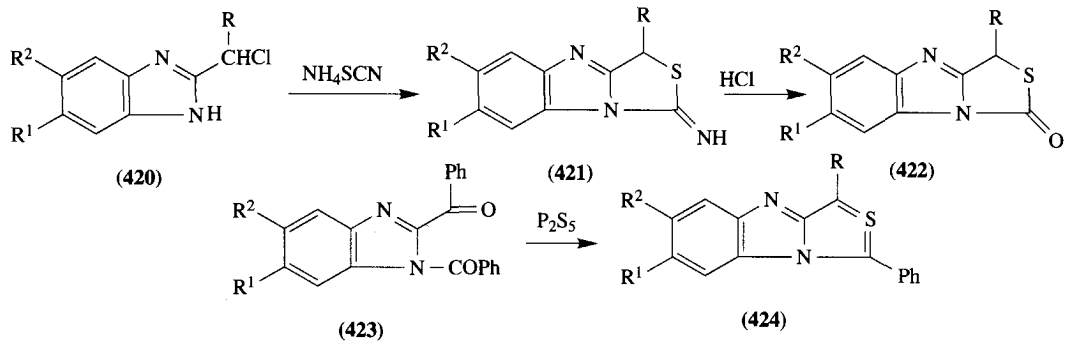
(c) Formation of the imidazole ring by photochemical and thermal ring closure processes. The photolysis and the acid-catalysed thermolysis of 1-(2-thiazolyl)benzotriazole (**419**) led to the thiazolo[3,2-*a*]benzimidazole (**85**) with 60% and 10% yields, respectively (Equation (14)) ⟨69JCS(D)328, 69JCS(C)1334⟩.



(14)

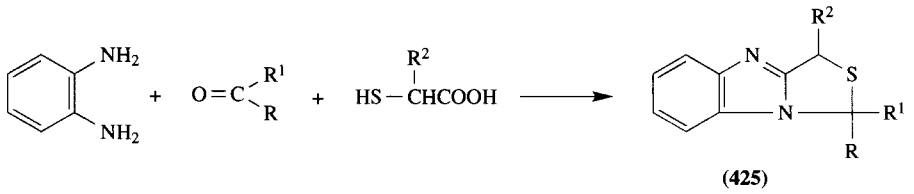
(ii) Thiazolo[3,4-a]benzimidazoles

(a) Formation of the thiazole ring from substituted benzimidazoles. The condensation of suitable substituted benzimidazoles with sulfur-containing compounds is the most general synthetic approach for the preparation of these fused systems, for example, the reaction of 2-(chloromethyl)benzimidazoles (**420**) with ammonium thiocyanate in methanol led to 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles (**421**) which, by treatment with concentrated HCl led to the thiazolo[3,4-*a*]benzimidazol-1-ones (**422**). On the other hand, cyclization of 1,2-dibenzoylbenzimidazole (**423**) with P_2S_5 led to (**424**), a new π-electron heterocycle containing tetravalent sulfur (Scheme 23) ⟨71GEP(O)2121395, 72GEP(O)2202704, 72USP3665007, 74USP3819618⟩.



Scheme 23

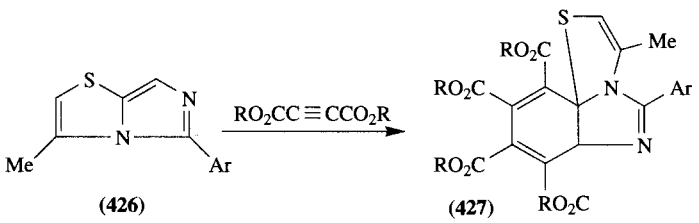
(b) Formation of the imidazole and thiazole rings by intermolecular condensations. A one-pot synthesis of 1*H*, 3*H*-thiazolo[3,4-*a*]benzimidazoles (**425**) has been developed by treatment of *o*-phenylenediamine with a variety of carbonyl compounds in an excess of 2-thiocarboxylic acids (Equation (15)) ⟨88S244⟩.



(425) (15)

(iii) Thiazolo[3,2-c]benzimidazoles

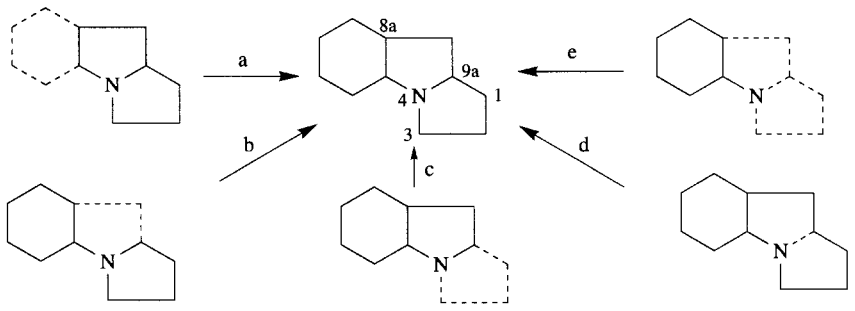
Ring formation via cycloaddition reactions has been illustrated by the [2 + 2 + 2] cycloaddition of 5-aryl-3-methylimidazo[5,1-*b*]thiazoles (**426**) with dialkyl ethynedicarboxylates. In an aprotic solvent, the reaction afforded several products, including the epimeric thiazolo[3,2-*c*]benzimidazoles (**427**) (Equation (16)) ⟨82BCJ2464⟩.



(426) (427) (16)

8.36.6.1.3 Annelated [a]indoles

The different approaches to the synthesis of the pyrrolo[1,2-*a*]indoles have been summarized in an excellent review, of which the greater part is dedicated to the preparation of 2,3,9,9a-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole, the "mitosane" basic skeleton of mitomycins. In 1993, an overview appeared on the total syntheses of mitomycins, in which the different approaches to the mitomycin ring system have been discussed ⟨93MI 836-01⟩. These approaches can be divided into five pathways as depicted in Scheme 24 ⟨86RTC199⟩.

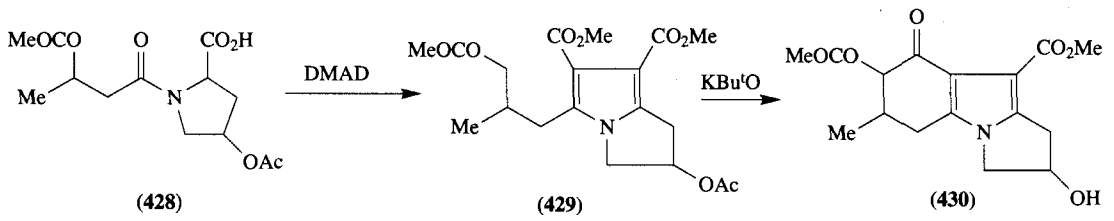


Scheme 24

(i) Formation of ring A (method a)

The strategy was based on a Huisgen pyrrole synthesis to build the B and C rings followed by a Dieckman cyclization to form ring A. The acetoxy acid (**428**) available in two steps from 4-hydroxy-

L-proline was coupled with DMAD to yield the bicyclic intermediate (**429**). The tricyclic compound (**430**) was obtained upon treatment with potassium *t*-butoxide with 35% yield (Scheme 25) ⟨81H(15)161, 81H(16)1173, 84JOC5164⟩.



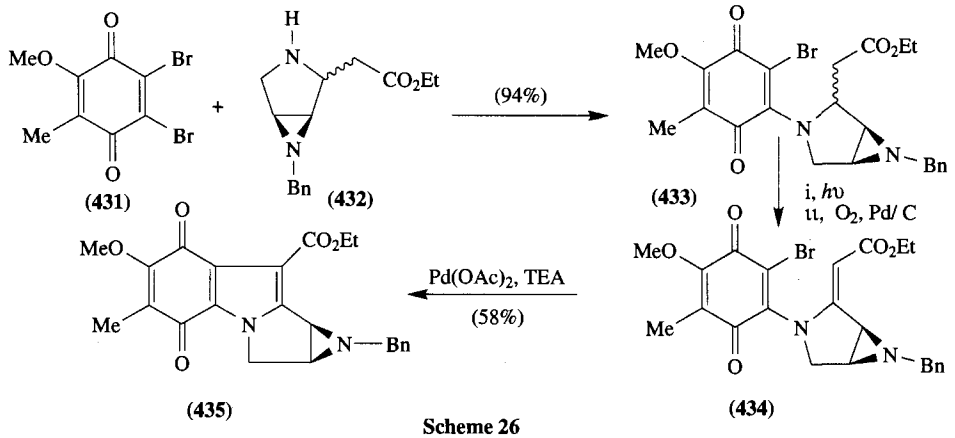
(428) (429) (430)

Scheme 25

(ii) Formation of ring B (method b)

The formation of ring B can be achieved by different approaches, as follows.

(a) Formation of the C(8a)—C(9) bond. The aziridinopyrrolidine (**432**) was prepared from *N*-carbobenzoxy-*D*-vinylglycine methyl ester. Regiospecific addition to the benzoquinone (**431**) gave the adduct (**433**) with 94% yield. Photochemical dismutation and palladium-catalysed oxidation yielded the alkene (**434**). Ring closure was effected by palladium diacetate to afford tetracyclic (**435**) with 58% yield (Scheme 26) ⟨85JOC4515⟩.



Scheme 26

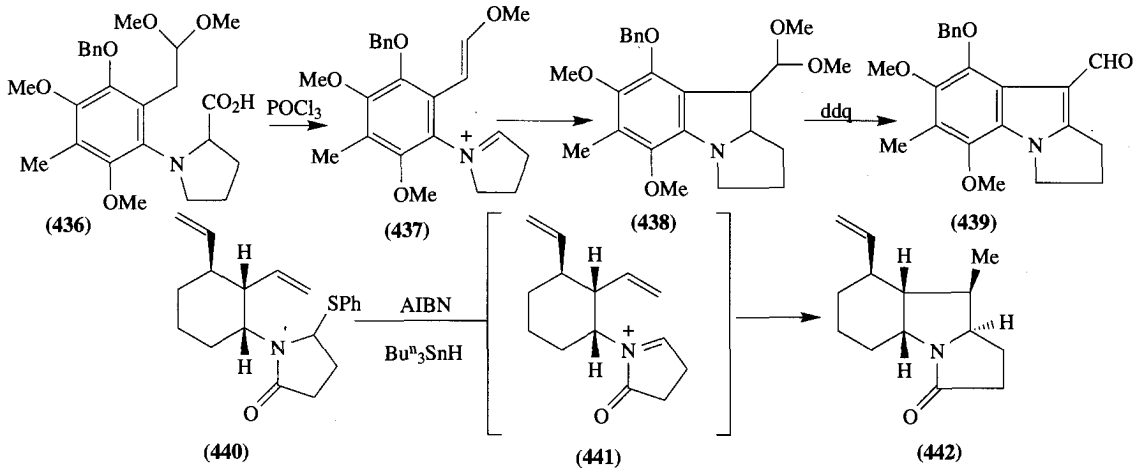
(b) Formation of the C(9)—C(9a) bond by iminium salt ring closure. Heating the aminoacid (**436**) with excess $POCl_3$, followed by cooling and quenching with methanol, gave a mixture of *cis*- and *trans*-(**438**) which was treated with DDQ to give (**439**) in 61% overall yield. The iminium intermediate (**437**) has been proposed as a precursor of (**438**) (Scheme 27) ⟨80JOC1260, 82JOC2404⟩.

(c) Formation of the C(9)—C(9a) bond by α-acylamino radical cyclization. Synthetic studies leading to *D,L*-gephyrotoxin revealed that the iminium salt (**441**) can be obtained upon treatment of sulfide (**440**) with tri-*n*-butyltin hydride and AIBN in a yield of 50% before leading to the pyrrolo[1,2-*a*]indole (**442**) (Scheme 27) ⟨83JA1255⟩.

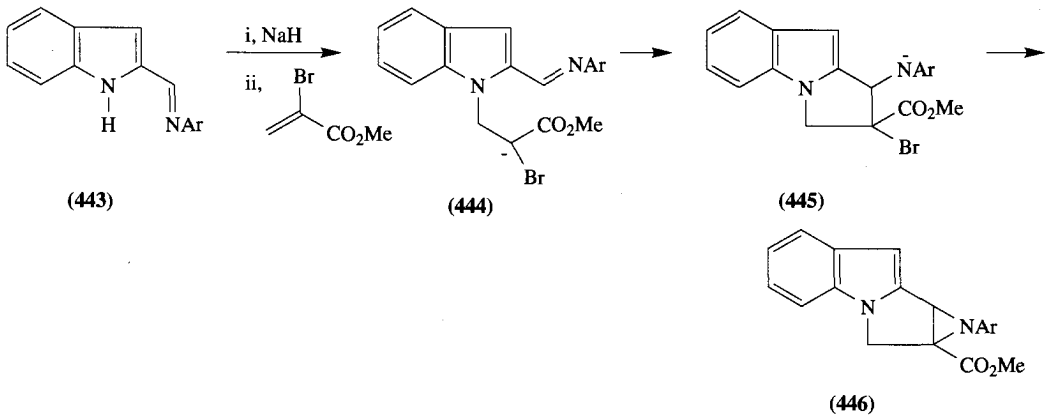
(iii) Formation of ring C (method c)

The third method involves the formation of ring carbon starting from indole or indoline derivatives.

(a) Formation of ring C by intramolecular Darzens reaction. Among the different approaches to the mitomycin ring system, a very effective route has been found which involves a one-step bicycloannulation. Treatment of 2-(*N*-phenylformimidoyl) indole (**443**) with sodium hydride followed by addition of methyl 2-bromopropenoate led to the azirino[2′,3′ : 3,4]pyrrolo[1,2-*a*] indole (**446**) through the anionic intermediates (**444**) and (**445**) (Scheme 28) ⟨83CC1244⟩.

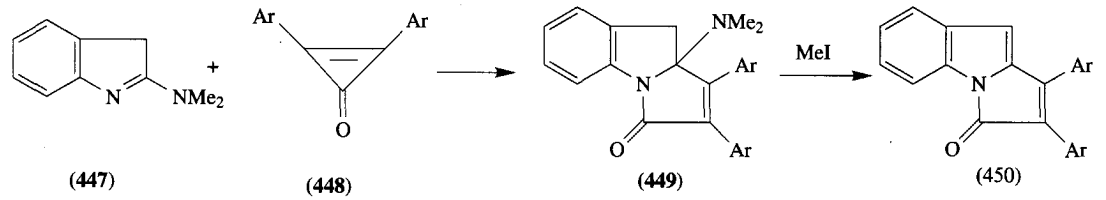


Scheme 27



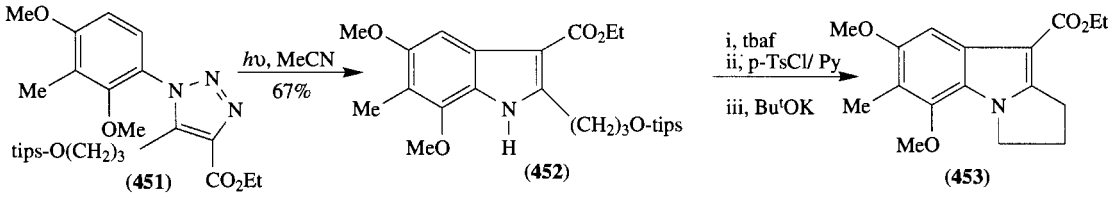
Scheme 28

(b) Formation of ring C by [3+2] cyclization. Reaction of amidine (**447**) with arylcyclopropenones (**448**) afforded the pyrrolo[1,2-*a*]indolone (**449**) in 59% yield. Further treatment with iodomethane led to the 3-oxo-3*H*-pyrrolo[1,2-*a*]indoles (**450**) in 69% yield (Scheme 29) ⟨85S619⟩.



Scheme 29

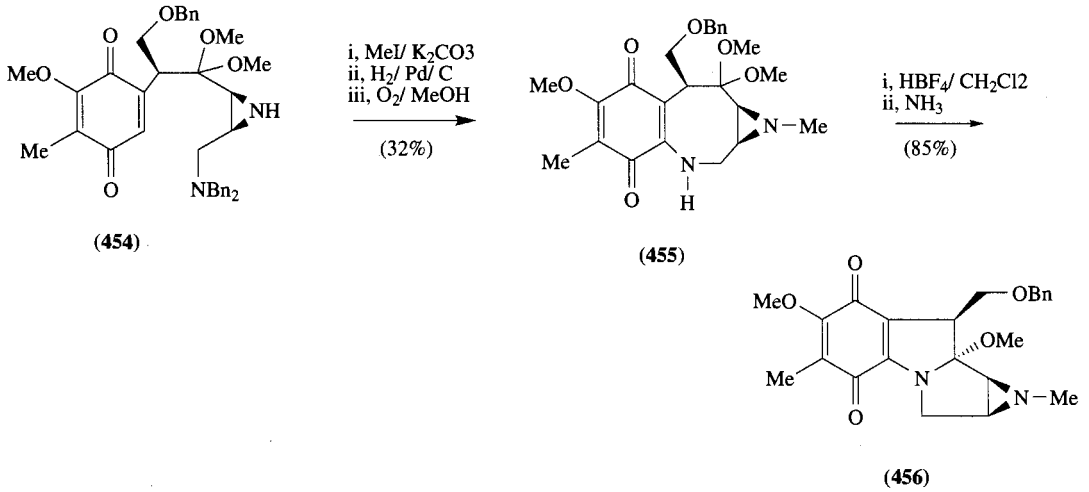
(c) Formation of ring C by intramolecular displacement. The 2,3-dihydropyrrolo[1,2-*a*]indole (**453**) has been assembled by taking advantage of a new method for indole formation by photolysis of *N*-alkenyl benzotriazole (**451**) which occurred in 67% yield. Intramolecular displacement was effected in three steps on the indole carboxylate (**452**) with 77% yield (Scheme 30) ⟨87TL6125⟩



Scheme 30

(iv) Formation of rings B and C by transannular cyclization (method d)

Several methods have been described for the formation of the N(4)—C(9a) bond; all of them involved a transannular cyclization of a benzazocine derivative. The first synthesis of porfiromycin was based on the transannular cyclization depicted on Scheme 31. Methylation of the aziridine and removal of benzyl protecting groups of (**454**) gave an amino hydroquinone, which in the presence of oxygen gave the eight-membered ring compound (**455**) via a quinone amine intermediate in 32% yield. The crucial transannular cyclization was achieved by treatment with fluoroboric acid to give the tetracyclic compound (**456**) ⟨77TL4295, 77JA8115, 79MI 836-01⟩.



Scheme 31

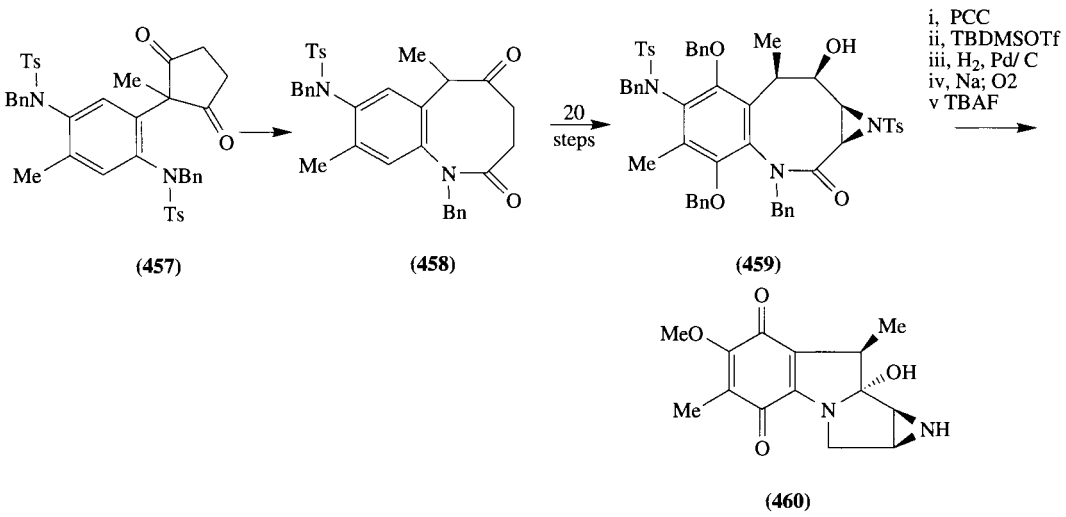
A "controlled crisscross annulation strategy" has been used to construct the eight-membered ring: compound (**457**) has been prepared in five steps. The key reaction was conducted under electrolytic reduction conditions to afford the benzazocine derivative (**458**), which was transformed to (**459**) in 20 steps. Oxidation of the alcohol and further treatment with *t*-butyldimethylsilyltriflate gave the tricyclic compound (**460**) (Scheme 32) ⟨88JOC5355⟩.

(v) Formation of rings B and C (method e)

This last method involves the formation of both rings B and C either in the same or in separate steps.

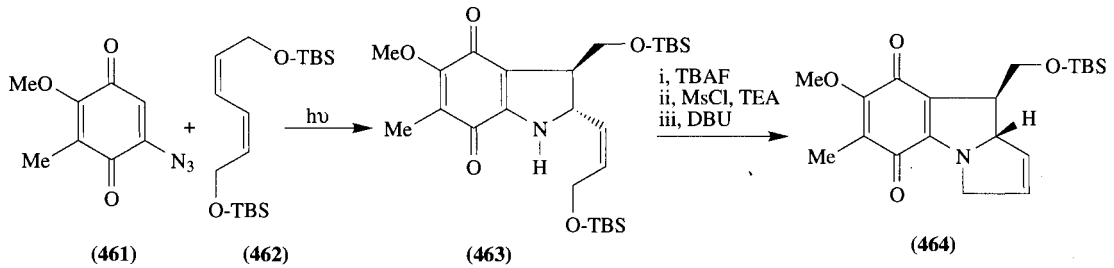
Intermolecular photocyclization of the azidoquinone (**461**) and the diene (**462**) afforded the corresponding 2,3-dihydroindolequinone (**463**) which was converted to (**464**) by making use of conventional chemistry. The overall yield of the process was 29% (Scheme 33) ⟨86CL1185⟩.

A stereospecific selenoamination–alkylation–oxidation sequence has been applied to the properly positioned hexenylaniline system (**465**) to yield, by reaction with *N*-phenylselenonaphthalimide (*N*-PSP) a diastereomeric mixture of selenides (**466**) which, upon oxidative deselenylation produced a 4 : 1 mixture of compounds (**467**) and (**468**) in 45% overall yield (Scheme 34) ⟨85JA3891⟩.



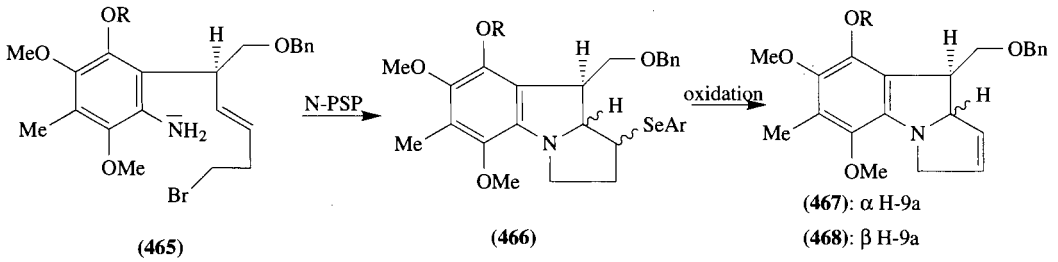
(457) (458) (459) (460)

Scheme 32



(461) (462) (463) (464)

Scheme 33

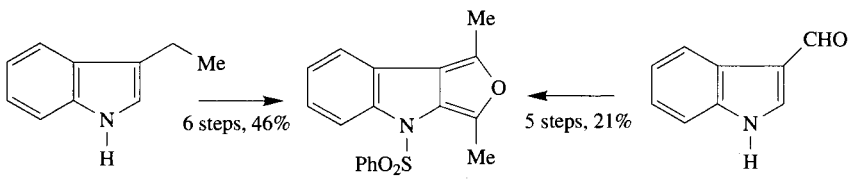


(465) (466) (467): α H-9a (468): β H-9a

Scheme 34

8.36.6.1.4 Annelated[b]indoles

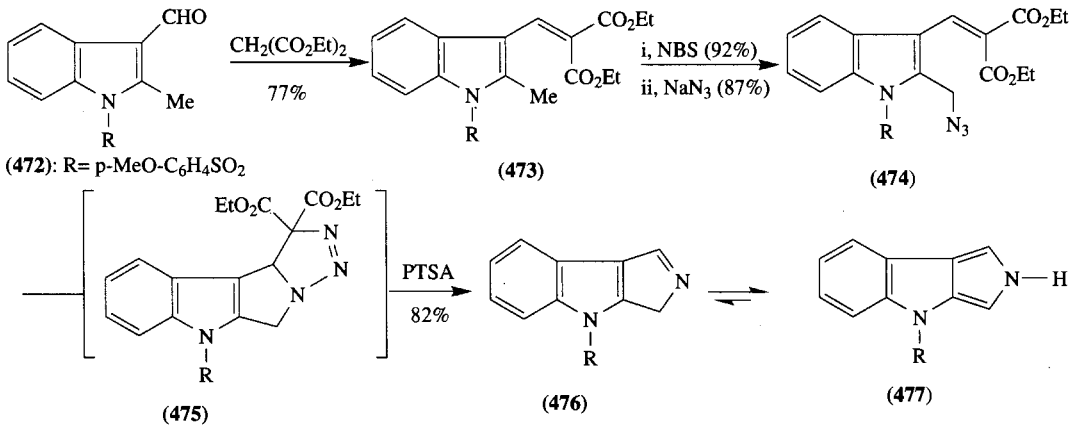
The synthesis of 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**471**) has been achieved either from 3-ethylindole (**469**) in six steps (46% yield) or from indole-3-carboxaldehyde (**470**) in five steps (21% yield) (Scheme 35) ⟨83TL5435, 84JOC4518⟩.



(469) (471) (470)

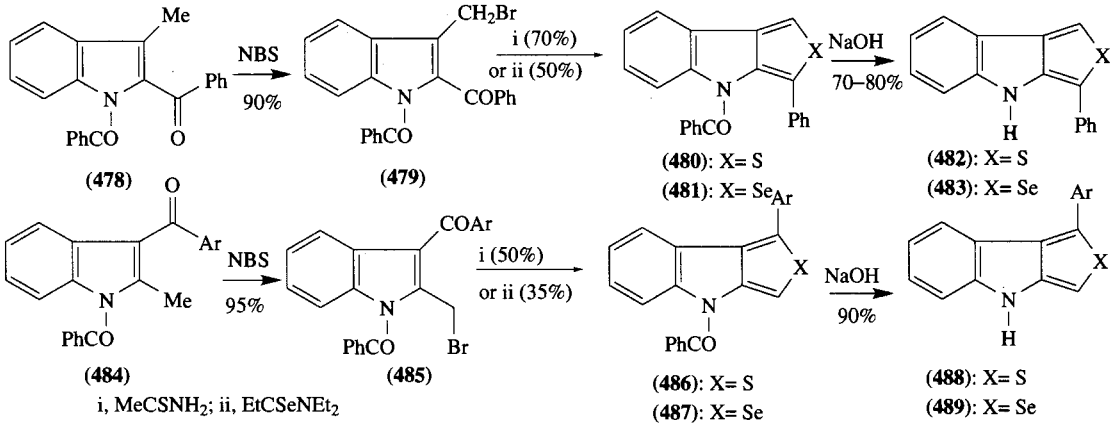
Scheme 3 5

The 2,4-dihydropyrrolo[3,4-*b*]indole (**477**) has been prepared as shown in Scheme 36 from the readily available formylindole (**472**) by the intramolecular 1,3-dipolar cycloaddition of the azidoalkylidenemalonate (**474**) followed by 1,3-dipolar cycloreversion of the triazoline intermediates (**475**) with 50% overall yield ⟨87JCS(P1)977⟩.



Scheme 36

The syntheses of thieno-, and selenolo[3,4-*b*]indoles (**482**), (**483**), (**488**), and (**489**), starting from phenyl 3-methylindol-2-yl ketone (**478**) and aryl 2-methyl-indole-3-yl ketones (**484**), have been also reported, as depicted in Scheme 37 ⟨76JOC2031, 82JHC227⟩.

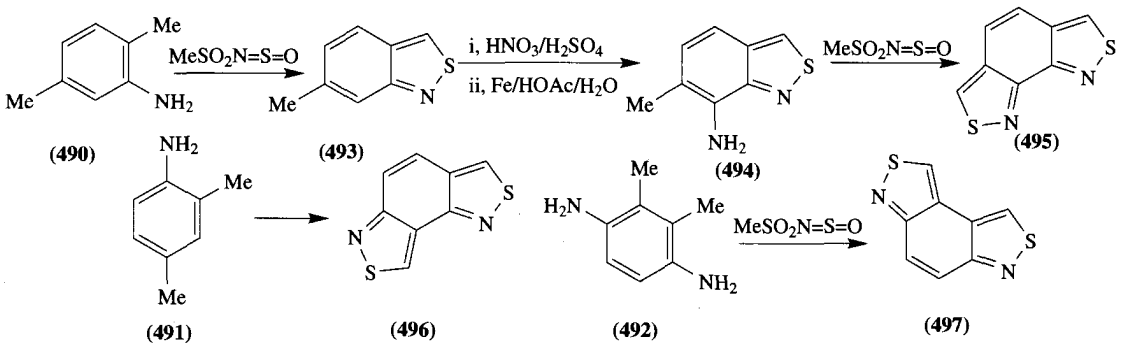


Scheme 37

8.36.6.1.5 Benzo[c]bisazoles

(i) Benzo[c]bisisothiazoles

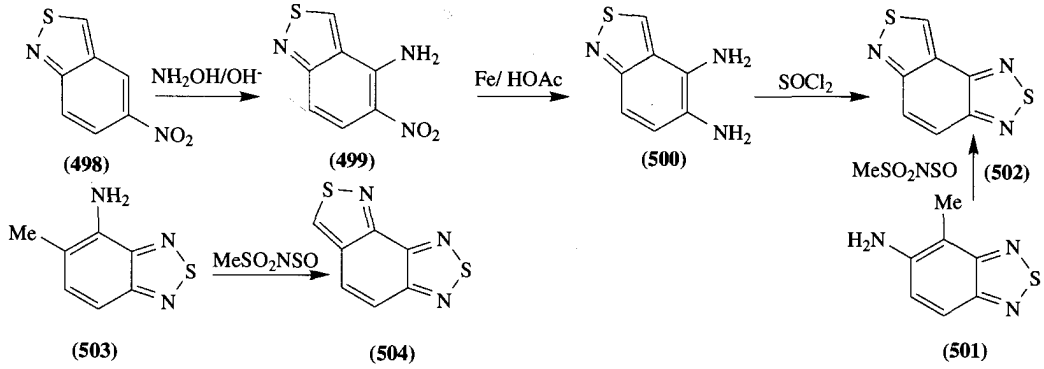
Benzo[2,1-*c*:3,4-*c*′]bisisothiazole (**495**), benzol[1,2-*c*:3,4-*c*′]bisisothiazole (**496**), and benzo[1,2-*c*:4,3-*c*′]bisisothiazole (**497**) have been prepared from easily available dimethylanilines as depicted in Scheme 38. The 2,5-dimethyl-aniline (**490**) was easily cyclized to the benzisothiazole (**493**) which upon nitration with a mixture of nitric and sulfuric acids and further reduction with iron and dilute acetic acid, yielded the aminobenzisothiazole (**494**). Treatment of (**494**) with *N*-sulfinylmethanesulfonamide afforded the benzo[2,1-*c*:3,4-*c*′]bisisothiazole (**495**). Analogously, (**496**) and (**497**) have been prepared from 2,4-dimethylaniline (**491**) and 1,4-diamino-2,3-dimethylbenzene (**492**), respectively ⟨80JHC533⟩.



Scheme 38

(ii) Isothiazolo[c]benzothiadiazoles

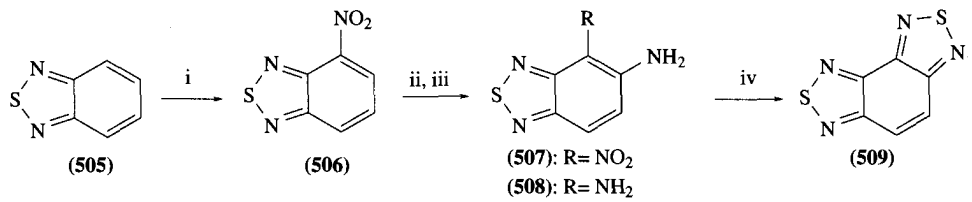
Isothiazolo[5,4-*c*]-2,1,3-benzothiadiazole (**502**) has been prepared by two methods. In the first, 5-nitro-2,1-benzoisothiazole (**498**) was converted to the nitroamine (**499**) by treatment with hydroxylamine in basic solution; this was reduced with iron and acetic acid, and the *o*-diamino product (**500**) cyclized to (**502**) with thionyl chloride. In a second approach, treatment of 5-amino-4-methyl-2,1,3-benzothiadiazole (**501**) with *N*-sulfinylmethanosulfonamide also led to (**502**). The isothiazolo[4,5-*c*]-2,1,3-benzothiadiazole (**504**) has been synthesized from 4-amino-5-methyl-2,1,3-benzothiadiazole (**503**) by an analogous procedure (Scheme 39) ⟨80JHC537⟩.



Scheme 39

(iii) Benzo[1,2-c:3,4-c′]bis[1,2,5]thiadiazole

Synthesis of the benzo[1,2-*c*:3,4-*c*′]bis[1,2,5]thiadiazole (**509**) required cyclization of diamine (**508**). Nitration of (**505**) led to 4-nitro-2,1,3-benzothiadiazole (**506**) in 95% yield. Amination of (**506**) with hydroxylamine in basic medium led to compound (**507**), immediately reduced to the diamino derivative (**508**). Ring closure of (**508**) with thionyl chloride and pyridine led to the benzo[1,2-*c*:3,4-*c*′]bis[1,2,5]thiadiazole (**509**) in 89% yield. Compound (**509**) has been successfully used in the synthesis of several fused tetracyclic compounds (Scheme 40) ⟨75JHC829⟩.

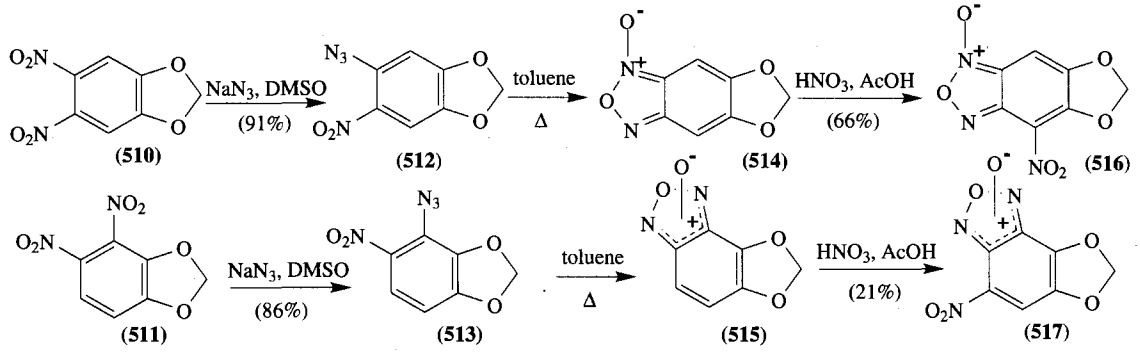


i, HNO_3/ H_2SO_4; ii, NH_2OH/ KOH; iii, $Na_2S_2O_4$; iv, $SOCl_2$, pyr

Scheme 40

8.36.6.1.6 1,2-Methylenedioxy-nitrobenzofuroxans

The main modes of preparation of benzofuroxans have been previously reviewed in Volume 6 of CHEC-I ⟨84CHEC-I(6)424⟩. The nitrobenzofuroxans (**516**) and (**517**) have been obtained via nucleophilic displacement of the dinitro derivatives (**510**) and (**511**) with azide ion followed by thermolysis in refluxing toluene and direct nitration of the unsubstituted furoxans (**514**) and (**515**) with 60% and 18% overall yields, respectively (Scheme 41) ⟨91T7157⟩.



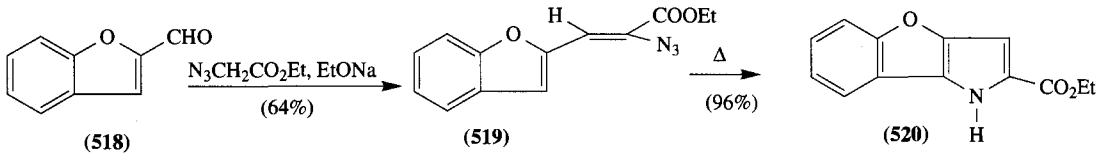
Scheme 41

8.36.6.1.7 Arylfurocondensed derivatives

The synthesis of condensed furan derivatives has been covered in CHEC-I as part of the study of furans and their benzo derivatives ⟨84CHEC-I(4)531, 84CHEC-I(4)657, 84CHEC-I(5)870, ⟨84CHEC-I(4)330⟩. More recently, in 1990, a review has appeared in which the synthesis of several condensed furan derivatives has been reported ⟨90CCC597⟩.

*(i) Benzo[*b*]furo[3,2-*b*]pyrroles*

Thermolysis of azidoacrylate (**519**) obtained by condensation of the appropriate benzo[*b*]furan-2-carbaldehyde (**518**) with ethyl azidoacetate afforded the corresponding alkyl benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylates (**520**) with 61% overall yield (Scheme 42) ⟨82CCC3288⟩.

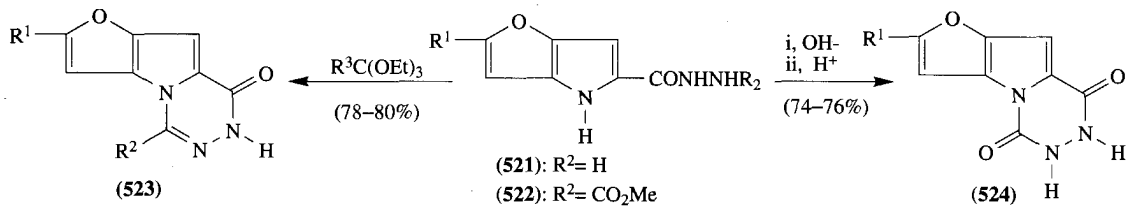


Scheme 42

*(ii) Furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazines*

Cyclization of furo[3,2-*b*]pyrrole-5-carboxyhydrazides (**521**) by treatment with triethyl orthoformate or orthoacetate led to furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazines (**523**) with good yields (78–80%). The *N*-methoxycarbonyl hydrazides (**522**) have been prepared by treatment of the

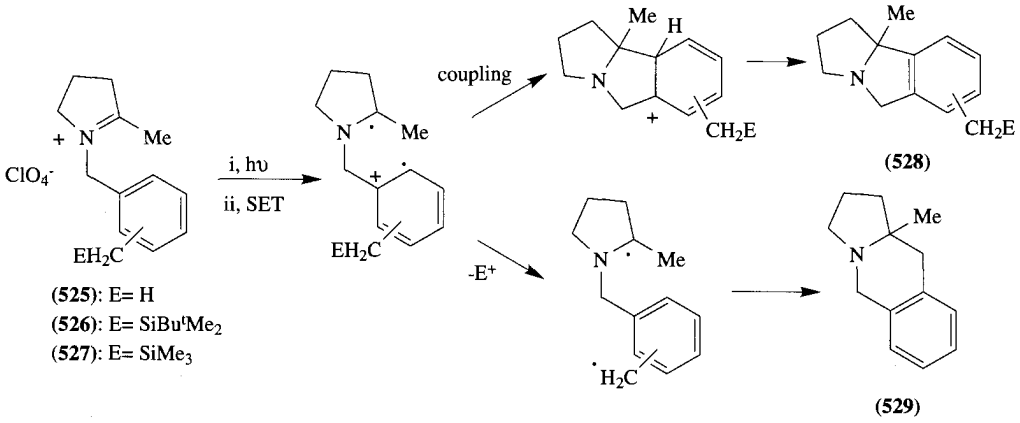
furo[3,2-*b*]pyrrole-5-carboxyhydrazides (**521**) with methyl chloroformate and led to furo-[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazines (**524**) by alkaline hydrolysis with high yields (74–76%). (Scheme 43) ⟨83CCC1878, 84CCC65, 84CCC1529⟩.



Scheme 43

8.36.6.1.8 Condensed pyrrolizidines

The electron-transfer-induced photocyclization reactions of a series of 1-benzyl-1-pyrrolinium salts have been investigated ⟨87JA2738, 88JOC1590, 90JA3594⟩. Studies with *ortho*-substituted *N*-benzyl-2-methylpyrrolinium perchlorates (**525**)–(**526**) show that diradical cation coupling is the predominant mechanistic pathway in either MeCN, MeOH or Me_2CO and led to the exclusive formation of benzopyrrolizidine products (**528**). On the other hand, the *ortho* CH_2SiMe_3 analogue (**527**) photocyclized in MeCN and led to a benzoindolizidine product (**529**) (Scheme 44).



Scheme 44

Photocyclizations of *meta*-(OH, OMe, $OSiBu^tMe_2$, CH_3, $CH_2SiBu^tMe_2$ and CH_2SiMe_3) substituted *N*-benzyl-2-methylpyrrolinium perchlorates proceed mainly or exclusively by cation.diradical coupling mechanisms and afford the corresponding benzopyrrolizidines in modest to excellent yields ⟨90JA3594⟩.

8.36.6.1.9 Condensed 1,2,4-triazolo[3,4-z]heterocycles

An overview has appeared in which the synthesis of 1,2,4-triazolo[3,4-*z*]heterocycles has been addressed ⟨90AHC(49)277⟩. Table 6 lists significant references leading to the tricyclic representatives.

8.36.6.2 Ortho- and Peri-fused Systems

8.36.6.2.1 [2.2.3]Cyclazines and aza[2.2.3]cyclazines

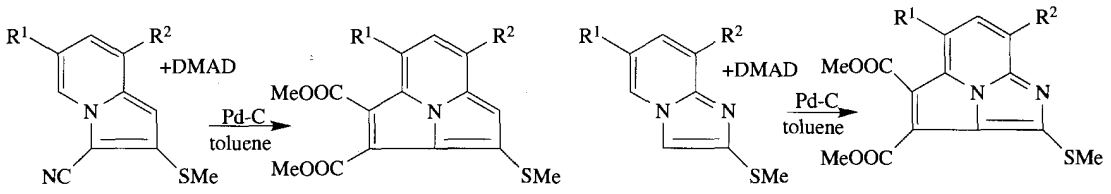
The preparation of [2.2.3]cyclazines has been summarized in CHEC-I ⟨84CHEC-I(4)479⟩. Developments in the synthesis of [2.2.3]cyclazines, 1-aza[2.2.3]cyclazines and 5-aza[2.2.3]cyclazines by the [8 + 2] cycloaddition of DMAD with various types of indolizidines have been presented

Table 6 Synthesis of tricyclic 1,2,4-triazolo[3,4-*z*]heterocycles.

Name	*References*
1,2,4-triazolo[4,3-*a*]indoles	75JHC717
1,2,4-triazolo[3,4-*a*]isoindoles	76UKZ1159
1,2,4-triazolo[4,3-*b*]indazoles	76H(4)1655
1,2,4-triazolo[4,3-*a*]benzimidazoles	82JCS(P1)2663, 59JOC1478, 84MI 836-03, 65ZOR136, 65ZOR139 84MI 836-04
1,2,4-triazolo[3,4*b*]1,3-benzoxazoles	58USP2861076, 59JOC1478, 62TL1193
1,2,4-triazolo[4,3-*b*]1,2-benzothiazoles	78USP4108860, 79USP4140693
1,2,4-triazolo[3,4,-*a*]1,3-benzothiazoles	74JOC3506, 75GEP(O)2509843, 79H(12)1171
1,2,4-triazolo[3,4-*b*]1,3-benzothiazoles	84KGS40, 57USP2786054, 73GEP(O)2250077, 57JCS727, 58USP2861076, 71JCS(C)2265, 79JIC742, 64E200, 70MI 836-01, 72JCS(P1)1519
1,2,4-triazolo[3,4-*b*]1,3-benzoselenazoles	59JOC1478
1,2,4-triazolo[4,3-*b*]cyclopent[1,2-*e*]pyridazines	71JPR780
Bis-1,2,4-triazolo[4,3-*b* : 4′,3′-*d*]1,2,4-triazines	69BSF3670, 67AC(R)366, 68CB3969
1,2,4-triazolo[3,4-*b*]pyrrolo[1,2-*d*]1,3,4-thiadiazines	82G345, 82JOC2757, 78GEP(O)2818395, 74IJC287, 78IJC(B)481, 80JIC(23)1112, 81IJC(B)369, 83JPS45, 86IJC(B)283, 86JCR(S)70, 86JHC1439, 78IJC(B)737, 81OPP123

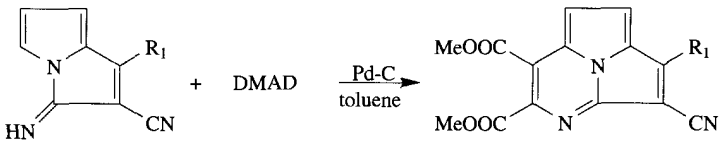
Source: ⟨90AHC(49)277⟩.

⟨88H(27)2251⟩. The cycloaddition of indolizines (**530**) and (**531**) with DMAD in boiling toluene in the presence of charcoal gave the expected [2.2.3]cyclazines (**532**) and (**533**) in 22% and 12% yields, respectively. Analogously, the imidazopyridines (**534**) and (**535**) gave the cyclized products dimethyl 2-methylthio-1-aza[2.2.3]cyclazine-3,4-dicarboxylates (**536**) and (**537**) in 36% and 40% yields, respectively (Scheme 45).



Scheme 45

The [8 + 2] cycloaddition of 3-imino-3*H*-pyrrolizine derivatives with DMAD has been also used to prepare 5-aza[2,2,3]cyclazines. Treatment of (**538**) with DMAD gave the dimethyl 4-cyano-3-methylthio-5-aza[2.2.3]cyclazine-6,7-dicarboxylate (**539**) in good yield. The 3-amino-5-aza-[2.2.3]cyclazine derivatives (**541**) have also been prepared from the corresponding 1-amino-3-imino-3*H*-pyrrolizine derivatives (**540**) (Equation (17)).



(17)

8.36.6.2.2 Orthoacetamides

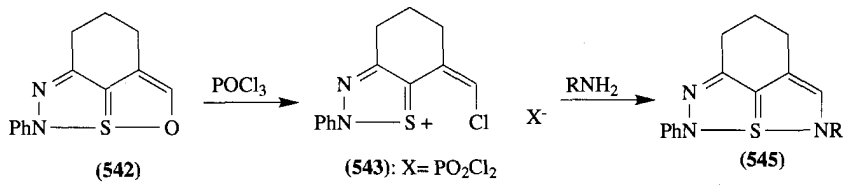
Tricyclic orthoacetamides and orthopropionamides have been obtained by condensation of macrocyclic triamines with *N*,*N*-dimethylacetamide dimethylacetal and *N*,*N*-dimethylpropionamide dimethylacetal, respectively ⟨81TL4365⟩.

8.36.6.2.3 Fused heteropentalenes

References to the methods of preparation of *ortho*- and *peri*-fused heteropentalenes have been made in Volume 6 of CHEC-I ⟨84CHEC-I(6)973, 84CHEC-I(6)1027, 84CHEC-I(6)1049⟩.

(i) 6a$^{\lambda4}$-thia-1,2,6-triazapentalenes and 6a$^{\lambda4}$-thia-6-selena-1,2-diazapentalenes

A versatile synthesis of 6a$^{\lambda4}$-thia-1,2,6-triazapentalenes and 6a$^{\lambda4}$-thia-6-selena-1,2-diazapentalenes has been reported from oxathiadiazapentalene (**542**) ⟨83JCS(P1)777⟩. Treatment of (**542**) with phosphoryl chloride in 1,2-dichloroethane gave the 5-(2-chlorovinyl)-2-phenyl-1,2,3-thiadiazolium phosphorodichloridate (**543**) which, when treated with perchloric acid in acetic acid, afforded the stable crystalline perchlorate (**544**) in nearly quantitative yield. The phosphorodichloridate (**543**) reacted with aliphatic and aryl amines to give the thiatriazapentalenes (**545**) in acceptable yields (44–97%) (Scheme 46).



(**542**)

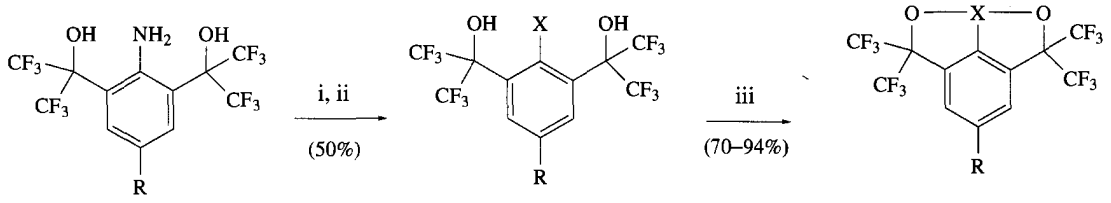
(**543**): X= PO_2Cl_2
(**544**): X= ClO_4

(**545**)

Scheme 46

(ii) Aryldialkoxybrominanes and aryldialkoxyiodinanes

Iodinanes (**549**) and brominanes (**550**) have been synthesized as shown in Scheme 47. Transformation of the amino diol (**546**) into either the iodobenzene (**547**) or the bromo benzene (**548**) involved diazotation and further treatment with potassium iodide or hydrobromic acid, respectively. Treatment of iododiols (**547**) with BrF_3 gave the iodinanes (**549**) with 70% yield. The oxidation of bromodiols (**548**) with *t*-butyl hypochlorite led to the stable brominanes (**550**) with high yields (70–94%) ⟨82JOC1024, 86JA3803⟩.



(**546**): R= Me, Bu^t

(**547**): X= I; R= Me, Bu^t
(**548**): X= Br; R= Me, Bu^t

(**549**): X= I; R= Me, Bu^t
(**550**): X= Br; R= Me, Bu^t

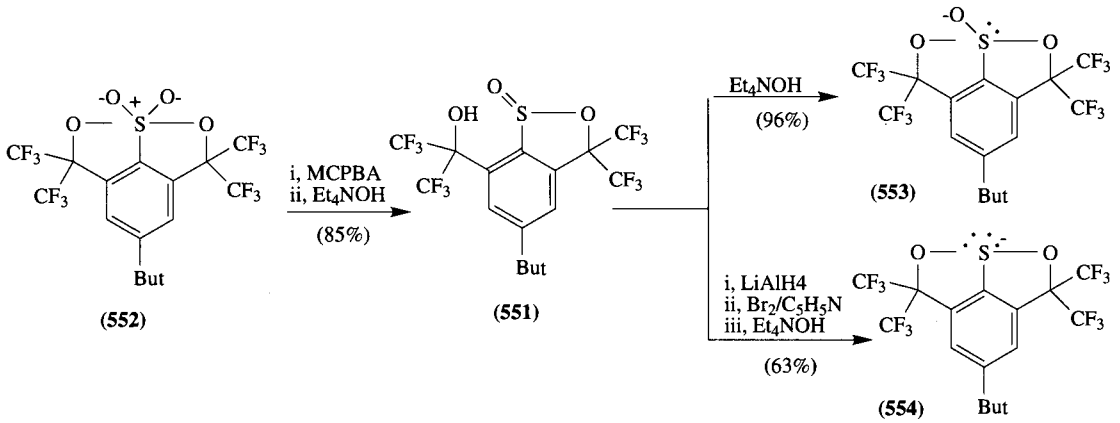
i, Diazotation; ii, KI, Cu or HBr, Cu; iii, BrF_3 or $(Me)_3COCl$

Scheme 47

(iii) Sulfuranide salts

The preparation and properties of anionic 10-*S*-5, 10-*S*-4 and 10-*S*-3 species (**552**)–(**554**) have been described ⟨83JA1377, 85JA3209⟩.

The conversion of (**551**) to compounds (**552**)–(**554**) was accomplished in the straightforward manner shown in Scheme 48. The preparation of T-shaped 9-*S*-3 π-sulfuranyl radicals permitted Electron Spin Resonance and Electron Spin Echo studies ⟨86JA3206, 86JA3211⟩.



Scheme 48

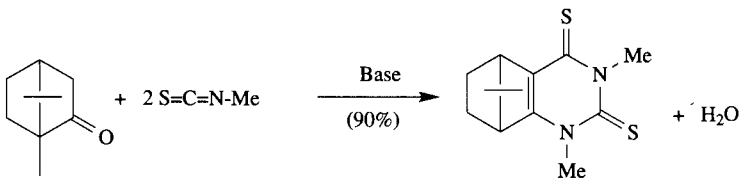
8.36.6.3 Bridged Systems

8.36.6.3.1 1,4-Epoxynaphthalenes

Isobenzofurans have long been recognized as outstanding dienes for the Diels–Alder and other cycloaddition reactions leading to oxabicyclo products. A 1988 review appeared in which the progress in the chemistry of isobenzofurans and the chemical transformations of oxabicyclo adducts has been intensively discussed ⟨88T2093⟩.

8.36.6.3.2 5,8-Methanoquinolines and 5,8-methanoquinazolines

The synthesis of octahydroquinazoline-dithiones (**556**) has been effected by reaction, in basic media, of alkyl or aryl isothiocyanates on ketones possessing at least one hydrogen atom in an α-position (**555**). It has been possible to reach the corresponding diones (**557**) by desulfurization of the dithiones (Equation (18)). A large number of similar transformations have been described ⟨81T2451⟩.



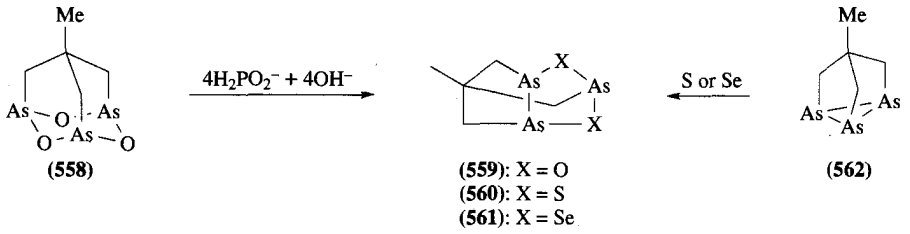
(18)

A simple method has been devised for the synthesis of 5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline starting from cyclohexanone ⟨79S221⟩.

8.36.6.3.3 5,8-Methanodiarsolodioxatriarsoles

The synthesis of heteronoradamantane systems such as 2,6-methano-5*H*-[1,2]diarsolo[1,2-*d*]-[1,2,3,4,5]dioxatriarsole (**559**) has been achieved by reduction of the heteroadamantane (**558**) with

alkaline hypophosphite solution. The homologous noradamantanes $CH_3C(CH_2As)_3X_2$ (X = S, Se) (**560**) and (**561**) resulted from the melting of (**562**) with elemental sulfur or selenium in the molar ratio of 1 : 2 with acceptable yields (Scheme 49) ⟨84CB2675⟩.



(**558**)

(**559**): X = O
(**560**): X = S
(**561**): X = Se

(**562**)

Scheme 49

8.36.7 IMPORTANT COMPOUNDS AND APPLICATIONS

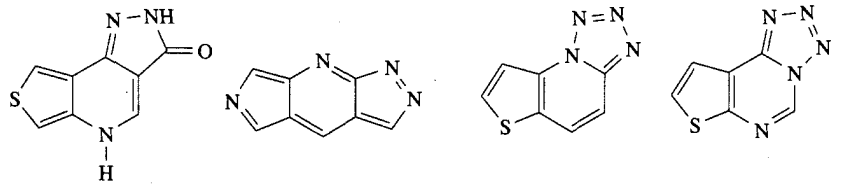
Although many of the applications found for compounds with three fused heterocyclic rings have been addressed in Volume 1 of CHEC-I, much of the information relating to the practical use of these derivatives has been spread throughout the seven volumes of CHEC-I (see Table 1). Here is summarized the most significant applications found in the literature for the derivatives already discussed in the preceding sections.

8.36.7.1 *Ortho*-fused Systems

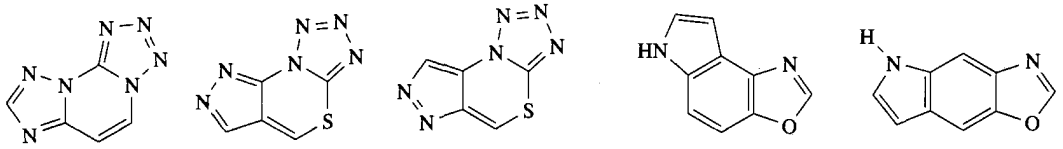
8.36.7.1.1 Condensed pyridines, pyrimidines, and thiazines

Derivatives of the 2,5-dihydro-3*H*-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridin-3-one (**563**) and the pyrazolo[3,4-*b*]pyrrolo[3,4-*e*]pyridine (**564**) have been claimed to have pharmacological application as anticonvulsants and tranquilizers ⟨84EUP115469⟩, anxyolytic ⟨83EUP94175, 84EUP126970, 86EUP178759, 86USP4563525⟩, antagonist of benzodiazepine receptors ⟨84EUP126970, 86EUP168350⟩ and depressants of the central nervous system ⟨86USP4563525⟩. Furthermore, some tetrazolyl derivatives of the tetrazolo[1,5-*a*]thieno[2,3-*e*]pyridine (**565**) have antiallergic activity ⟨86USP4581455⟩, and derivatives of the tetrazolopyrimidines (**566**) and (**567**) have been claimed to develop analgesic, anti-inflammatory, antihypertensive, diuretic, and vasodilatory activity ⟨82IJC(B)666, 85EUP152841⟩.

Several derivatives of the pyrazolothiazines (**568**) and (**569**) have found application as photographic couplers ⟨85JAP(K)60233649, 85JAP(K)60237447⟩.



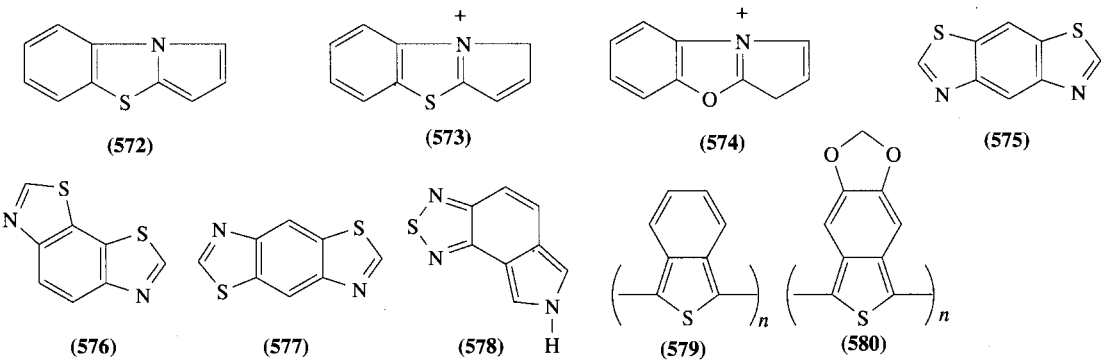
(**563**) (**564**) (**565**) (**566**)



(**567**) (**568**) (**569**) (**570**) (**571**)

8.36.7.1.2 Benzodiazoles

3,5-Dimethylbenzol[1,2-*c*: 5,4-*c'*]dipyrazoles (**40**), (**41**) and (**48**) display affinity for adenosine A_1 (rat brain) and A_2 (human platetlet) receptors ⟨88JMC2034⟩. Derivatives of the pyrrolobenzoxazole (**570**) and (**571**) have bactericidal and antiinflammatory activity ⟨86EUP173520, 83IJC(B)437⟩; the properties found for several derivatives of pyrrolo[2,1-*b*]benzothiazole (**572**) have found application for photoelectric solar cells and some pyrrolo[2,1-*b*]benzothiazolium and pyrrolo[2,1-*b*]benzoxazolium derivatives (**573**)–(**574**) are used as spectral photographic sensitizers for silver halide photographic emulsions ⟨85USP4524128, 84JAP(K)5977435⟩.



Polymers derived from benzo[1,2-*d*: 5,4-*d'*], [1,2-*d*: 4,3-*d'*], [1,2-*d*: 5,4-*d'*], and [1,2-*d*: 4,5-*d'*]bisthiazole (**575**)–(**577**) have been used to develop heat-resistant polymers ⟨86JAP(K)6128530⟩, electrophotographic toners ⟨84JAP(K)5915256, 83JAP(K)58176644⟩ and liquid crystals for fibres and films ⟨84MI P8401160⟩.

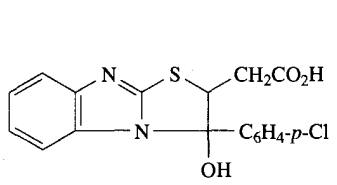
Pyrroles annulated with various kinds of polycyclic aromatic compounds such as the pyrrolo benzothiadiazole (**578**) have been claimed to be good precursors for polypyrroles. The polymers derived from (**578**) have a lowered band gap and interesting properties such as the high stability of the cation radicals formed by electrochemical oxidation. They also show ESR signals which are not affected after storage at room temperature for long periods of time in a laboratory atmosphere ⟨94CC1019⟩.

Polyisothianaphthene (PITN), whose monomer consists of a thiophene unit with a benzene ring fused onto the two carbon-atom units, (**579**), has the smallest energy gap (1.0 eV) for any known conjugated organic polymer. However, one of the disadvantages of PITN is that it undergoes atmospheric oxidation at high dopant levels with a concomitant dedoping process. A derivative of PITN, namely poly(5,6-dioxymethyleneisothianaphthene (PDOMITN), retains the advantages of PITN, but is resistant to atmospheric attack at high doping levels. Its monomer consists of an isothianaphthene ring with a dioxymethylene group at the 5- and 6-positions (**580**). PDOMITN is one of the smallest energy gap conducting polymers, with an E_{gap} comparable to that of PITN ⟨92MI 836-01⟩.

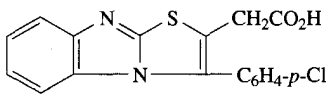
8.36.7.1.3 Thiazolo-, pyrrolo-, and pyrazolobenzimidazoles

Interesting aspects such as the pharmaceutical, agrochemical, and the biological applications of thiazolobenzimidazoles have been intensively reported ⟨88H(27)1975⟩. Numerous studies on the biological activity of 2,3-dihydro-3-hydroxy-3-(*p*-chlorophenyl)-thiazolo[3,2-*a*]benzimidazol-2-acetic acid (**581**) have been reported. In addition to the immunomodulating effects, this compound shows antitumor and antimetastatic activities ⟨76MI 836-01, 77MI 836-01⟩. Its dehydration product, the 3-(*p*-chlorophenyl)thiazolo[3,2-*a*]benzimidazol-2-acetic acid (**582**) shows antineoplastic ⟨80USP4214089, 84MI 836-05⟩, antimetastatic ⟨80MI 836-01, 81MI 836-01⟩, immunomodulatory ⟨83MI 836-02, 85MI 836-01⟩, and antiinflammatory ⟨85MI 836-02, 86MI 836-01⟩ activity. With regard to [3,4-*a*]benzimidazoles, 1*H*,3*H*-1-oxo and 1-imino derivatives (**583**) showed anthelmintic ⟨74USP3819618⟩, rodenticide ⟨71GEP(O)2121395⟩, parasiticide, and antiinflammatory properties ⟨71GEP(O)2121395, 72GEP(O)2202704, 72USP3665007⟩.

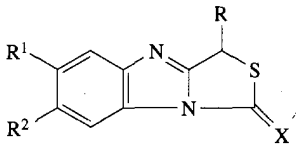
Some derivatives of the pyrrolobenzimidazoles (**584**)–(**586**) have found pharmacological use as cardiovascular agents ⟨86GEP(O)3445669⟩, inflammation inhibitors ⟨85PHA462⟩, and industrial application in the preparation of bleed fast printing inks ⟨85GEP(O)3329340⟩. Several derivatives of



(581)

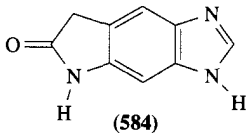


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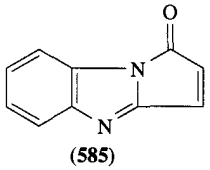


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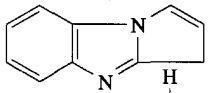
X= O, NH, NNHCONHR



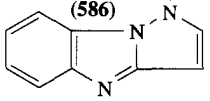
(584)



(585)



(586)

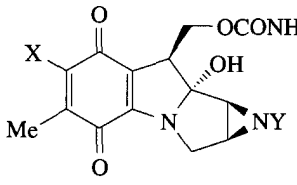


(587)

pyrazolo[1,5-*a*]benzimidazole (**587**) have found pharmacological use on account of their antiulcer, antipyretic, analgesic, antiinflammatory, and antihypertensive activity ⟨82EUP43961, 83FES35⟩ and industrial application in the preparation of blocked magenta couplers for high-sensitivity photographic emulsions ⟨83JAP(K)58113938, 83JAP(K)59206836⟩.

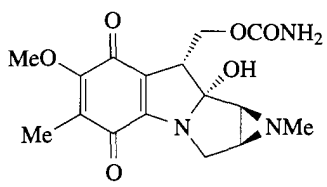
8.36.7.1.4 Annelated indoles, isoindoles, and indazoles

Previous references to mitomycins have been made in CHEC-I ⟨84CHEC-I(4)374, 84CHEC-I(7)93⟩. There are fifteen mitomycins reported which have been isolated from natural sources (mitomycin A to M, porfiromycin, mitiromycin, and albomitomycin); some of them are represented as (**588**)–(**591**) ⟨90MI 836-01⟩.



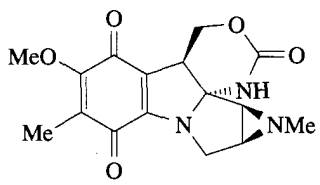
Mitomycin A: X= MeO; Y= H
Mitomycin C: X= NH_2; Y= H
Porfiromycin: X= NH_2; Y= Me

(588)



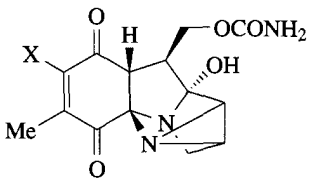
Mitomycin B

(589)



Mitiromycin

(590)



Albomitomycin A

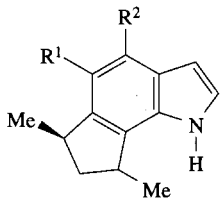
(591)

Mitomycin C has a potent activity against a wide spectrum of tumors and bacteria. Although it is highly toxic, mitomycin C is extensively used in chemotherapy in treating gastrointestinal cancers ⟨B-79MI 836-02, B-80MI 836-02⟩.

Analgesic and antiinflammatory activities have been claimed for 2-(morpholinocarbonyl)furo[3,2-*b*]indole derivatives (**341**) ⟨86JMC2284⟩.

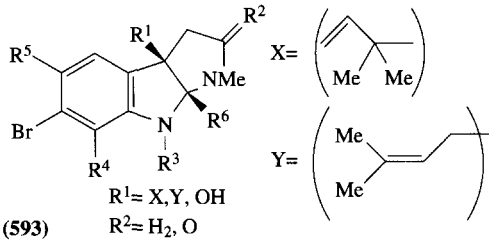
The structures, biological activities, and syntheses of marine natural products containing indole and dihydroindole nuclei have been reviewed ⟨91H(32)1391⟩. Among them, several cyclopent[*g*]indoles

(**592**) named trikentrines have been claimed to be cytotoxic against KB cells ⟨90T3089⟩, and numerous pyrrolo[2,3-*b*]indoles named flustramines (**593**) were shown to be muscle relaxants ⟨83MI 836-03⟩.



(**592**)

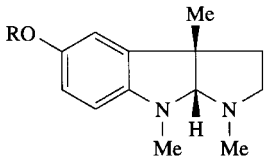
R^1: H, Me, CH=CHEt
R^2: H, Me, Et, CH=CHEt
CH_2CH=CHEt



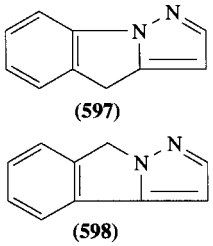
(**593**)

R^1= X,Y, OH
R^2= H_2, O
R^3=Y, H
R^4= Y, H
R^5= Y, H
R^6= X, H

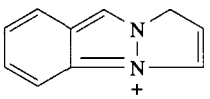
Comments on the application of the major alkaloid component of the calabar bean (*Physostigma venenosum*, Balf (−)-physostigmine (**594**) either as insecticide or as pharmaceutical have been made in CHEC-I ⟨84CHEC-I(1)158, 84CHEC-I(1)197⟩. Meanwhile, synthetic efforts to prepare the neurotoxic tricyclic aminals *d,l*-eserethole (**595**) and *d,l*-deoxyeseroline (**596**) have been made in order to study their inhibitor character against acetylcholinesterase and their potential myotic action ⟨83CC210, 83JOC1554, 85T3559⟩.



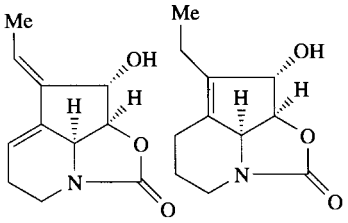
(**594**): R= CONHMe
(**595**): R= Et
(**596**): R= H



(**597**) (**598**)



(**599**)



(**600**) (**601**)

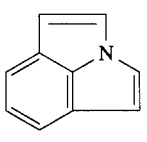
Several derivatives of 4*H*-pyrazolo[1,5-*a*]indole (**597**) and 8*H*-pyrazolo[5,1-*a*]isoindole (**598**) have been found to have contraceptive activity ⟨84EJM215, 82EJM223, 84GEP(O)3314843⟩, and some of the 1*H*-pyrazolo[1,2-*a*]indazol-4-ium derivatives (**599**) have been found to act as bronchodilators ⟨82EUP55450⟩.

8.36.7.2 *Ortho*- and *Peri*-fused Systems

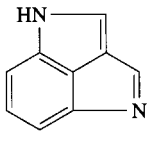
Streptazolin (**600**) is a lipophilic compound first isolated from *Streptomyces viridochromogenes* ⟨81HCA1752, 82HCA1432⟩. Because of the ease with which it polymerizes in concentrated form, its purification and characterization were made difficult. Its dihydro derivative (**601**) is a stable compound and exhibits antifungal activity.

Synthetic efforts towards the preparation of streptazolin through the aza analogue of the Ferrier rearrangement have been successful ⟨84JOC1674, 85JA1763⟩.

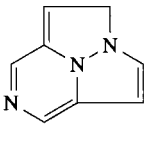
Derivatives of pyrrolo[3,2,1-*hi*]indole (**602**) exhibit antibacterial and mutagenic activity ⟨84MI 836-06⟩ and several derivatives of 1*H*-pyrrolo[4,3,2-*cd*]indole (**603**) exhibit properties to be used in the construction of photoelectric solar cells ⟨84JPC934⟩. 2*H*-2a,6,7b-triazacyclopent[*cd*]indene (**604**) and 6*H*,2a,6,7b-triazacyclopent[*cd*]indene (**605**) exhibit fluorescence and phosphorescence properties ⟨82JPC1270⟩.



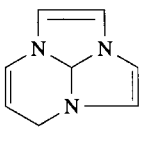
(**602**)



(**603**)



(**604**)

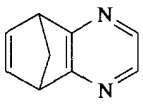


(**605**)

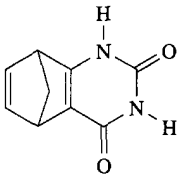
8.36.7.3 Bridged Systems

The 5,8-methanoquinoxaline (**606**) has been used as cigarette flavorant ⟨84USP4481957⟩, and 5,8-methanoquinazoline-2,4-(1*H*, 3*H*)-dione (**607**) has found pharmacological application in the preparation of virucides ⟨85BEP902231⟩.

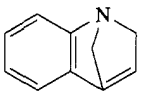
Several perfluoro derivatives of 2*H*-1,4-methanoquinoline (**608**) and 5,8-methanoquinoline (**609**) have found application as oxygen carriers for blood substitutes ⟨84JAP(K)5927889, 85USP4535085⟩.



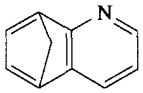
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(607)



(608)



(609)

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8.37
Three Heterocyclic Rings Fused (5 : 6 : 6)

MEI-XIANG WANG
University of Sunderland, UK

8.37.1 INTRODUCTION 1024

8.37.2 FUSED TRICYCLIC HETEROCYCLES WITHOUT A RING JUNCTION HETEROATOM 1024

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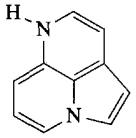
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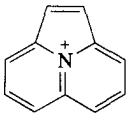
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8.37.1 INTRODUCTION

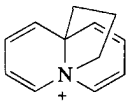
A survey on the "*ortho*-fused" tricyclic heterocyclic compounds in which each ring contains one heteroatom is given in this chapter. Therefore, "*ortho*- and *peri*-fused" tricyclic systems such as 1*H*-pyrrolo[3,2,1-*de*][1,5]naphthyridine (**A**) and pyrrolo[2,1,5-*de*]quinolizinium (**B**) are not included, neither are the bridged compounds such as 5,9a-propanoquinolizinium (**C**). Benzenoid tetracycles are discussed only where a benzene ring is fused to the five-membered ring moiety; for example, indolo[2,3-*a*]quinolizine system is reviewed in Section 8.37.3 while other benzenoid systems such as benzo[*a*]pyrrolo[2,3-*f*]quinolizine (**D**) are excluded. The chapter is divided into two parts; one is concerned with the ring systems without any ring junction heteroatom and the other with those having one ring junction heteroatom.



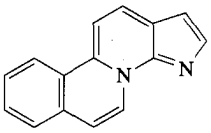
(A)



(B)



(C)



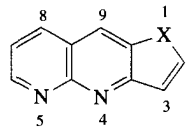
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8.37.2 FUSED TRICYCLIC HETEROCYCLES WITHOUT A RING JUNCTION HETEROATOM

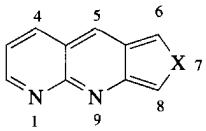
8.37.2.1 Introduction

Most of the compounds reported in this chapter are the naphthyridines fused with a five-membered ring containing one heteroatom, i.e. pyrrolo-, furo- and thienonaphthyridine compounds. Some other ring systems, which are the few known examples of the numerous possible structures, have only been studied sparsely and they will be presented briefly in Section 8.37.2.8.

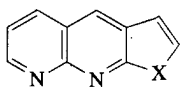
Theoretically, there are 36 possible isomers of each of the fully conjugated pyrrolo-, furo-, and thienonaphthyridine compounds (**1**–**36**). These structures can be classified as linear and angular fused-ring systems, the latter being further divided into two types in which one has nitrogen of the middle ring bound to the five-membered ring and the other to the six-membered ring. Numbering of these compounds is very confused in literature. In this chapter, the numbering system follows the nomenclature recommended by IUPAC, which is also used in *Chemical Abstracts*.



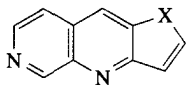
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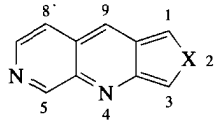
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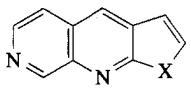
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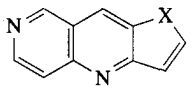
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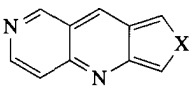
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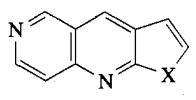
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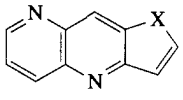
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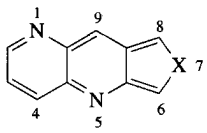
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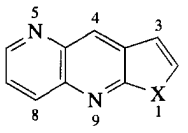
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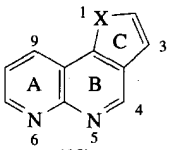
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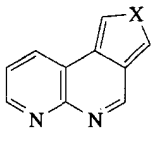


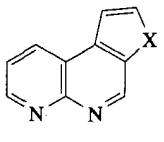
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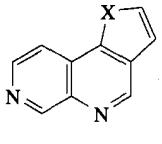


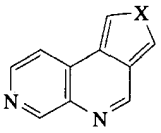
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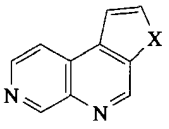

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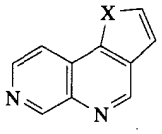

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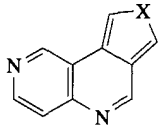

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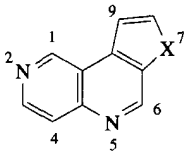

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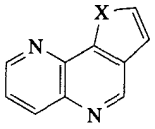

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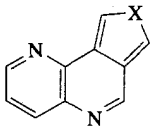

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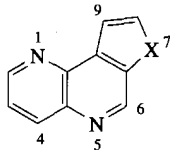

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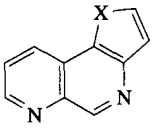

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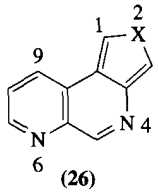

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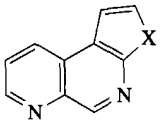

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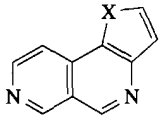

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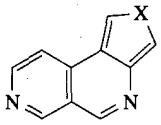

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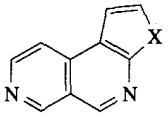

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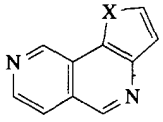

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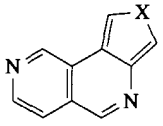

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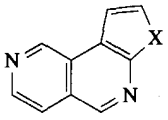

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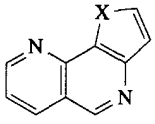

(29)

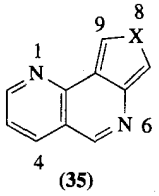

(30)

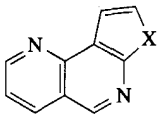

(31)


(32)


(33)


(34)


(35)


(36)

X = NH, O, S

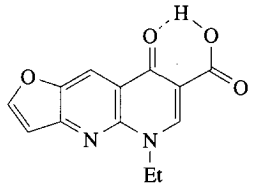
It should be noted that study of these ring systems is only of recent interest. Almost none of the possible structures were reported in the literature until the late 1980s. Neither the parent pyrrolonaphthyridines (X = NH), nor the furonaphthyridines (X = O) are known up to 1995, although the first synthesis of derivatives of pyrrolonaphthyridines appeared in 1960 ⟨60JCS1509⟩. In contrast to the pyrrolo and furo analogues, however, most of the thienonaphthyridines have been obtained and a review with respect to the synthesis and their reactivity has been published

⟨94JHC641⟩. Some of their benzenoid derivatives have been prepared, and examples are indolo-[2,3-*b*]-, indolo[3,2-*b*] and indolo[3,2-*c*]naphthyridines ⟨76JHC97, 77JOC1725, 80TL4485⟩, benzofuro-[2,3-*b*]naphthyridines ⟨93JHC909⟩ and benzothieno[2,3-*c*]naphthyridines ⟨87JHC1009⟩.

8.37.2.2 Experimental Structural Methods

8.37.2.2.1 Crystal structure

No crystal structures of the parent compounds have been reported although they are all crystalline products. X-ray analysis of the crystal structure of 5-ethyl-5,8-dihydro-8-oxofuro[3,2-*b*][1,8]-naphthyridine-7-carboxylic acid (**37**) indicates that the molecule is almost planar, except for the *N*-ethyl group which is approximately perpendicular to the tricyclic ring. The carboxyl group is in the unionized form and forms an intramolecular hydrogen bond with the ketone group ⟨91MI 837-01⟩.



(37)

8.37.2.2.2 NMR spectroscopy

As it is now a common practice to record ^{1}H NMR spectra, numerous ^{1}H-NMR data of the fused tricyclic heterocyclic compounds have been reported and can be obtained from the references given in later sections.

^{1}H-NMR spectra of thieno-fused naphthyridines with an angular annelation pattern have been studied by Gronowitz and coworkers. Chemical shifts and coupling constants of the protons of all 24 isomers are listed in Tables 1 and 2. The assignments were made unambiguously on the basis of ^{1}H–^{13}C heteronuclear shift correlation (HETCOR) spectra. The spectra have also been compared with those of related compounds such as thienopyridines and naphthyridines. In order to make clear comparisons of the chemical shifts and coupling constants of the protons, all compounds are numbered as shown for thieno[3,2-*c*][1,8]naphthyridine (**13**). As shown in Table 1, a characteristic chemical shift order is followed in general; H-4 of compounds (**13–24**), H-5 of compounds (**25–36**) and the proton α to the nitrogen in the A ring are most deshielded, followed by the proton γ to the nitrogen atom and finally the thiophene protons and the proton β to the nitrogen in ring A. The signal of H-1 is shifted downfield, especially in the cases of the thieno[1,5]- and thieno[1,6]naphthyridine compounds, because of the deshielding effect of the nitrogen atom in ring A. This deshielding effect becomes less significant when the nitrogen atom moves away from the thiophene moiety. The coupling constants in the naphthyridine moiety are comparable to the values of the parent naphthyridines ⟨70AHC(11)123⟩, and so are the thiophene protons. Interestingly, a coupling between H-5 and H-6 ($J = 0.9$ Hz) in (**31**) has been observed, which is not known for the corresponding parent naphthyridine, while the coupling between H-5 and H-9, which is well known for the 1,6- and 1,7-naphthyridines ⟨70AHC(11)123⟩, has only been found for compound (**25**) ⟨94JHC1161⟩. It is also noteworthy that the long-range coupling between the protons in the thiophene ring and azomethine proton ($J_{1,4}$) is observed in the range of 0.8–0.9 Hz ⟨91CCC2340, 94JHC11⟩.

Carbon-13 NMR data of thienonaphthyridines (**13–36**) is summarised in Table 3. The carbon chemical shifts of the naphthyridine moieties are in good agreement with those of the corresponding naphthyridines ⟨83AHC(33)147⟩. Generally, the carbons α to the nitrogen atoms resonate at the lowest field, followed by the carbons γ to the nitrogen atoms and then the carbons β to the nitrogen atoms. The thiophene carbons appear in the highest field and chemical shifts of the α carbons are larger than those of the β carbons, which is opposite to the simple thiophene system. The coupling

Table 1 ^{1}H NMR spectral data of thienonaphthyridines (**13–36**) in $CDCl_3$.

Compound	*δ (^{1}H)* (ppm)									*Ref.*
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*	*H-9*	
13	–	7.68	7.65	9.47	–	–	9.12	7.58	8.51	94JHC11
14	8.12	–	8.19	9.30	–	–	9.11	7.60	8.66	94JHC11
15	8.00	7.96	–	9.52	–	–	9.11	7.60	8.66	94JHC11
16	–	7.78	7.69	9.39	–	9.60	–	8.72	7.94	94JHC11
17	8.24	–	8.16	9.11	–	9.32	–	8.68	7.97	94JHC11
18	7.97	7.94	–	9.37	–	9.56	–	8.71	8.03	94JHC11
19	–	7.69	7.67	9.43	–	8.03	8.81	–	9.62	91CCC2340
20	8.18	–	8.19	9.18	–	7.82	8.74	–	9.52	91CCC2340
21	8.14	8.05	–	9.50	–	8.08	8.82	–	9.77	91CCC2340
22	–	7.74	7.66	9.50	–	8.52	7.67	8.97	–	91CCC2340
23	8.57	–	8.17	9.12	–	8.31	7.56	8.83	–	91CCC2340
24	8.83	7.92	–	9.37	–	8.52	7.67	9.01	–	91CCC2340
25	–	7.76	7.73	–	9.45	–	9.03	7.68	8.41	94JHC1161
26	8.05	–	8.01	–	9.10	–	8.89	7.63	8.45	94JHC1161
27	7.81	7.71	–	–	9.36	–	9.02	7.69	8.55	94JHC1161
28	–	7.85	7.74	–	9.30	9.44	–	8.80	7.84	94JHC1161
29	8.20	–	8.02	–	8.97	9.20	–	8.84	7.98	94JHC1161
30	7.84	7.72	–	–	9.24	9.49	–	8.87	8.03	94JHC1161
31	–	7.81	7.76	–	9.24	7.87	8.78	–	9.59	94JHC1161
32	8.17	–	8.07	–	8.99	7.69	8.80	–	9.59	94JHC1161
33	7.98	7.79	–	–	9.76	7.88	9.79	–	9.15	94JHC1161
34	–	7.85	7.77	–	9.25	8.42	7.59	9.12	–	92TL2199
35	8.54	–	8.05	–	8.92	8.21	7.55	9.01	–	92TL2199
36	8.18	7.70	–	–	9.15	8.42	7.60	9.16	–	92TL2199

Table 2 Coupling constants (Hz).

Compound	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{6,7}$	$J_{6,8}$	$J_{6,9}$	$J_{7,8}$	$J_{7,9}$	$J_{8,9}$	*Other*	*Ref.*
13	–	–	–	5.3	–	–	–	4.3	1.9	8.1		94JHC11
14	–	3.9	0.9	–	–	–	–	4.6	1.9	7.9		94JHC11
15	5.3	–	0.7	–	–	–	–	4.3	1.0	8.2		94JHC11
16	–	–	–	5.3	–	–	0.8	–	–	5.6		94JHC11
17	–	2.9	0.9	–	–	–	0.8	–	–	5.3		94JHC11
18	5.3	–	0.8	–	–	–	0.9	–	–	5.6		94JHC11
19	–	–	–	5.3	5.8	–	0.8	–	–	–		91CCC2340
20	–	2.9	0.8	–	5.5	–	0.8	–	–	–		91CCC2340
21	5.3	–	0.8	–	5.8	–	0.8	–	–	–		91CCC2340
22	–	–	–	5.3	8.4	1.6	–	4.3	–	–		91CCC2340
23	–	3.1	0.9	–	8.2	1.7	–	4.6	–	–		91CCC2340
24	5.3	–	0.8	–	8.4	1.7	–	4.3	–	–		91CCC2340
25	–	–	–	5.4	–	–	–	4.3	1.6	8.4	$J_{5,9}=0.8$	94JHC1161
26	–	3.2	–	–	–	–	–	4.5	1.5	8.1		94JHC1161
27	5.9	–	–	–	–	–	–	4.2	1.6	8.4		94JHC1161
28	–	–	–	5.4	–	–	–	–	–	5.6		94JHC1161
29	–	3.2	–	–	–	–	–	–	–	5.5		94JHC1161
30	5.9	–	–	–	–	–	–	–	–	5.4		94JHC1161
31	–	–	–	5.4	5.6	–	–	–	–	–	$J_{5,6}=0.9$	94JHC1161
32	–	3.2	–	–	5.2	–	–	–	–	–		94JHC1161
33	5.8	–	–	–	5.6	–	–	–	–	–		94JHC1161
34	–	–	–	5.4	8.1	1.7	–	4.4	–	–		92TL2199
35	–	3.4	–	–	7.9	1.7	–	4.7	–	–		92TL2199
36	5.9	–	–	–	8.2	1.8	–	4.4	–	–		92TL2199

constants of carbon and hydrogen have also been measured; one-bond and two-bond coupling constants in A and C rings are, in general, of the same magnitude in pyridine and thiophene, respectively. Long-range couplings such as ^{3}J and ^{4}J are also reported ⟨91CCC2340, 94JHC11, 94JHC1161⟩.

Table 3 ^{13}C NMR spectral data of thienonaphthyridines (**13–36**) in $CDCl_3$.

Compound	*δ (^{13}C)* (ppm)									*Ref.*
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	
13	—	127.8	123.9	149.5	—	—	151.8	122.2	132.6	94JHC11
14	117.3	—	125.6	152.0	—	—	150.0	122.5	132.3	94JHC11
15	121.5	133.3	—	148.1	—	—	151.4	122.0	132.6	94JHC11
16	—	129.2	124.2	148.2	—	154.2	—	144.7	116.1	94JHC11
17	119.4	—	125.6	150.2	—	152.3	—	146.7	116.6	94JHC11
18	121.7	132.8	—	146.6	—	153.8	—	144.7	116.2	94JHC11
19	—	127.4	123.9	150.7	—	122.8	146.7	—	148.0	91CCC2340
20	116.4	—	126.4	153.1	—	122.7	148.1	—	146.7	91CCC2340
21	120.7	123.9	—	149.5	—	122.5	146.5	—	148.2	91CCC2340
22	—	129.4	123.7	147.2	—	137.8	123.5	150.1	—	91CCC2340
23	119.6	—	125.0	149.4	—	136.8	123.1	148.9	—	91CCC2340
24	122.7	132.1	—	145.8	—	137.4	123.2	149.9	—	91CCC2340
25	—	128.1	126.3	—	152.6	—	150.7	125.2	131.0	94JHC1161
26	116.4	—	120.4	—	155.1	—	149.9	125.5	130.8	94JHC1161
27	119.5	127.6	—	—	151.1	—	150.4	125.0	131.0	94JHC1161
28	—	129.7	126.5	—	150.6	153.1	—	148.0	115.8	94JHC1161
29	118.6	—	120.5	—	152.0	151.5	—	150.1	116.5	94JHC1161
30	119.7	127.3	—	—	149.2	152.8	—	147.8	116.0	94JHC1161
31	—	128.0	126.2	—	149.9	120.3	144.8	—	147.8	94JHC1161
32	115.7	—	121.2	—	152.2	120.7	147.1	—	146.6	94JHC1161
33	118.9	128.3	—	—	148.4	119.9	144.4	—	148.0	94JHC1161
34	—	128.9	126.0	—	151.0	136.6	122.1	153.8	—	94JHC1161
35	118.8	—	120.1	—	153.0	136.9	122.4	155.3	—	94JHC1161
36	120.6	126.5	—	—	149.6	136.2	121.7	153.9	—	94JHC1161

8.37.2.2.3 Mass spectrometry

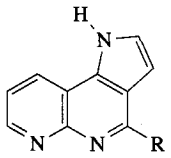
All the thienonaphthyridines (**13–36**) give the molecular ion as base peak in the mass spectrum due to their extensively conjugated structures. Isomeric compounds show almost identical fragmentation patterns; compounds (**13–24**) give fragment ions at *m/e* 160 and *m/e* 159, formed by expulsion of C_2H_2 and HCN, respectively, while isomers (**25–36**) show no peak at *m/e* 160 ⟨91CCC2340, 94JHC11, 94JHC1161⟩.

8.37.2.2.4 UV and IR spectroscopy

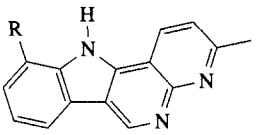
No systematic studies of UV and IR spectra of the parent tricyclic rings have appeared in literature. UV Spectra data of some 1*H*-pyrrolo[3,2-*c*][1,8]naphthyridine (**38**), 11*H*-indolo[3,2-*c*][1,8]naphthyridine (**39**) and 10*H*-indolo[2,3-*b*]naphthyridine (**40**) derivatives is listed in Table 4.

Table 4 UV spectra of some pyrrolonaphthyridine derivatives in ethanol.

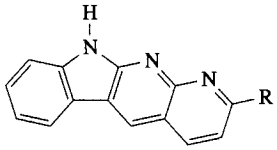
Compound	*R*	λ_{max} (nm) *(log ε)*	*Ref.*
38	Ph	258 (4.62), 345 (3.91)	60JCS1509
	4-MeOPh	259 (4.36)	60JCS1509
	4-NO_2Ph	252 (4.47), 360 (3.97)	60JCS1509
	2-ClPh	216 (4.53), 256 (4.75), 338 (3.81)	60JCS1509
	2-BrPh	216 (4.59), 256 (4.62), 337 (3.87)	60JCS1509
39	H	234 (4.63), 257 (sh.)(4.23), 280 (4.73)	76JHC97
	MeO	236 (4.68), 264 (4.44), 286 (4.60)	76JHC97
	F	230 (4.61), 258 (sh.)(4.22), 280 (4.71)	76JHC97
	Cl	242 (4.68), 260 (sh.)(4.18), 281 (4.70)	76JHC97
	Br	244 (4.68), 260 (sh.)(4.21), 282 (4.72)	76JHC97
40	H	224 (4.53), 269 (4.56), 290 (4.16), 328 (4.16)	77JOC1725
	MeO	226 (4.60), 260 (4.50), 286 (4.42), 340 (4.21)	77JOC1725
	Cl	227 (4.48), 270 (4.56), 291 (4.29), 336 (4.19)	77JOC1725
	NH_2	230 (4.52), 261 (4.45), 275 (4.43), 284 (4.43), 382 (4.48)	77JOC1725
	SH	228 (4.48), 259 (4.28), 282 (4.45)	77JOC1725



(38)

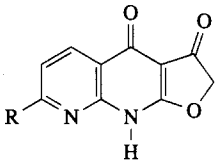


(39)



(40)

The IR spectra of compounds (**41**) display a N—H absorption band around 3010 cm^{-1} and two carbonyl absorption bands at ca. 1710 cm^{-1} and 1645 cm^{-1} indicative of no "hydroxyl" form of the compounds ⟨88CPB4403⟩.



(41)

8.37.2.3 Thermodynamic Aspects

8.37.2.3.1 Intermolecular forces

All fused tricyclic heterocycles reported are crystalline solids. A selection of melting points of thienonaphthyridines is listed in Table 5.

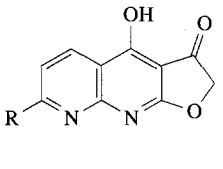
Table 5 Melting points of some thienonaphthyridines.

Compound	*m.p.* (°C)	*Ref.*
13	119–121	94JHC11
14	144–147	94JHC11
15	72–76 (dec.)	94JHC11
16	99–103	94JHC11
17	149–150	94JHC11
18	138–140	94JHC11
19	144–146	91CCC2340
20	148–160	91CCC2340
21	139–141	91CCC2340
22	99–101	91CCC2340
23	96–98	91CCC2340
24	74–74	91CCC2340
25	128–131	94JHC1161
26	118–120	94JHC1161
27	110–111	94JHC1161
28	140–141	94JHC1161
29	157–164	94JHC1161
30	112–116	94JHC1161
31	131–132	94JHC1161
32	165–169	94JHC1161
33	130–131	94JHC1161
34	120–122	94JHC1161
35	86–88	94JHC1161
36	117–119	94JHC1161

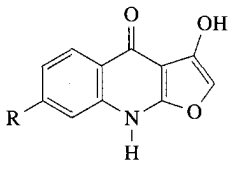
8.37.2.3.2 Tautomerism

Although furo[2,3-*b*]naphthyridine (**41**) possesses, in principle, four tautomeric forms such as monohydroxy structures (**41a**) and (**41b**) and dihydroxy structure (**41c**), only the diketone form (**41**)

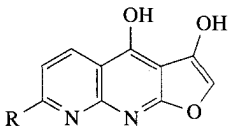
has been observed ⟨88CPB4403⟩. Compounds (**42**–**44**) and (**45**) exist exclusively in the forms of lactam and thiolactam, respectively ⟨77H(6)29, 95ACS744⟩, and so do their benzenoid analogues ⟨77H(6)29, 77(8)421, 87JHC1009⟩. On the other hand, compounds (**46**), (**47**) and (**48**) have been reported to adopt amino- and hydroxyl-substituted tautomeric forms, although no spectra data was given for the latter two compounds, mainly due to the stability gained from aromatization and intramolecular hydrogen bonding between amino, hydroxyl, and adjacent ester groups ⟨74JHC151, 94EUP587473⟩.



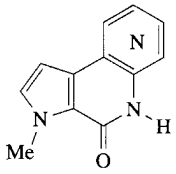
(**41a**)



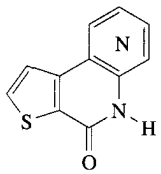
(**41b**)



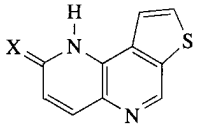
(**41c**)



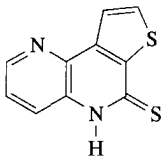
(**42**)



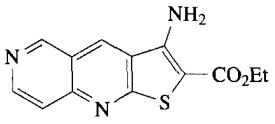
(**43**)



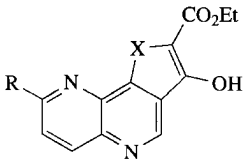
(**44**) X = O, S



(**45**)



(**46**)

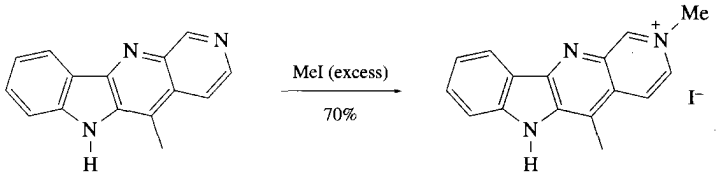


(**47**) X = NH
(**48**) X = S

8.37.2.4 Reactivity of Fully Conjugated Rings

8.37.2.4.1 Electrophilic attack at nitrogen

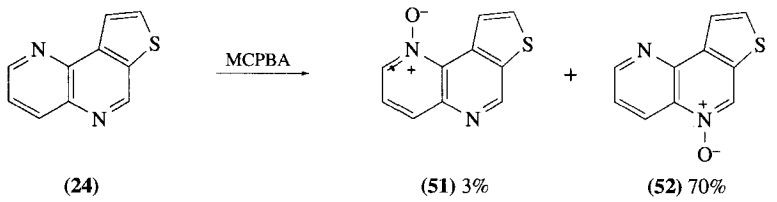
Methylation of indolonaphthyridines has been reported to take place on the nitrogen of the terminal pyridine ⟨80TL4485⟩; for example, 6*H*-indolo[3,2-*b*][1,7]naphthyridine (**49**) reacted with excess methyl iodide to afford quaternary salt (**50**) (Equation (1)) ⟨89JHC105⟩.

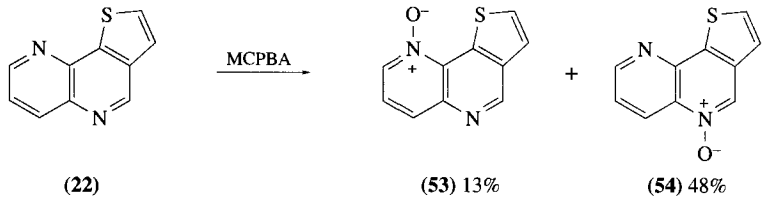


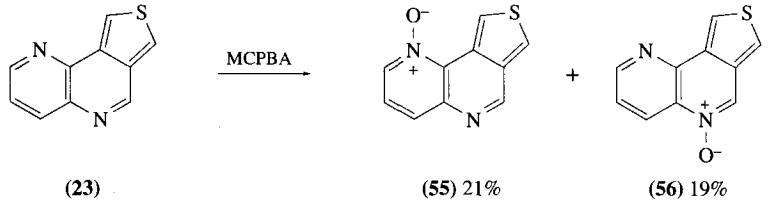
(**49**) (**50**)

(1)

Oxidation of thieno[*c*]naphthyridines using MCPBA has shown that the mode of annelation has a great effect on the reactivity of the pyridinic nitrogen atoms. Thieno[2,3-*c*][1,5]naphthyridine (**24**) was almost exclusively oxidized at 5-nitrogen, giving a convenient preparation of thieno[2,3-*c*][1,5]naphthyridine 5*N*-oxide (**52**) (Equation (2)). A fairly good selective oxidation was obtained when thieno[3,2-*c*][1,5]naphthyridine (**22**) was used (Equation (3)), while thieno[3,4-*c*][1,5]naphthyridine (**23**) gave no selectivity in oxidation reaction and about equal amounts of the 1*N*-oxide (**55**) and 5*N*-oxide (**56**) products were formed in lower yield (Equation (4)). It is worth noting that no oxidation occurred at the sulfur atom under the reaction conditions ⟨93H(35)245⟩.

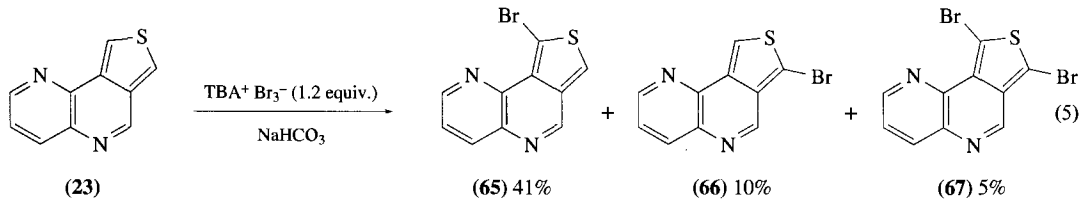




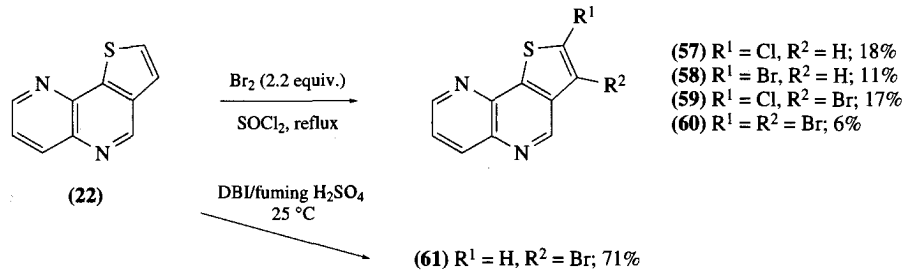


8.37.2.4.2 Electrophilic attack at carbon

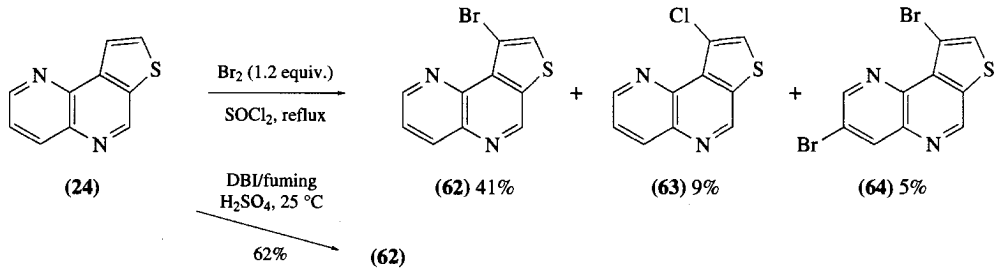
Bromination of thieno-fused 1,5-naphthyridines has been extensively investigated. As expected for these tricyclic ring systems which consist of one strongly π-deficient naphthyridine and one π-excessive five-membered moiety, electrophilic attack preferentially takes place at the thiophene ring. If electrophilic reaction should occur on the naphthyridine ring, the *meta* position to the nitrogen would be the reactive site. The outcome of the bromination varied according to the conditions employed as illustrated in Scheme 1. Bromination of thieno[3,2-*c*][1,5]naphthyridine (**22**) using tetrabutylammonium perbromide ($TBA^+Br_3^-$) or bromine in concentrated sulfuric acid was unsuccessful. Reaction with bromine in refluxing thionyl chloride gave a mixture of halogenated compounds in low yields, and decreasing the molar ratio of bromine from 2.2 to 1.2 equivalents did not improve selectivity and chemical yield significantly although no dibrominated compound was obtained. The formation of chloro-substituted compounds (**57**) and (**59**) may result from halogen exchange with the bromo derivatives or from direct reaction with thionyl chloride ⟨94H(37)331⟩. The best result was achieved when (**22**) was brominated with dibromoisocyanuric acid (DBI) ⟨68M815⟩ in fuming H_2SO_4 at room temperature leading to the exclusive formation of 3-bromothieno[3,2-*c*][1,5]naphthyridine (**61**) in good yield ⟨94JHC521⟩. Thieno[2,3-*c*][1,5]naphthyridine (**24**) underwent bromination selectively with bromine in boiling thionyl chloride (Scheme 2), 9-bromothieno[2,3-*c*][1,5]naphthyridine (**62**) being formed in 41% yield. The second bromination took place on the pyridine ring, giving dibrominated derivative (**64**) and the yield was increased to 12% when 2.2 equivalents of bromine were employed ⟨94H(37)331⟩. As for (**22**), bromination of (**24**) with DBI afforded 9-brominated compound (**62**) as the sole product ⟨94JHC521⟩. Thieno[3,4-*c*][1,5]naphthyridine (**23**) was brominated by $TBA^+Br_3^-$ to produce 9-bromo, 7-bromo and 7,9-dibromo compounds (**65**), (**66**) and (**67**) in the yield of 41%, 10% and 5%, respectively (Equation (5)) ⟨94H(37)331⟩.



Thieno[3,2-*c*][1,5]naphthyridine 5*N*-oxide (**54**) and 9*N*-oxide (**53**) underwent non-selective bromination with DBI and the corresponding mono- and dibrominated compounds were formed in

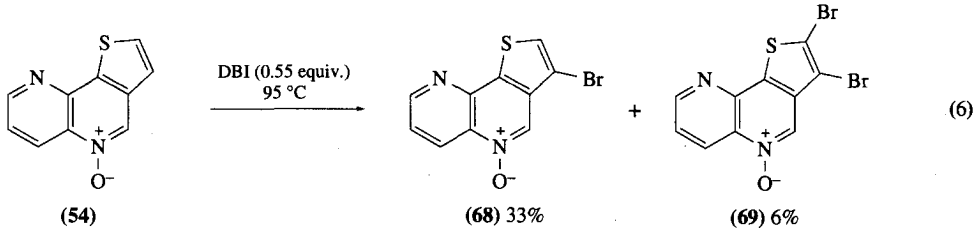


Scheme 1

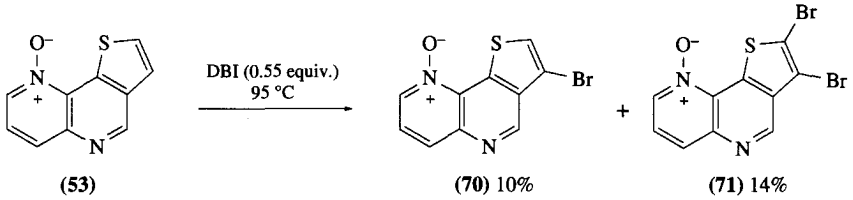


Scheme 2

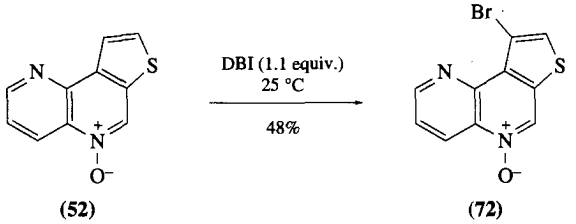
low yields. On treatment with an equimolar amount of DBI, thieno[2,3-*c*][1,5]naphthyridine 5*N*-oxide (**52**) was brominated at the β position of the thiophene ring to give compound (**72**) in 48% yield, while its 1*N*-oxide analogue (**51**) was converted into product (**62**) with loss of the oxygen atom. In neither case was dibromination found ⟨94JHC521⟩. Selective monobromination of thieno[3,4-*c*][1,5]naphthyridine 5*N*-oxide (**56**) using tetrabutylammonium perbromide led to 7-bromothieno[3,4-*c*][1,5]naphthyridine 5*N*-oxide (**73**) ⟨94H(37)331⟩ (Equations (6)–(10)).



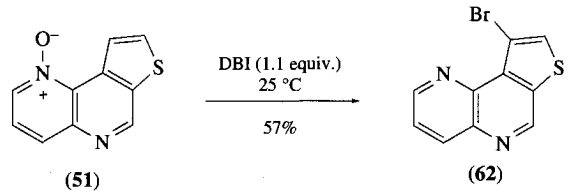
(6)



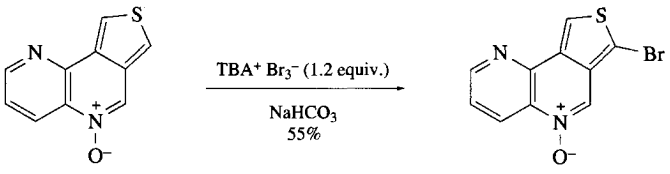
(7)



(8)



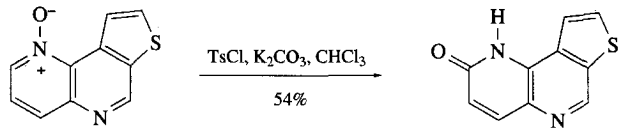
(51) (62) (9)



(56) (73) (10)

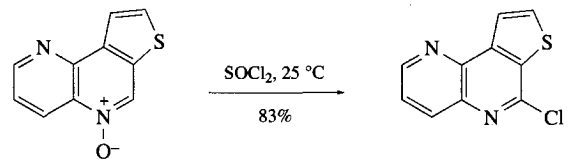
8.37.2.4.3 Nucleophilic attack at carbon

By analogy with pyridine oxide, thieno[2,3-*c*]naphthyridine 1*N*-oxide (**51**) was transformed into the corresponding pyridinone (**44**) in 54% yield by the action of tosyl chloride (Equation (11)) ⟨95ACS744⟩.

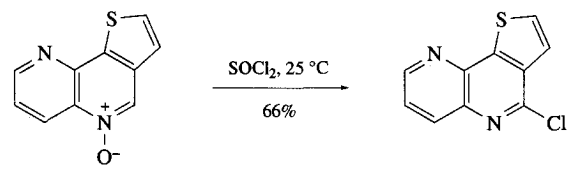


(51) (44) (11)

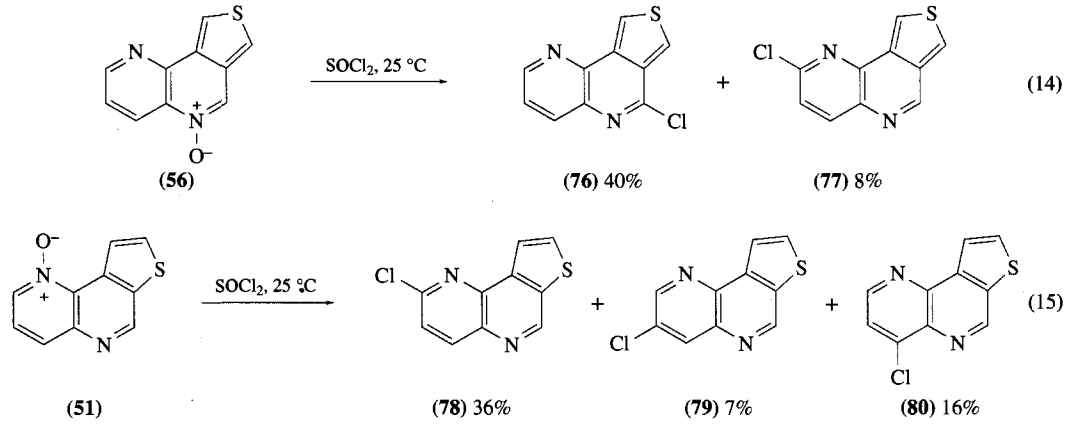
The reaction of the 5*N*-oxides of thieno[2,3-*c*] and thieno[3,2-*c*][1,5]naphthyridines (**52**) and (**54**) with thionyl chloride proceeded readily at ambient temperature, most likely through the same general addition–elimination sequence as the reaction of pyridine *N*-oxide with phosphorus oxychloride and sulfuryl chloride ⟨71JOC1720, 72JOC3101⟩, to give chloro-substituted compounds (**74**) and (**75**) in 83% and 66% yields, respectively (Equations (12) and (13)). Thieno[3,4-*c*][1,5]naphthyridine 5*N*-oxide (**56**) underwent a similar reaction with thionyl chloride (Equation (14)), but surprisingly, in addition to the expected product (**76**) (40%), a small amount (8%) of 2-chloro derivative (**77**) was also obtained. The same reaction of (**51**) led to a mixture of 2-, 3- and 4-chlorothieno[2,3-*c*][1,5]naphthyridines (**78**)–(**80**); nucleophilic attack mostly took place at positions α and γ to the nitrogen atom, which is the same as the reaction pattern of pyridine and naphthyridine oxides. It should be noted that the use of thionyl bromide did not result in the bromo derivatives, and instead, deoxygenation occurred to give the parent thienonaphthyridines in good yield ⟨95ACS744⟩.



(52) (74) (12)



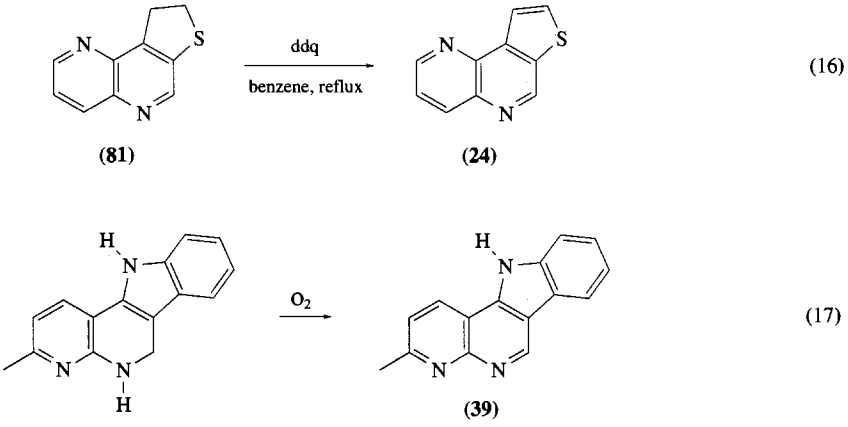
(54) (75) (13)



8.37.2.5 Reactivity of Nonconjugated Rings

8.37.2.5.1 Aromatization of dihydro derivatives

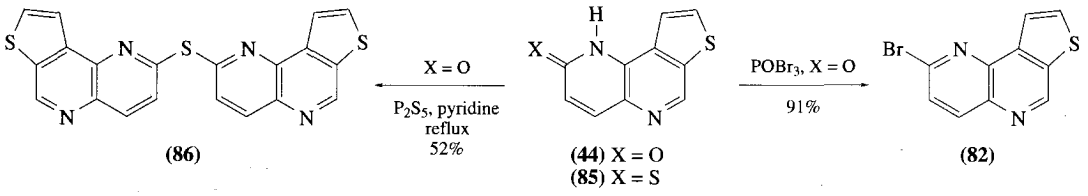
8,9-Dihydrothieno[2,3-*h*]-1,6-naphthyridine (**81**) was dehydrogenated by refluxing in benzene with ddq to afford the parent compound (**24**) in 38% yield (Equation (16)) ⟨94CC1767, 95H(41)1307⟩. 5,6-Dihydro-11*H*-indolo[3,2-*c*][1,8]naphthyridine compounds, which are very stable in the solid state, undergo rapid aromatization in solution to yield fully conjugated products of type (**39**) quantitatively (Equation (17)) ⟨76JHC97⟩.



8.37.2.6 Reactivity of Substituents Attached to Ring Carbon Atoms

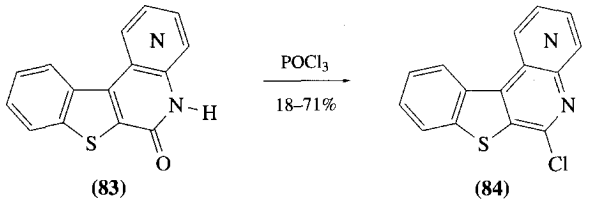
8.37.2.6.1 Nucleophilic displacement of carbonyl oxygen

Thieno[2,3-*c*][1,6]naphthyridin-2-one (**44**) was converted into the 2-bromo derivative (**82**) in excellent yield with $POBr_3$ (Scheme 3) ⟨95ACS774⟩, and interaction of a few [*l*]benzothieno[2,3-*c*]naphthyridin-6-ones (**83**) with $POCl_3$ gave the corresponding chloro-substituted products (**84**) (Equation (18)) ⟨87JHC1009⟩. Attempts to convert the carbonyl group of (**44**) into the thiocarbonyl group (**85**) utilizing phosphorus pentasulfide in boiling pyridine, however, led to the exclusive formation of sulfide (**86**). Thionation of (**44**) was realized in *N*,*N*′-dimethyl-*N*,*N*′-propyleneurea (DMPU) at 100 °C using excess of *p*-methoxyphenylthionophosphine sulfide (Lawesson's reagent) ⟨78BSB229⟩ and (**85**) was isolated, albeit in 35% yield, together with a minor amount of (**86**) ⟨95ACS744⟩.



(86) (44) X = O (85) X = S (82)

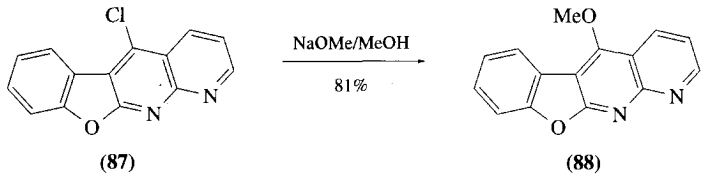
Scheme 3



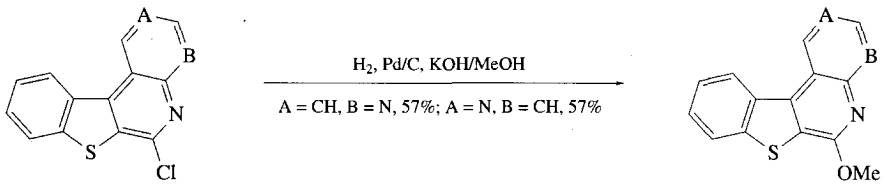
(83) (84) (18)

8.37.2.6.2 Nucleophilic substitution of halogen

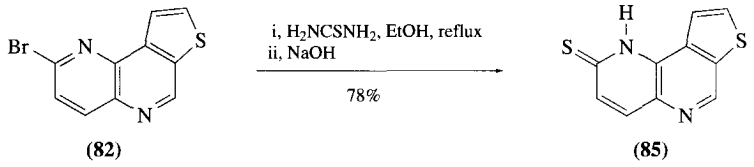
Halogen atoms attached to the naphthyridine moiety can be easily replaced by other nucleophiles such as alkoxides and amines (Equations (19)–(22)) ⟨87JHC1009, 91JHC1997, 93JHC909, 95ACS744⟩. Reaction of 2-bromothieno[2,3-*c*][1,5]naphthyridine (**82**) with thiourea followed by the treatment with sodium hydroxide afforded 2-thioxo-1,2-dihydrothieno[2,3-*c*]naphthyridine (**85**) in good yield (Scheme 3) ⟨95ACS744⟩.



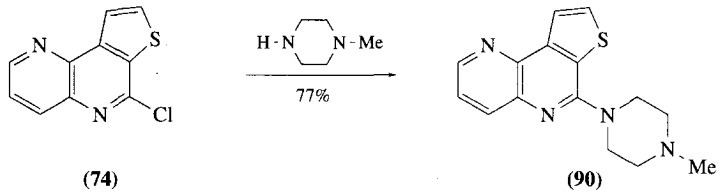
(87) (88) (19)



(84) (89) (20)



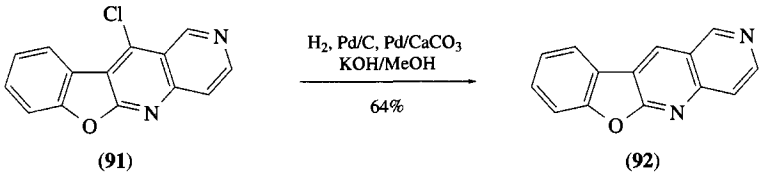
(82) (85) (21)



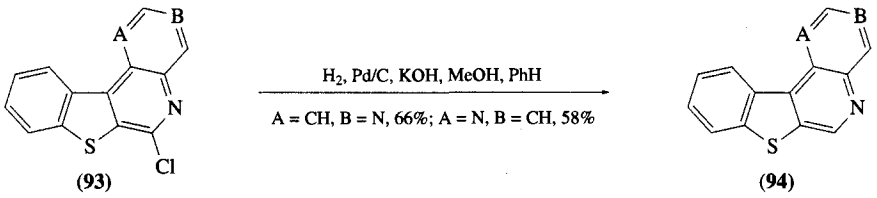
(74) (90) (22)

Catalytic hydrogenation of these chloro-substituted tricyclic compounds leads to dechlorination yielding the parent ring structures; thus, benzofuronaphthyridine (**92**) and benzothieno-naphthyridine (**94**) have been prepared in good yields from chloro compounds (**91**) and (**93**)

(Equations (23) and (24)) ⟨87JHC1009, 93JHC909⟩. It should be noted that hydrogenation of compounds (**84**) under the same reaction conditions does not give the parent ring structures, and instead, chlorine was displaced by the methoxy group and compounds (**89**) were obtained ⟨87JHC1009⟩.



(91) (92) (23)



(93) (94) (24)

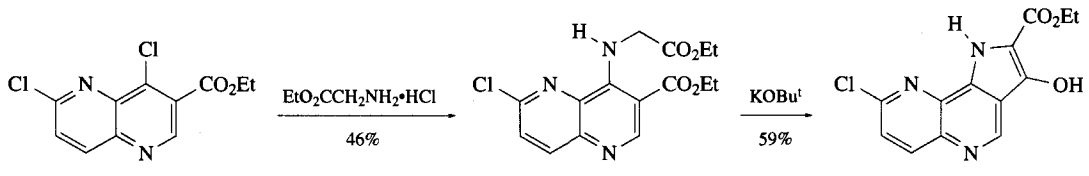
8.37.2.7 Synthesis

Although many methods of synthesis have been used for the construction of the tricyclic rings, almost all of these are categorized into three types according to the formation of five-membered ring, terminal pyridine ring, or the middle pyridine rings during the annelation. Syntheses of pyrrolo-, furo-, and thienonaphthyridines are treated separately.

8.37.2.7.1 Synthesis of pyrrolonaphthyridines

(i) Annelation with the formation of pyrrole ring

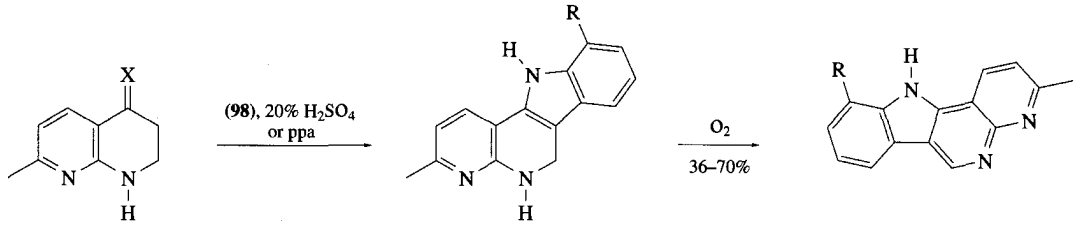
Preparation of pyrrolo[3,2-*c*][1,5]- and pyrrolo[3,2-*c*][1,8]naphthyridine derivatives has been reported through the formation of the pyrrole moiety starting from appropriately substituted naphthyridines ⟨89USP4859669, 91USP4996212, 94BMC1327⟩, for example, cyclization in the presence of potassium *t*-butoxide of intermediate (**96**), which is derived from substitution of (**95**) by glycine ester (Scheme 4), forms the 1*H*-pyrrolo[3,2-*c*][1,5]naphthyridine product (**47**) ⟨94EUP587473⟩. A convenient approach to the synthesis of indolonaphthyridines is to use the Fischer indole synthesis ⟨76FES587, 78FES770⟩; thus, indolization of phenylhydrazones (**98**) prepared from 2,3-dihydro[1,8]naphthyridin-4(1*H*)-one (**97**) gave intermediate (**82**) which underwent spontaneous dehydrogenation during the course of reaction forming indolo[3,2-*c*][1,8]naphthyridine product (**39**) in 36–70% yields (Scheme 5) ⟨76JHC97⟩.



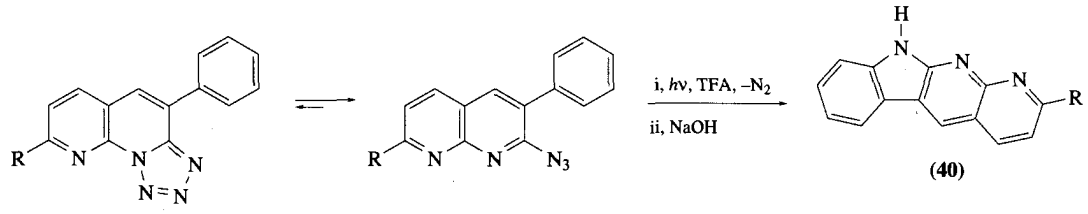
(95) (96) (47)

Scheme 4

A one-step synthesis of 10*H*-indolo[2,3-*b*][1,8]naphthyridines (**40**) has been achieved efficiently by photolyzing tetrazolonaphthyridines in TFA and products were obtained in very good yield (84–97%) (Scheme 6) ⟨77JOC1725, 86FES577⟩.



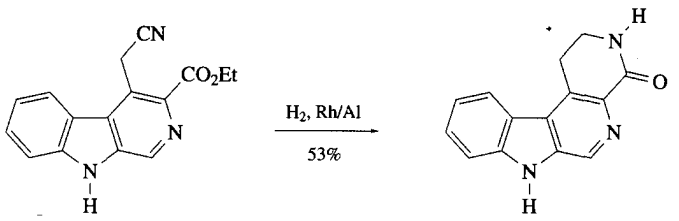
Scheme 5



Scheme 6

(ii) Annelation with the formation of the terminal pyridine ring

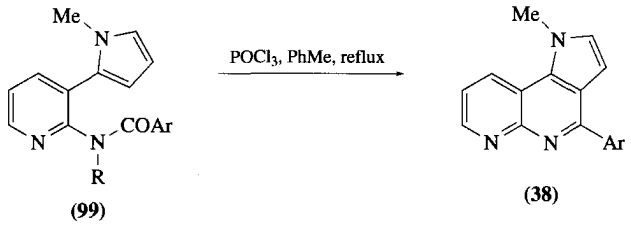
The only known example based on this synthetic strategy is the preparation of 4-oxo-1,2,3,4-tetrahydro-7*H*-indolo[2,3-*c*][1,7]naphthyridine from the reduction and cyclization of 4-cyanomethyl-β-carboline as shown below (Equation (25)) ⟨89JMC1799⟩.



(25)

(iii) Annelation with the formation of the middle pyridine ring

N-Aroyl derivatives of α-aminonicotyrine (**99**) underwent the Bischler–Napieralski cyclization reaction to give 1*H*-pyrrolo[3,2-*c*][1,8]naphthyridine products (**38**) in excellent yield, the first example of the preparation of pyrrolonaphthyridine compounds being reported in 1960 (Equation (26)) ⟨60JCS1509⟩.

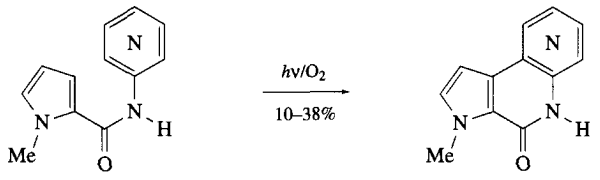


(99) (38)

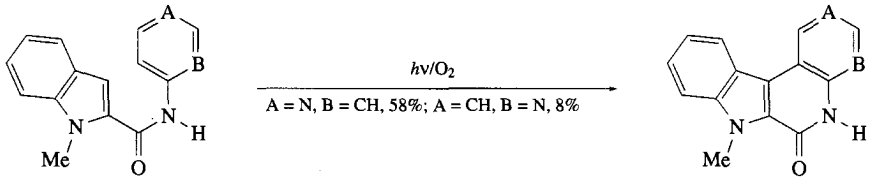
(26)

R = H, Ar; Ar = Ph, 4-MeOPh, 4-NO_2Ph, 2-BrPh

Oxidative photocyclization of the aroylaminopyridines including pyrrole and indole derivatives (**100**) and (**101**) led to the formation of pyridone (**42**) and its benzenoid analogue (**102**) (Equations (27) and (28), respectively), albeit in low yields ⟨77H(6)29⟩.

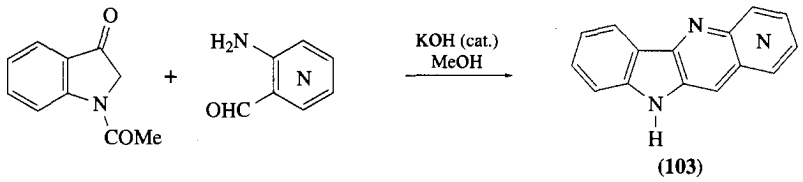


(100) (42) (27)



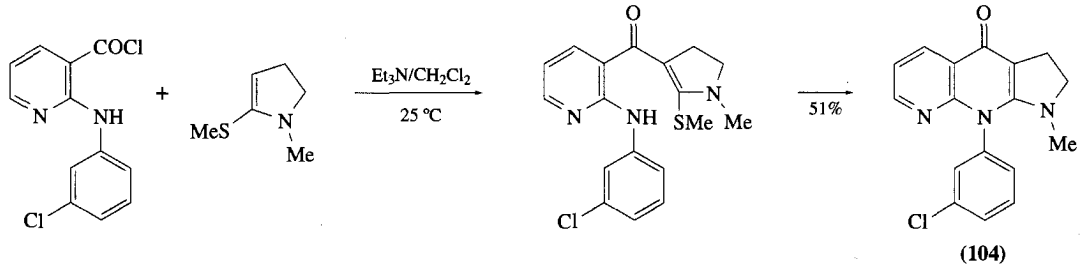
(101) (102) (28)

Friedländer condensation provides a simple and direct synthetic route to the tricyclic ring system and it has been widely used in preparing linear pyrrolonaphthyridine compounds ⟨77GEP2617101, 78KGS1671, 80TL4485, 89JHC105⟩, for example condensation reaction between *o*-aminoformylpyridines and indol-3-one using potassium hydroxide as a catalyst, yielded the corresponding indolo[3,2-*b*]naphthyridines (**103**) (Equation (29)) ⟨80TL4485⟩.



(103) (29)

Some other preparative methods have also been reported in the literature ⟨76RTC220, 90TL131⟩. A more general synthetic method is the condensation reaction between 2-arylaminonicotinic acid chloride and cyclic enamines, one example being the synthesis of compound (**104**) (Scheme 7) ⟨86MI 837-05, 89USP4810708, 93T7169⟩.



(104)

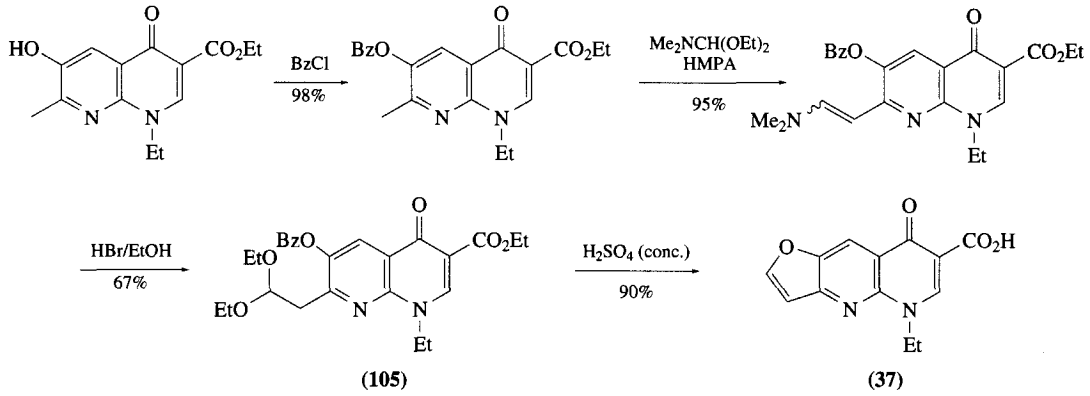
Scheme 7

8.37.2.7.2 Synthesis of furonaphthyridines

(i) Annelation with the formation of the furan ring

Efforts have been focused on the synthesis of 5-ethyl-5,8-dihydro-8-oxofuro[3,2-*b*][1,8]naphthyridine 7-carboxylic acid (**37**), known as DJ-6783, due to its wide spectrum of potent antimicrobial activity ⟨86MI 837-01⟩. A few synthetic routes have been studied, which were all based on the strategy of constructing the furan ring from naphthyridine derivatives. A synthetic route demonstrated in

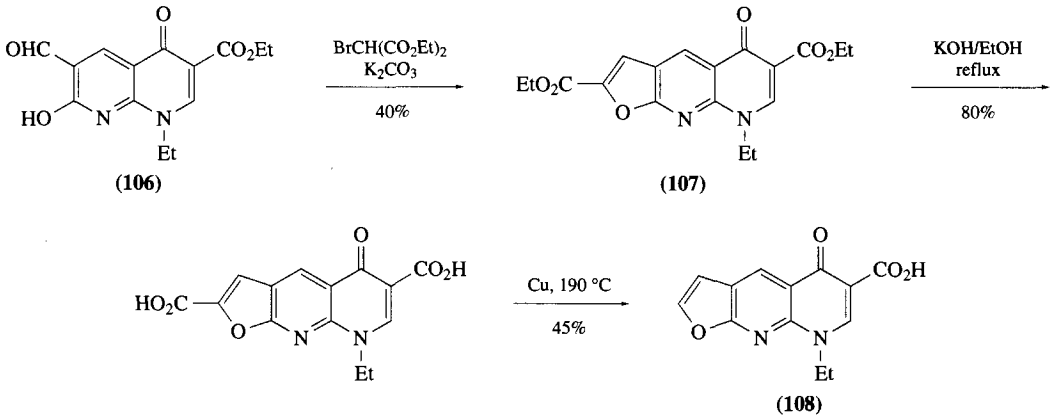
Scheme 8, which offers the advantages of high yield in each step and the ease of purification, involves the cyclization of acetal (**105**) with concentrated sulfuric acid at room temperature ⟨84CPB4914⟩.



(105) (37)

Scheme 8

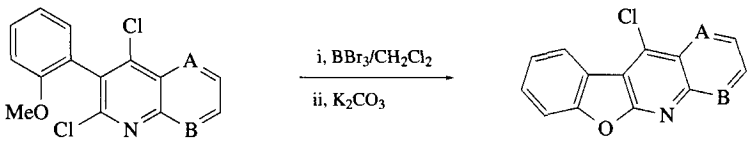
During the course of the preparation of 8-ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-6-carboxylic acid (**108**) which is an isomer of (**37**), the furan ring was constructed by reacting (**106**) with ethyl bromomalonate (Scheme 9) ⟨80CPB761⟩.



(106) (107) (108)

Scheme 9

Benzofuronaphthyridine compound (**91**) was synthesized through an intramolecular substitution reaction (Equation (30)); thus, demethylation of (**109**) with boron tribromide, followed by treatment with potassium carbonate in refluxing acetone, gave almost quantitative yield of the linear fused products (**91**) ⟨93JHC909⟩.

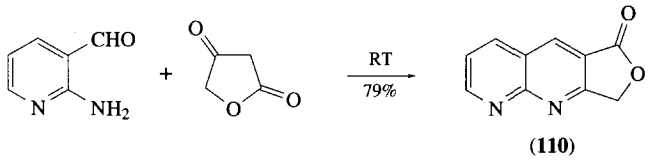


(109) A = N, B = CH, 93%; A = CH, B = N, 95% (91) (30)

(ii) Annelation with the formation of the middle pyridine ring

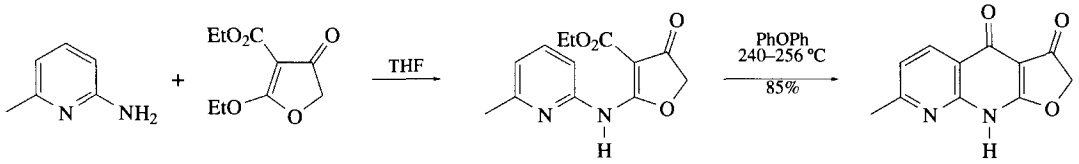
Condensation of 2,4(3*H*,5*H*)-furandione with 2-amino-3-formylpyridine affords tricyclic compound (**110**) in 79% yield (Equation (31)) ⟨83JOC1914⟩. 2-Amino-6-methylpyridine reacts with ethyl 2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate to give the intermediate (**111**) which is converted into tricycle (**41**) in good yield through thermal cyclization in boiling diphenyl ether (Scheme 10). However, this method cannot be extended to other aminopyridines without a methyl group attached at the 6-position, since such intermediates of type (**111**) undergo another cyclization pattern leading

to the 4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-diones (**112**) as the major product. Apparently, the orientation of cyclization is strongly influenced by the steric effects of the substituents on the pyridine ring ⟨88CPB4403⟩.



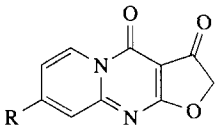
(31)

(**110**)



(**111**) (**41**)

Scheme 10

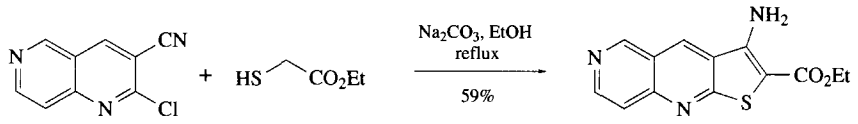


(**112**)

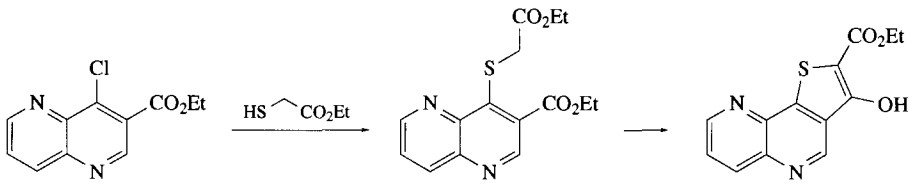
8.37.2.7.3 Synthesis of thienonaphthyridines

(i) Annelation with the formation of thiophene ring

As illustrated in Equation (32) and Scheme 11, reaction of ethyl thiolacetate and *o*-chlorocyanonaphthyridine or an *o*-chloroethoxycarbonylnaphthyridine, followed by cyclocondensation, provides a simple and convenient method for the synthesis of thieno[2,3-*b*][1,6]- and thieno[3,2-*c*][1,5]naphthyridine derivatives, respectively ⟨74JHC151, 94EUP587473⟩. The method is general for the preparation of other ring systems when a suitable starting naphthyridine is employed ⟨80CPB761, 93BCJ3716⟩.



(32)

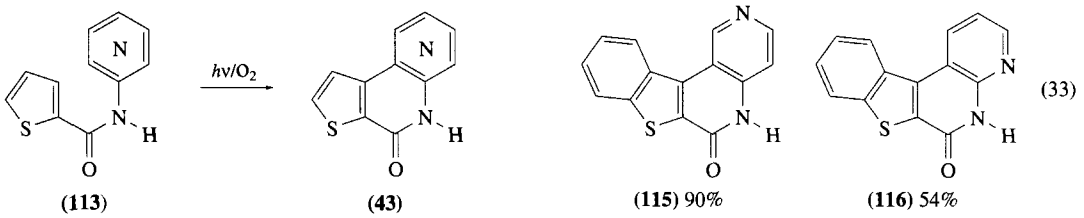


Scheme 11

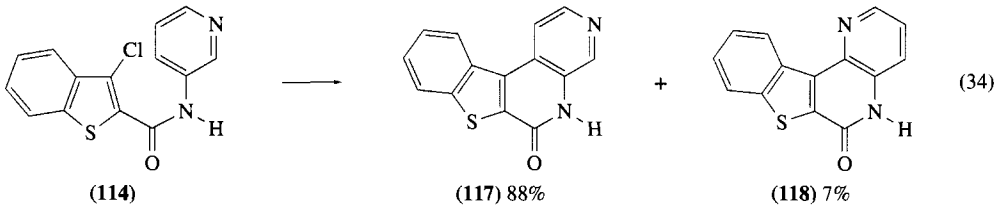
(ii) Annelation with the formation of the middle pyridine ring

A useful synthetic route to thienonaphthyridine structures is the oxidative photocyclization of *N*-pyridyl-2-thiophenecarboxamides; thienonaphthyridinones (**43**), have thus been obtained in mod-

erate yield from the irradiation of (**113**) (Equation (33)) ⟨77H(6)29⟩. With a chlorine atom substituted at the 3-position of the thiophene ring, photocyclization proceeds more efficiently, as exemplified by the high yield production of [*l*]benzothieno[2,3-*c*][1,6]- (**115**) and [*l*]benzothieno[2,3-*c*][1,8]naphthyridin-6(5*H*)-ones (**116**). When the amide (**114**) derived from 3-aminopyridine was irradiated (Equation (34)), [*l*]benzothieno[2,3-*c*][1,7]naphthyridin-6(*H*)-one (**117**) was formed predominantly (in 88% yield), and its isomer (**118**) was isolated as the minor product ⟨77H(8)421, 87JHC1009, 91JHC203, 91JHC1997⟩.

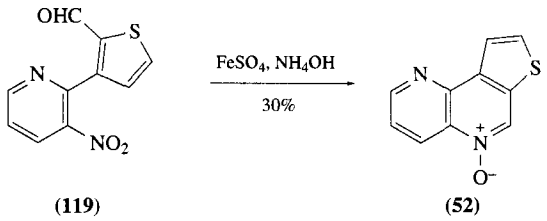


(33)

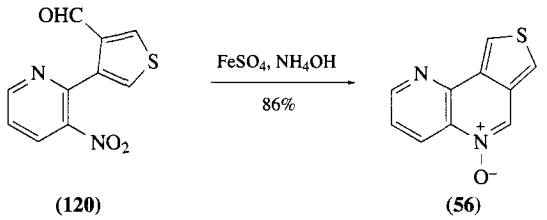


(34)

Reductive cyclization of 2-(*o*-formylthienyl)-3-nitropyridine (**119**) and (**120**), which were obtained by the Pd(0)-catalysed coupling reaction of 2-bromo-3-nitropyridine and *o*-formylthienyl boronic acids, by the action of ferrous sulfate in aqueous ammonia, gave thienonaphthyridine *N*-oxides (**52**) and (**56**) in 30 and 86% yields (Equations (35) and (36), respectively). Surprisingly, the other isomer, thieno[3,2-*c*][1,5]naphthyridine 5*N*-oxide (**54**) cannot be obtained using the same method ⟨93H(35)245⟩.



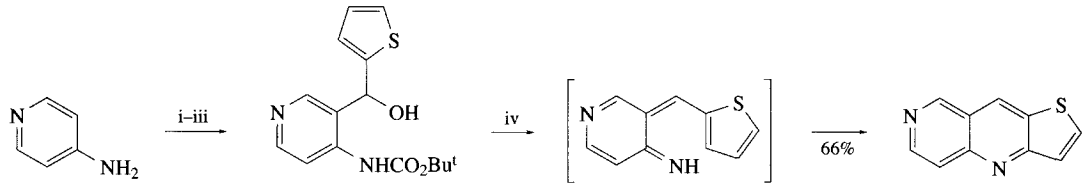
(35)



(36)

Thieno[3,2-*b*][1,6]naphthyridine (**123**), the only known linear parent tricyclic structure in the literature, has been synthesized by a flash vacuum pyrolysis (FVP) method; thus, compound (**121**) prepared in three steps from 4-aminopyridine gave (**123**) in 66% yield on FVP by intramolecular Diels–Alder reaction of (**122**) (Scheme 12) ⟨84CC1304⟩.

Using the Suzuki reaction between aromatic boronic acids and aromatic halides ⟨81SC513⟩ and the Stille reaction ⟨86AG(E)508⟩, Gronowitz and coworkers have developed efficient Pd(0)-catalysed coupling reactions between *o*-formylhetarylboronic acids or *o*-formylhetaryltin trialkyl derivatives and *o*-amino- or protected *o*-aminohetaryl halides. The coupled products undergo cyclization spontaneously during the course of reaction to give the desired tricyclic systems ⟨94JHC641⟩. Using these convenient one-pot procedures, all 24 isomeric thienonaphthyridines (**13**–**36**) with angular annelation patterns have been synthesized in moderate to good yields ⟨86CS311, 91CCC2340, 92TL2199,

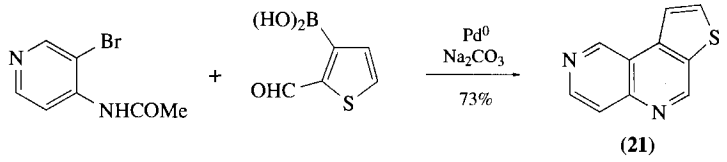


(121) (122) (123)

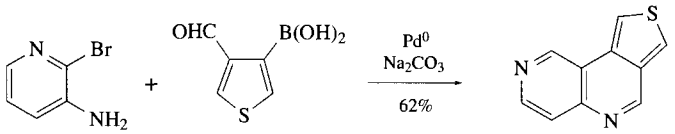
i, $(Bu^tOCO)_2O$; ii, Bu^tLi, –78 °C; iii, 2-thiophenecarboxaldehyde; iv, 600 °C/10^{-2} Torr

Scheme 12

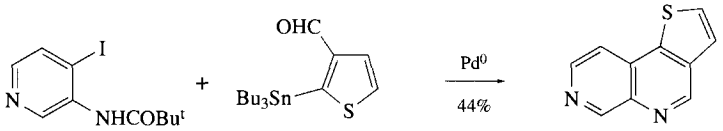
94JHC11, 94JHC1161) (Equations (37)–(42)). For the preparation of thienonaphthyridines having the middle ring nitrogen bound to the thiophene moiety, use of dichloro(diphenylphosphinebutane)palladium(II) as catalyst, and sometimes in the presence of copper(II) oxide as coreagent, improved chemical yield greatly ⟨95JHC751⟩.



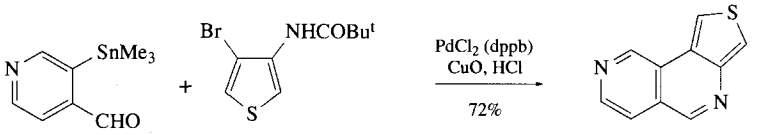
(21) (37)



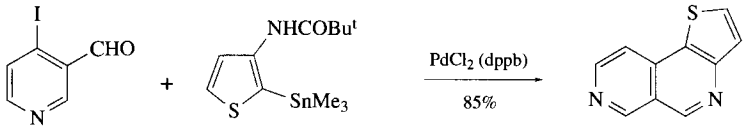
(20) (38)



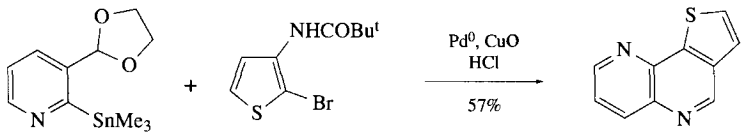
(16) (39)



(32) (40)



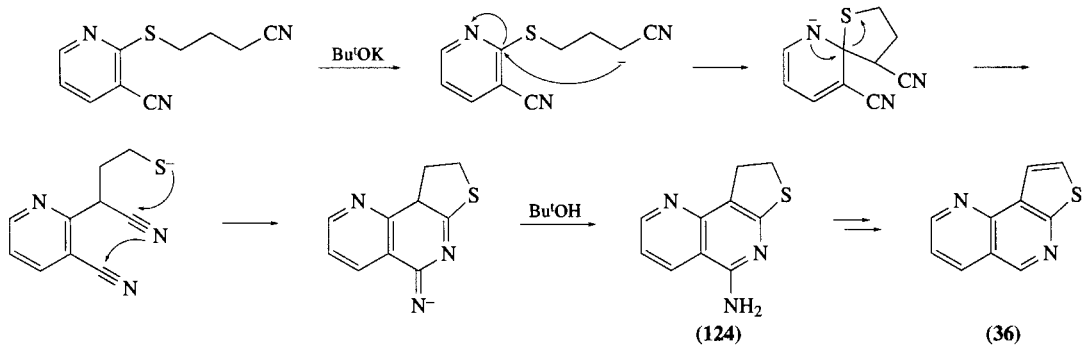
(28) (41)



(34) (42)

(iii) Miscellaneous methods

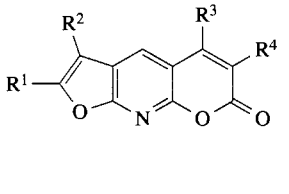
Several methods have been reported for the preparation of partially unconjugated ring systems ⟨93JHC667, 93T7169, 94CC1767, 95H(41)1307⟩. An interesting example is the formation of 5-amino-8,9-dihydrothieno[2,3-*h*][1,6]naphthyridine (**124**) from 2-(3-cyanopropylthio)pyridine 3-carbonitrile on treatment with potassium *t*-butoxide; a mechanism proposed, as depicted in Scheme 13, is via a Smiles-type rearrangement reaction followed by a cyclization (Scheme 13) ⟨94CC1767, 95H(41)1307⟩.



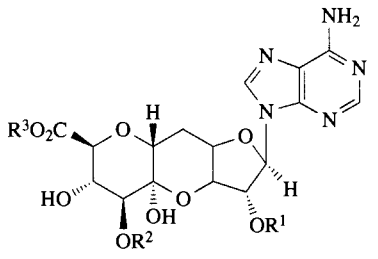
Scheme 13

8.37.2.8 Important Compounds and Applications

5-Ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine 7-carboxylic acid (**37**), known as DJ-6783, is a new keto carboxylic acid having an expanded antimicrobial activity, when compared with nalidixic acid or cinoxacin, against Enterobacteriaceae, *Acinetobacter* sp., *Pseudomonas* sp., *P. aeruginosa*, *Staphylococcus* sp., *Haemophilus influenzae* and *Neisseria* sp. ⟨86MI 837-01⟩. Azapsoralens (**125**) have been prepared in the search for alternatives to furocoumarines (psoralens) for the photochemotherapy of cutaneous diseases ⟨88G513, 90JOC895⟩. Physicochemical studies have shown that azapsoralens display high antiproliferative activity, low mutagenic activity and phototoxicity ⟨B-89MI 837-01, 91MI 837-02⟩, and a preliminary clinical trial has been performed ⟨91FES1407⟩. These compounds can form furan-side cycloadducts with DNA and the monoadducts with pyrimidine bases have been isolated ⟨91FES1407, 93FES1475, 94MI 837-01⟩.



(**125**) R^1, R^2, R^3, R^4 = H, Me



(**126**)

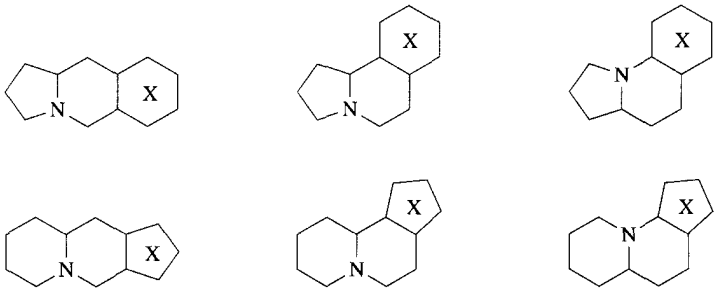
Herbicidin B: $R^1 = R^3$ = Me, R^2 = H
Herbicidin G: R^1 = H, R^2 = (*E*)–CO(Me)C=CHMe, R^3 = Me
Aureonuclemycin: $R^1 = R^2 = R^3$ = H

The herbicidins, a series of undecose nucleoside antibiotics from *Streptomyces saganonensis*, consist of a furo-pyrano-pyran ring skeleton as described as (**126**). They exhibit herbicidal and antialgal activity, and some of them are efficient inhibitors of *Xanthomanas oryzae*, a bacterium that causes leaf blight infection in rice crops ⟨82MI 837-01, 82JAN1711, B-83MI 837-01, 87JAP(K)62238218, 88MI 837-01⟩. A similar ring structure has also been found as a fragment in other naturally occurring products such as halichondrin B ⟨85JA4796, 86PAC701⟩. Syntheses of such ring systems have been attempted ⟨87TL3463, 90JOC863, 93JA6430, 94SL38⟩.

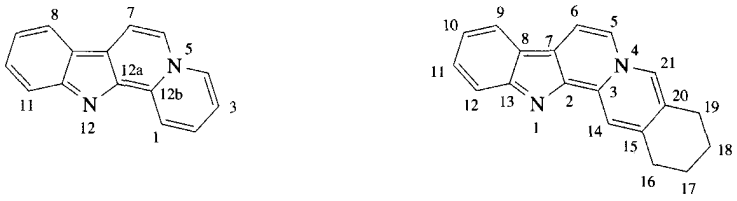
8.37.3 FUSED TRICYCLIC HETEROCYCLES WITH A RING JUNCTION HETEROATOM

8.37.3.1 Introduction

Since there is no report of compounds having heteroatoms other than nitrogen as ring junction atoms all tricyclic heterocycles discussed in this chapter can be viewed as indolizine or quinolizine or the quinolizinium ion in fusion with one heteroatom-containing six-membered and five-membered rings, respectively. Few of the numerous possible structures, which are represented by the skeletons shown below, have been reported and much of their chemistry remains unexplored, although compounds such as thieno[2,3-*b*]- and thieno[3,2-*b*]quinolizinium salts were obtained in the 1950s ⟨57JA4380⟩. In contrast to their parent tricyclic systems, however, the benzenoid derivatives and especially indolo[2,3-*a*]quinolizine compounds, have been extensively investigated, which is mainly due to the fact that they represent the ring structure of the naturally occurring products including corynantheine and yohimbine alkaloids. A series of reviews published in *The Alkaloids* ⟨B-52MI 837-01, B-65MI 837-01, B-68MI 837-01⟩ provide valuable information on the chemistry and physiology of the indolo[2,3-*a*]quinolizidine alkaloids, and the one by Szantay and coworkers ⟨86MI 837-02⟩ is particularly useful. Also, a review by Gribble ⟨88MI 837-02⟩ on the synthesis of zwitterionic indolo[2,3-*a*]quinolizine alkaloids should be consulted.



Most of the compounds are named on the basis of indolizine and quinolizine nuclei with the exception of pyrrolo[1,2]naphthyridines, i.e. indolizine fused to a pyridine ring. In practice, two systems are used for numbering indolo[2,3-*a*]quinolizine; examples shown below are indolo[2,3-*a*]quinolizine which is numbered according to the IUPAC recommendations also used in *Chemical Abstracts*, and tetrahydroindolo[2,3-*a*]benzo[*g*]quinolizine numbered following the generally accepted biogenetic numbering system.

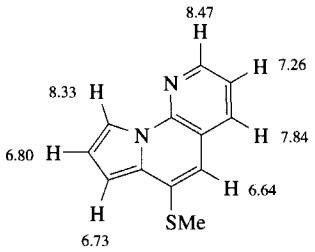


8.37.3.2 Experimental Structural Methods

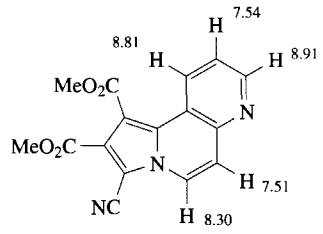
8.37.3.2.1 NMR spectroscopy

In spite of the fact that NMR spectroscopy has been used routinely in characterization of organic compounds, no systematic studies appear on the spectral properties of the parent tricyclic rings. This is mainly due to the lack of these compounds and to the difficulty of unambiguous assignments of the resonance signals in earlier times. The ^{1}H NMR spectral data of some pyrrolonaphthyridine derivatives are shown below, assignments being made on the basis of ^{1}H–^{1}H correlation spectroscopy (COSY) and ^{1}H–^{13}C HETCOR spectra ⟨93(H)(36)1945, 93(H)(36)2513⟩.

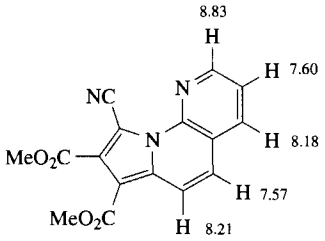
NMR spectra of indolo[2,3-*a*]quinolizidine alkaloids have been investigated more extensively and have been summarized in review papers ⟨75MI 1, 78MI2, 82MI3, 86MI 837-02⟩. ^{1}H NMR has been used as an important tool to establish the stereochemistry of the CD ring fusion in these compounds by



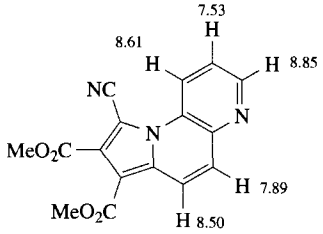
$J_{2,3} = 4.7$, $J_{3,4} = 7.8$, $J_{2,4} = 1.7$
$J_{7,8} = 3.7$, $J_{8,9} = 2.9$, $J_{7,9} = 1.5$



$J_{1,2} = 8.4$, $J_{2,3} = 4.5$, $J_{1,3} = 1.9$, $J_{5,6} = 7.5$

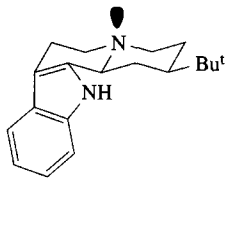


$J_{2,3} = 4.6$, $J_{3,4} = 7.9$, $J_{2,4} = 1.8$, $J_{5,6} = 9.4$

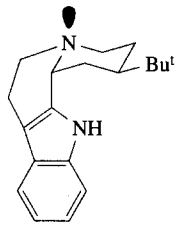


$J_{1,2} = 8.8$, $J_{2,3} = 4.4$, $J_{1,3} = 3.9$, $J_{5,6} = 9.7$

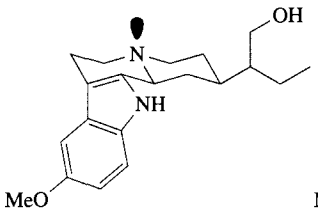
locating the signal for the angular C-12b proton. The C-12b proton absorbs at much lower field when it is gauche with respect to the nitrogen lone pair (i.e. *cis* CD ring fusion) than when it is situated *trans* and axial with respect to an axial nitrogen lone pair (i.e. *trans* CD ring fusion) ⟨61JA4816, 69T5319, 73JOC2831, B-75MI 837-01⟩, for example, compounds (**127**) and (**129**) give a resonance peak of C-12b proton at ca. 3.3 ppm while their cisoid isomers (**128**) and (**130**) show the C-12b proton signal at 4.44 and 4.13 ppm, respectively ⟨69T5319, 73JOC2831⟩.



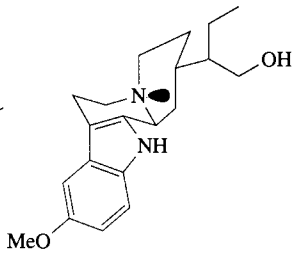
(**127**)



(**128**)



(**129**)



(**130**)

While ^{13}C NMR spectral data of some pyrrolonaphthyridine derivatives was reported in the early 1990s ⟨93H(36)1945, 93H(36)2513⟩, studies of indolo[2,3-*a*]quinolizidine alkaloids using ^{13}C NMR spectroscopy are well documented and reviews containing the ^{13}C NMR spectra data of corynantheine, yohimbine and related alkaloids have been published ⟨74ACR46, B-78MI 837-02, 86MI 837-02⟩. The spectrum of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**131**), the simplest naturally occurring indolo[2,3-*a*]quinolizidine alkaloid ⟨66AJC1951⟩ and a simple model for the general class of corynanthe–yohimbe indole alkaloids, has been investigated in detail using the techniques of carbon deuteration and spin-lattice relaxation times ⟨74ACR46, 75JOC2836, 75JOC3720, 76JA3645⟩. The chemical shifts provide an important basis for the structure elucidation and analysis of indolo[2,3-*a*]quinolizidine alkaloids ⟨74ACR46, B-78MI 837-02⟩. The ^{13}C NMR spectral data in Table 6 show that compounds (**131**) and (**127**) both having a *trans* CD ring fusion give almost identical spectra with the exception of C-2 in (**127**) which experiences an α-effect of the *t*-butyl group of +22.34 ppm (downfield). The *cis*-fused structure (**128**) shows striking chemical shift differences in ^{13}C NMR, however, which has been ascribed to the steric compression and electronic effects ⟨75JOC3720⟩.

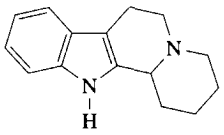
Table 6 ^{13}C NMR Spectral data of indolo[2,3-*a*]quinozidine compounds (131), (127), and (128) in $CDCl_3$ ⟨75JOC3720⟩.

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-6*	*C-7*	*C-7a*	*C-7b*	*C-8*	*C-9*	*C-10*	*C-11*	*C-11a*	*C-12a*	*C-12b*
131	29.96	24.31	25.74	55.75	53.51	21.62	108.11	127.59	118.06	119.31	121.20	110.75	136.08	135.24	60.27
127	31.05	46.65	26.72	56.09	53.11	21.76	108.06	127.58	118.14	119.38	121.27	110.79	136.12	135.29	60.31
128	28.72	41.03	26.42	50.82	45.83	16.78	107.61	127.74	118.07	119.53	121.52	111.09	135.90	132.85	54.30

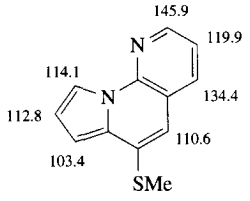
Table 7 UV Spectra of some pyrrolo[2,3-*a*]quinolizinium derivatives (132).

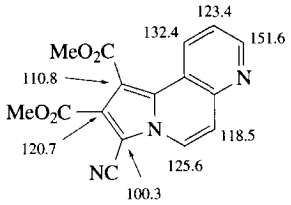
R^1	R^2	R^3	λ_{max} (nm) *(log ε) (neutral)*[a]	λ_{max} (nm) *(log ε) (alkaline)*[b]	*Ref.*
H	H	H	220(4.69), 293(4.19), 343(4.27), 386(4.13)	227(4.42), 241(4.32), 289(4.43), 320(4.09), 349(4.26), 370(4.22), 449 (3.63)	58JCS1750, 58JCS2024
Me	H	H	224(4.52), 248(4.31), 293(4.08), 336(4.27), 399(4.07)	225(4.51), 253(4.33), 330(4.27), 400(4.08)	58JCS2024
H	$(CH_2)_4$		242(4.63), 248(4.65), 297(4.25), 346(4.29), 387(4.28)	245(4.46), 289(4.48), 322(4.15), 360(4.32), 435(3.75)	58JCS2038
Me	$(CH_2)_4$		241(4.56), 250(4.49), 292(4.20), 330(4.28), 395(4.22)		49JA379(B)
H	Me	H	224(4.54)[c], 246.5(4.61), 293(4.09), 342.5(4.33), 384.5(4.24)	228(4.39), 242(4.33), 289.5(4.38), 360(4.34), 460(3.72)	63JCS3440
H	H	Et	238(4.57)[c], 294(4.22), 350(4.31), 389(4.21)	231(4.39), 236(4.38), 289(4.51), 319(4.09), 365(4.36), 450(3.73)	61T5

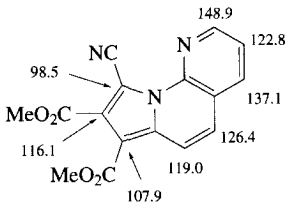
[a] In EtOH. [b] In 0.015N KOH/EtOH. [c] In 0.015% HCl/EtOH.

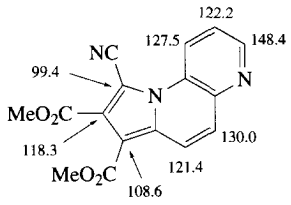


(131)









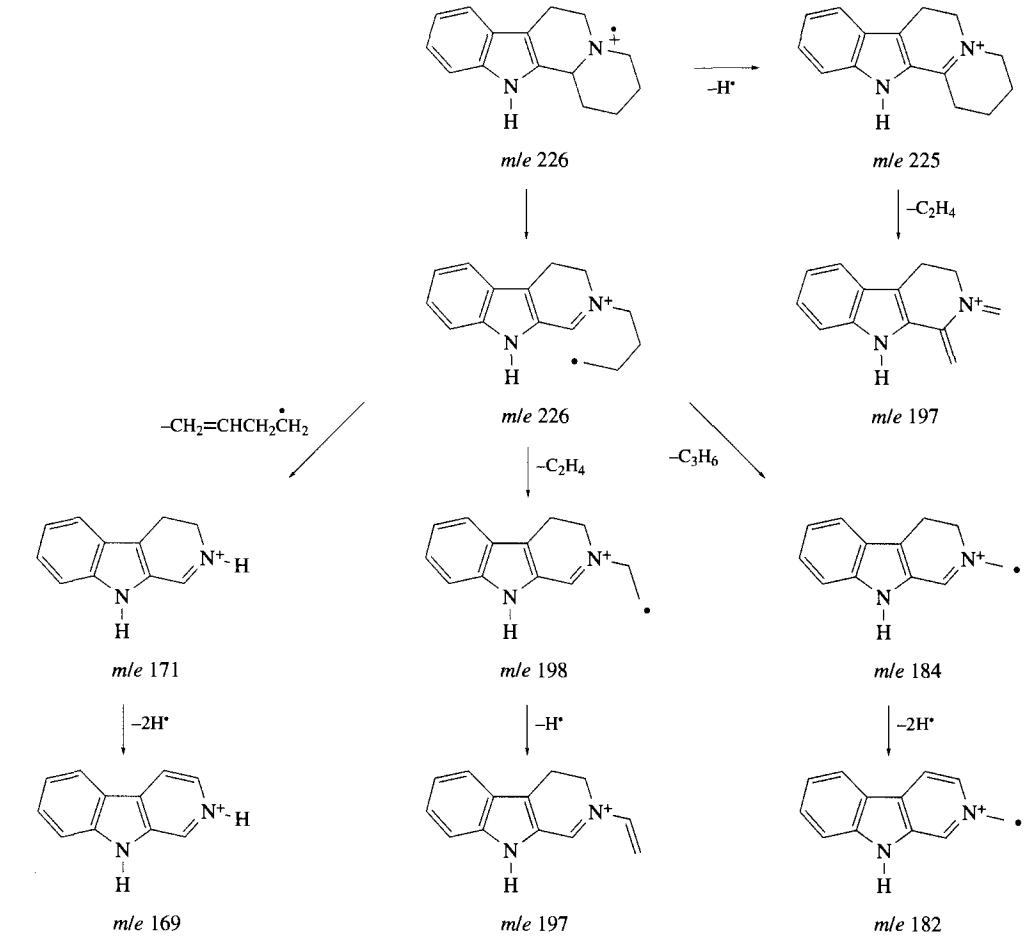
The ^{15}N NMR spectra of indolo[2,3-*a*]quinolizidine alkaloids and model compounds including compounds (**127**) and (**128**) have been recorded and ^{15}N shifts (to high frequency of external anhydrous liquid ammonia) show shielding of the nitrogen in the *cis* C/D compounds, for example ^{15}N resonance peaks of ring junction nitrogen atoms appear at 57.0 and 43.8 ppm for (**127**) and (**128**), respectively. This has been interpreted in terms of a hyperconjugative interaction between the antiperiplanar C—H bonds and the nitrogen lone pair in the *trans*-fused structures that increase the C—N π-bond character resulting in a deshielding of the nitrogen ⟨79JA1549⟩.

8.37.3.2.2 Mass spectrometry

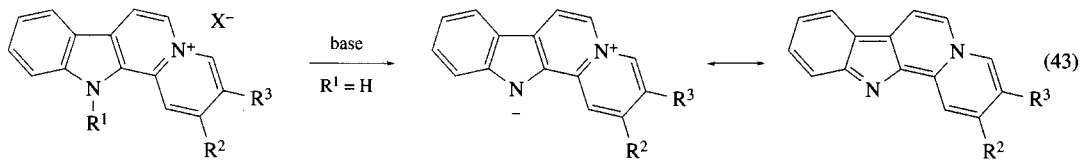
Mass spectroscopy of indolo[2,3-*a*]quinolizidine (**131**) has been studied in detail ⟨62JA2161, 66AJC1951, 74CJC2064, 74JOC1845⟩ and the derivation of the characteristic fragments has been interpreted by Gribble and Nelson who investigated C-3, C-5, C-6, C-20 and C-21 deuterated derivatives of indolo[2,3-*a*]quinolizidine (**131**). Important fragmentation patterns are described in Scheme 14. For results and data gathered on mass spectroscopy of other indolo[2,3-*a*]quinolizidine alkaloids, a review by Hesse ⟨B-74MI 837-01⟩ should be consulted.

8.37.3.2.3 IR and UV spectroscopy

An IR spectroscopic method has been used by Woodward and Witkop ⟨49JA379(A)⟩ to demonstrate the betaine structure of sempervirine (**133** and **134**; R^2, $R^3 = (CH_2)_4$) (Equation (43)). Another important use of IR spectra has been in establishing the stereochemistry of C/D ring fusion of the indolo[2,3-*a*]quinolizidine compounds. Correlation between "Bohlmann bands" and stereochemistry of ring fusion, which proved to be of critical importance in establishing the conformation of the quinolizidine nucleus ⟨71CRV109⟩, has been examined. As for the quinolizidine, indolo[2,3-*a*]quinolizidines with a *trans*-C/D ring fusion such as (**127**) and (**131**) show two characteristic Bohlmann absorption bands in the region of 2810–2700 cm^{-1}, while the cisoid analogues are devoid of absorption in this region ⟨73JOC2831⟩.



Scheme 14



(132) **(133)** **(134)**

UV spectroscopy has been employed extensively to study structural properties of indolo[2,3-*a*]quinolizinium compounds ⟨53JA3361⟩. As can be seen from Table 7, the most striking feature is that the ultraviolet spectra of 12*H*-indolo[2,3-*a*]quinoliziniums (**132**) are pH dependent; thus, under neutral and acidic conditions they give essentially identical spectrum while different spectra are observed with bathochromical shifts of the absorption bands in alkaline solution. The 12-methylated compounds (R^1 = Me) show no such spectral variation in different solutions. The change of UV spectrum from acidic to alkaline solution reflects the formation of zwitterionic species (**133**) or their resonance structures (**134**) from the deprotonation of (**132**). Similar pH dependent UV spectra have been observed for 6,7-dihydroindolo[2,3-*a*]quinolizinium ⟨58JCS1750, 58JCS2038, 61T5, 61T11, 63JCS3440⟩ and for 6,7-dihydro-8*H*-indolo[3,2-*b*]quinolizine ⟨88JCR(S)218, 88JCR(M)1666⟩.

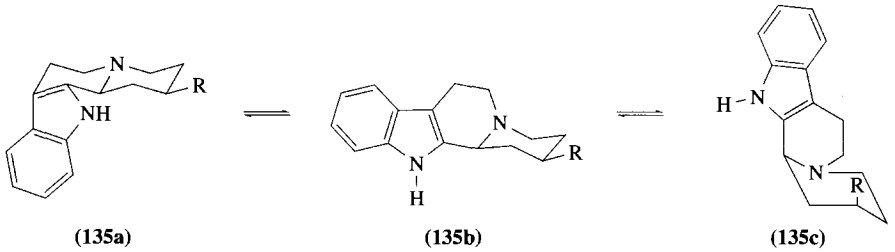
8.37.3.2.4 Dipole moments

The dipole moment of sempervirine (**133**↔**134**, R^2,R^3 = $(CH_2)_4$) in benzene or dioxane is unusually high (7–8 D), indicating the great contribution of zwitterionic structure (**133**) to the actual state of the molecule ⟨49NAT141, 49ACS1447⟩.

8.37.3.3 Thermodynamic Aspects

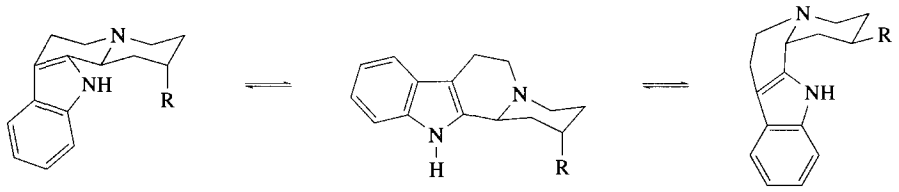
As discussed in previous sections, the indolo[2,3-*a*]quinolizine ring exists in two resonance structures with the great contribution of zwitterionic form, evidenced by the colored nature and the high dipole moments of compounds of this type, as well as by their pH-dependent UV spectra. 6,7-Dihydro analogues, like the parent systems, can also be represented by the two mesomeric forms. Although these compounds are stable, they are readily protonated on the indole nitrogen atom and, in fact, these compounds are normally isolated and purified via their acid salts.

Conformations of indolo[2,3-*a*]quinolizidine compounds have been studied ⟨73JOC2831⟩. Octahydroindolo[2,3-*a*]quinolizine (**131**), the simplest compound of this type, adopts a *trans*-fused ring conformation because, for quinolizidine, the *trans* fusion is 2.6 kcal mol^{-1} more stable than the *cis* fusion ⟨68TL6191, 71CRV109⟩. Substitution of an alkyl group at the 2-position would result in six possible conformations (two configurations), with equilibration by nitrogen inversion and *cis*-decalin ring inversion. Regardless of the size of the R group in the *cis*-2-H,12b-H configuration, conformer (**135a**) with all substituents equatorial on the D ring dominates the equilibrium (Scheme 15). Conformer (**135b**) with an ethyl like-axial substituent on nitrogen may contribute about 5% to equilibrium, while the contribution from conformer (**135c**) with a *cis*-1,3-diaxial interaction between substituents is negligible. Compounds having the *trans*-2-H,12b-H configuration exist as equilibrium mixture of (**136a**) and (**136c**) when R is methyl, ethyl, and phenyl (Scheme 16) ⟨66RTC491, 62JA4914⟩. The *t*-butyl-substituted analogue, in contrast, exists essentially only as the *cis*-fused conformer (**136c**) due to the overwhelming equatorial preference of the *t*-butyl group ⟨73JOC2831⟩.



(135a) (135b) (135c)

Scheme 15



(136a) (136b) (136c)

Scheme 16

8.37.3.4 Reactivity of Fully Conjugated Rings

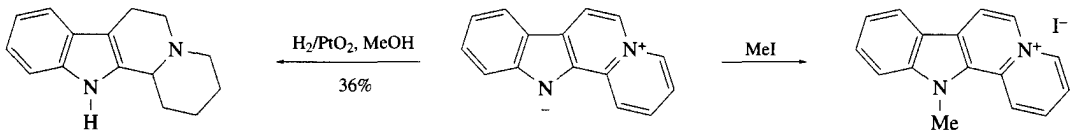
Few reports have appeared in literature on the reactivity of fully conjugated rings.

As can be expected from the structure, indolo[2,3-*a*]quinolizine undergoes alkylation readily on the indole nitrogen; thus, the 12-methylated product (**138**) has been obtained from the reaction of (**137**) with methyl iodide (Scheme 17) ⟨50HCA1463, 58JCS2024, 63JCS3440⟩.

Reduction of the fully conjugated ring system by catalytic hydrogenation affords the partially conjugated ring compound (**131**) ⟨52BSF1091, 87TL5259⟩.

8.37.3.5 Reactivity of Partially Conjugated Rings

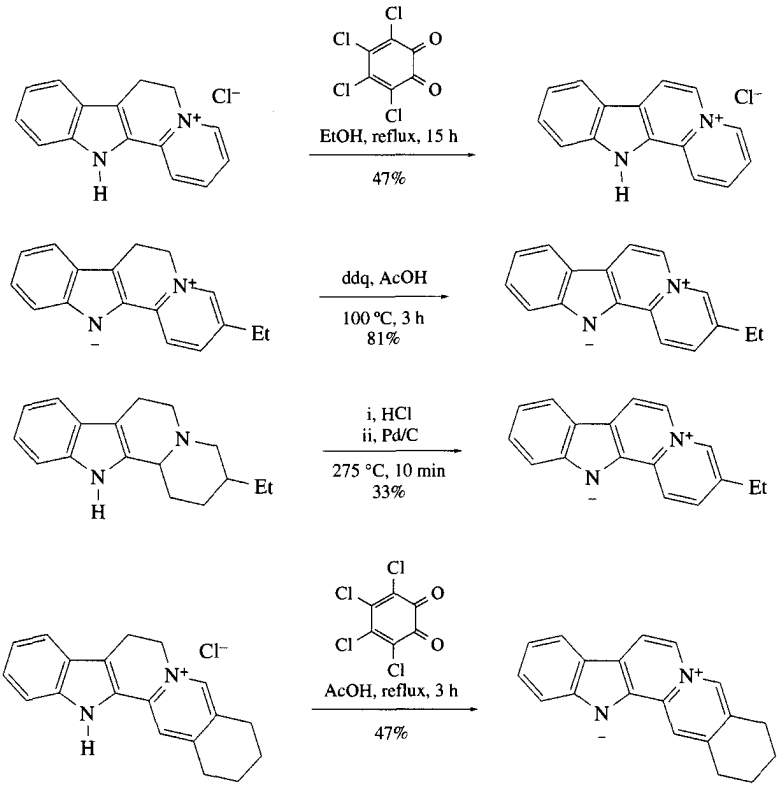
The most important reaction is the aromatization of partially conjugated indolo[2,3-*a*]quinolizine compounds, a very useful synthetic route to the fully conjugated ring system. Catalytic dehydro-



(131) (137) (138)

Scheme 17

genation with palladium leads to the conversion of dihydro, hexahydro, and octahydro derivatives into the parent indolo[2,3-*a*]quinolizine, albeit in less than satisfactory yields in most cases ⟨52HCA867, 54BSF863, 58BSF551, 58JCS1750, 59E127, 63JOC3066, 80CC860, 84JCS(P1)2035⟩. An efficient method has been the oxidative dehydrogenation of 6,7-dihydroindolo[2,3-*a*]quinolizinium using tetrachloro-*o*-benzoquinone ⟨58JCS2024, 58JCS2038, 61T5, 61T11, 62JA3393, 68CPB549⟩ or ddq ⟨80CC860, 84H(22)233⟩. These reactions are summarized in Equations (44) ⟨58JCS2024⟩, (45) ⟨84H(22)233⟩, (46) ⟨62JA4914⟩, and (47) ⟨58JCS2038⟩.



(44)

(45)

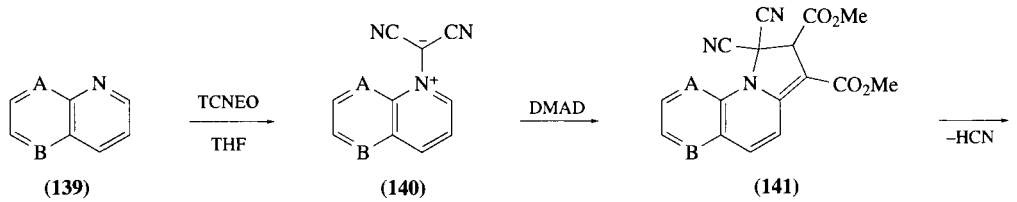
(46)

(47)

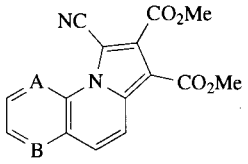
8.37.3.6 Synthesis of Fused Tricyclic Heterocycles with a Junction Nitrogen Atom between Five- and Six-membered Rings

8.37.3.6.1 Annelation with the formation of the five-membered ring

The synthesis of pyrrolonaphthyridine derivatives has been reported from 1,3-dipolar cycloaddition reaction of naphthyridinium dicyanomethylides with DMAD. Starting from [1,5]- and [1,8]-naphthyridines (**139**), dicyanomethylides (**140**) were prepared on treatment with tetracyanoethylene oxide (TCNEO) in THF and they underwent 1,3-cycloaddition with DMAD in acetonitrile to afford aromatic products (**142**) after elimination of HCN from the adducts (**141**) (Scheme 18). Pyrrolo[2,1-*f*]naphthyridine (**143**) was obtained when the *N*-6 dicyanomethylide of [1,6]-naphthyridinium was employed ⟨93H(36)1945⟩.



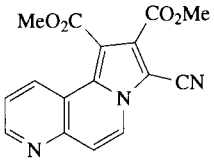
(139) (140) (141)



(142)

A = N, B = CH; A = CH, B = N

Scheme 18



(143)

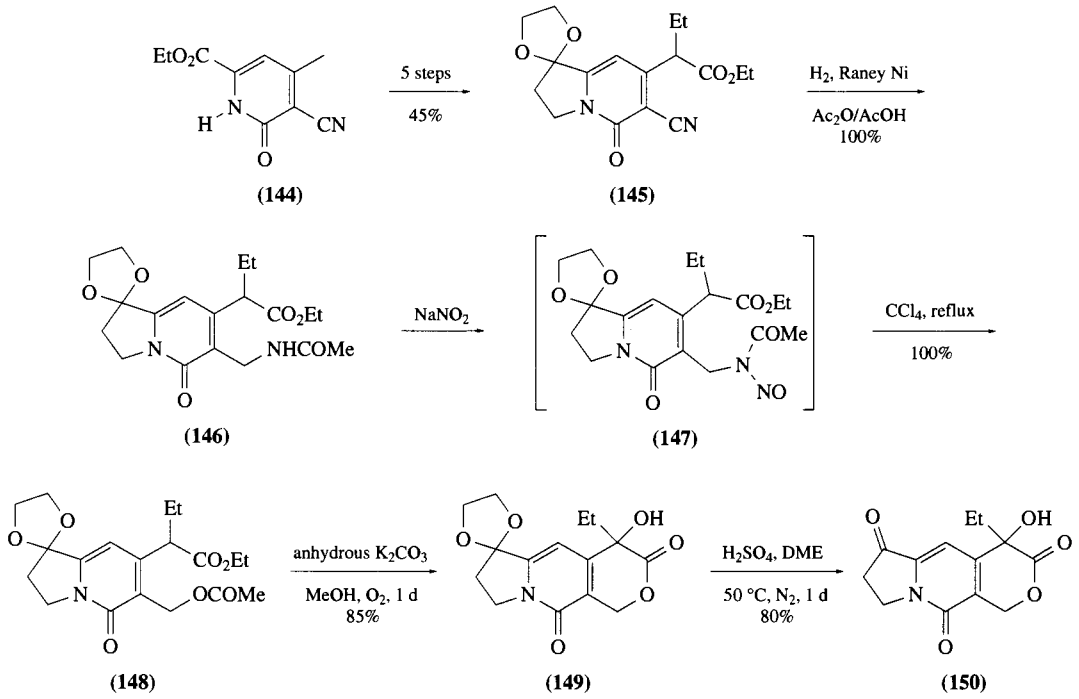
8.37.3.6.2 Annelation with the formation of the terminal six-membered ring

The strategy of forming a terminal six-membered ring has been widely applied in the construction of pyranoindolizines starting from indolizine intermediates. The best example is the synthesis of 4-ethyl-4-hydroxy-1,4,7,8-tetrahydropyrano[3,4-*f*]indolizin-3,6,10-trione (**150**), the most important intermediate for synthesizing camptothecin and its analogues ⟨B-83MI 837-01⟩. Most of the syntheses accomplished involve lactonization as the key step ⟨72JA8613, 74JOC303⟩. An efficient synthetic route, developed initially by Chinese scientists ⟨78MI 837-01, 81ASIN171⟩ and improved by Wall, Wani and their coworkers ⟨80JMC554, 86JMC1553⟩, shown in Scheme 19, starts from pyridone (**144**) and involves the transformation of (**145**) into (**148**). Simultaneous ring closure and oxygenation afforded, in good yield, tricyclic ketal (**149**) which is converted into (**150**) upon hydrolysis. Resolution of *R* and *S* enantiomers of (**150**) has been achieved by reacting it with (*R*)-(+)-α-methylbenzylamine, and the diastereomeric amide pair formed was well resolved by normal-phase high-pressure liquid chromatography and separated on a preparative scale ⟨87JMC2317, 89CPB3382⟩.

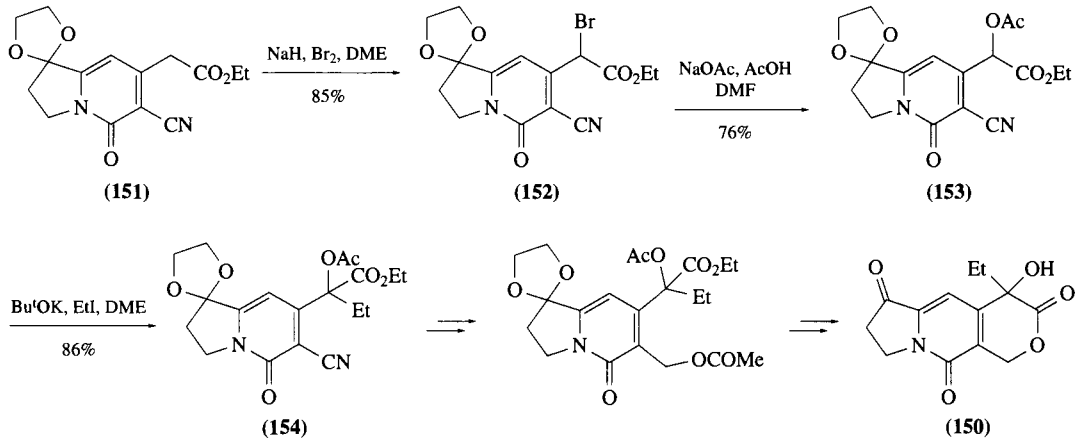
An alternative route to (**150**) has been reported to proceed through bromination of ester (**151**) to give (**152**), followed by the substitution with sodium acetate giving (**153**) and alkylation to give (**154**) as shown in Scheme 20. Compound (**150**) was obtained from (**154**) using the same reaction sequences as described in Scheme 19 ⟨90JCS(P1)27, 92CPB683⟩. When a chiral auxiliary such as *N*-tosyl-(*R*)-proline was used as a stereocontrolling unit, asymmetric synthesis of the *S*-enantiomer of (**150**) was accomplished through the diastereoselective ethylation ⟨89TL2639, 90JCS(P1)27⟩.

Other synthetic approaches to intermediate (**150**) have been attempted by forming the pyran ring ⟨73T1949, 74JOC3430⟩. Scheme 21 demonstrates an efficient and direct method, developed by Danishefsky and coworkers ⟨74JOC3430, 93JOC611, 94JOC7033⟩, for the preparation of tricyclic compound (**156**). Thus, "lactomethylation" of ester intermediate (**155**), prepared easily from the enamine in two steps, with paraformaldehyde in the presence of concentrated sulfuric acid, affords (**156**) in excellent yield.

The synthesis of the pyrano[3,2-*f*]indolizine ring system was exemplified by the reductive cyclization of enamine (**157**) (Scheme 22) ⟨94TL8617⟩. Condensation between 7-hydroxyindolizin-5-one (**159**; R^1 = H) with reactive malonates (**160**) (Scheme 23) at elevated temperature led to the formation of (**161**) (R^2 = H, R^3 = Bz, 65%; R^2 = H, R^3 = Ph, 72%; R^2 = CO_2Me, R^3 = Ph, 90%). When the 6-position of (**159**) was blocked with a substituent (R^1 = Ph, Bz), a different annelation pattern took place, giving the angular tricyclic compound (**162**) (R^1 = Bz, R^3 = Ph, 78%; R^1 = Ph, R^3 = Bz, 67%) ⟨87EJM505⟩.



Scheme 19

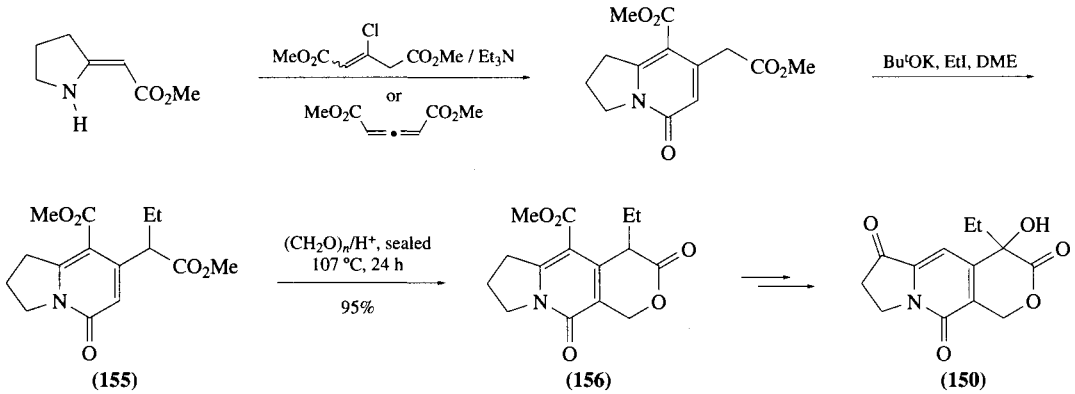


Scheme 20

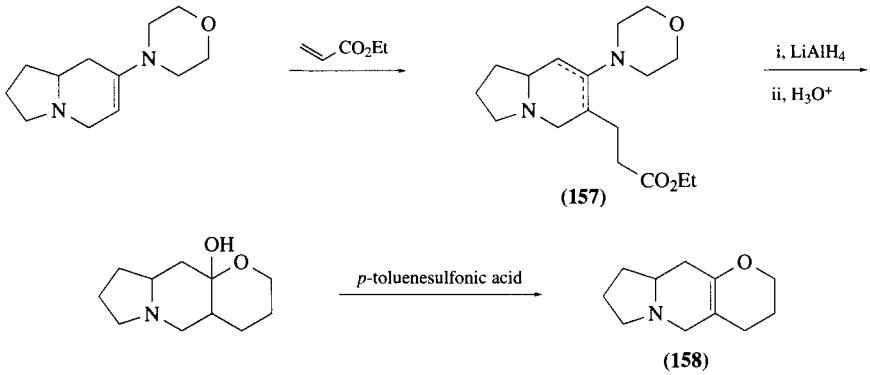
8.37.3.6.3 Annelation with the formation of the middle ring

Most of the pyrrolonaphthyridines have been obtained by this method, for example pyrrolo[1,2-*b*]naphthyridine compound (**164**) was obtained (Scheme 24) in high yield from cyclization of (**163**). Similarly synthesized are pyrrolo[1,2-*g*][1,6]naphthyridin-5,10-dione ⟨94MI 837-02⟩ and indolonaphthyridine derivatives (**165**) ⟨82JOC2810, 83JOC2690, 85JOC5451, 89JOC3264, 92H(34)1613⟩, the latter compounds being used as important intermediates in the synthesis of natural products such as ellipticine and many of its analogues ⟨82JOC2810, 83JOC2690, 83TL3831, 86MI 837-03, 90TL5845, 91T6539⟩. Formation of a C—N bond in the construction of the middle ring moiety has also been reported in the synthesis of indole alkaloid goniomitine ⟨88TL4563, 91CC462⟩ and 5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridine (**168**), a "bridged nicotine" ⟨78JOC2125, 86LS323⟩.

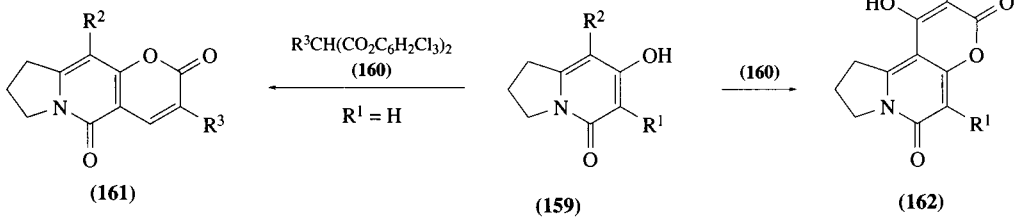
A fully conjugated ring system, pyrrolo[1,2-*a*][1,8]naphthyridine (**170**), has been constructed by refluxing 3-[2-(1-pyrrolyl)pyridyl]acetic acid (**169**) in acetic anhydride (Scheme 25). An alternative



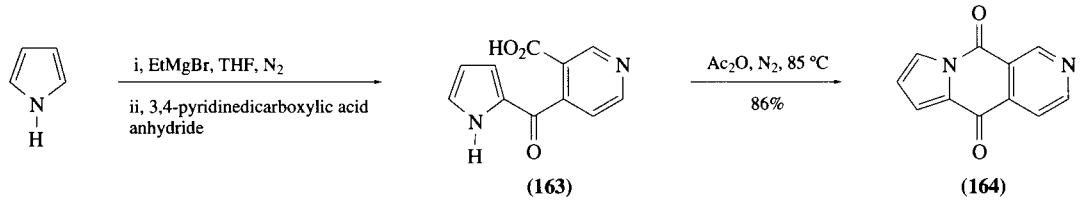
Scheme 21



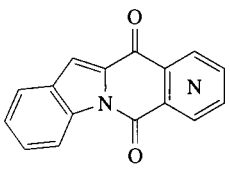
Scheme 22



Scheme 23

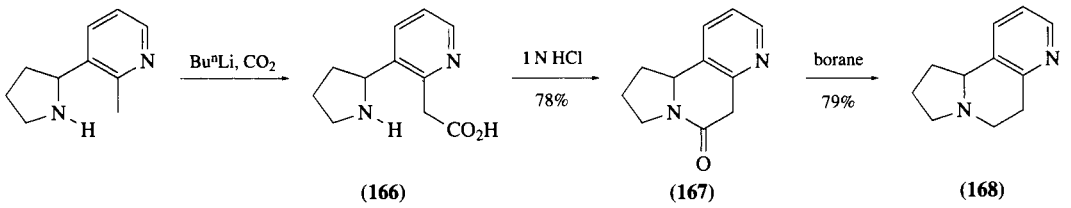


Scheme 24



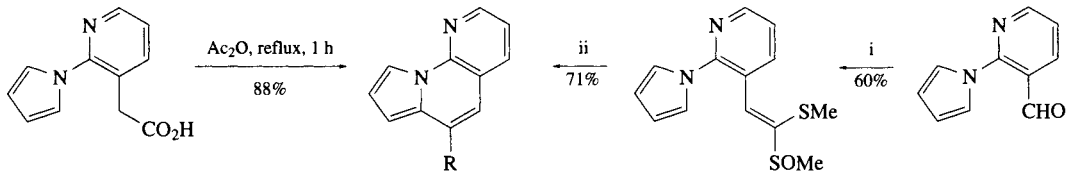
(165)

route from the aldehyde (**171**) gives (**172**) which is cyclized in ethanolic hydrogen chloride, to give the 6-methylthio derivative (**173**) in 71% yield (Scheme 26) ⟨93H(36)2513⟩.



(**166**) (**167**) (**168**)

Scheme 25

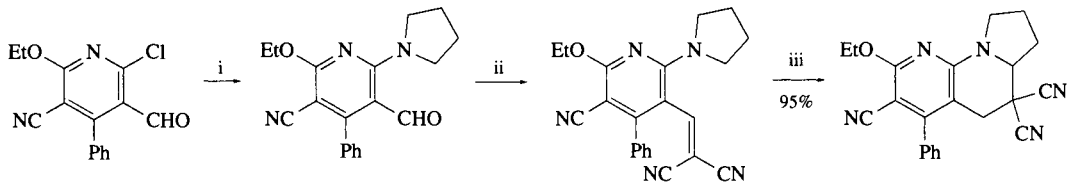


(**169**) (**170**) R = OAc (**173**) R = SMe (**172**) (**171**)

i, $MeOCH_2SMe$, Triton-B, THF; ii, HCl, EtOH

Scheme 26

Among other methods reported ⟨67ACS580, 69T2275, 87CPB142⟩, an efficient route to partially saturated pyrrolonaphthyridine derivatives is from an *o*-chloroformylpyridine as shown in Scheme 27; thus, by heating (**174**) in polar solvents such as pentanol and DMSO, compound (**175**) was formed in almost quantitative yield ⟨92S798⟩. Transformation from (**174**) into (**175**) involves a thermal 1,5-hydrogen shift and consecutive cyclization, a procedure known as the "*tert*-amino effect" ⟨72AHC(14)211, 90RTC311⟩.



(**174**) (**175**)

i, pyrrolidine, Et_3N, THF, reflux; ii, malononitrile, $C_4H_9NH_2$, NH_4OAc, toluene, reflux; iii, DMSO, 140 °C

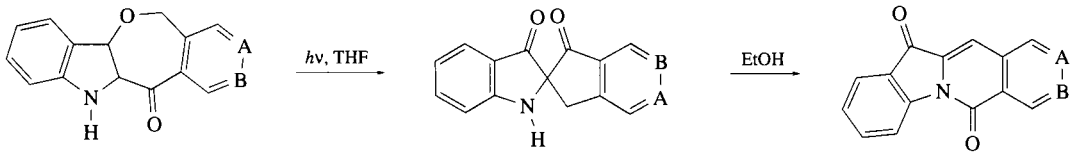
Scheme 27

8.37.3.6.4 Miscellaneous methods

Exposed to the daylight in ethanol solution in air, oxepino[3,2-*b*]indolones (**176**) undergo ring transformation, through the spiro intermediates (**177**), to produce compounds (**178**) in moderate yield (Scheme 28) ⟨83JCS(P1)2413⟩.

8.37.3.7 Synthesis of Fused Tricyclic Heterocycles with a Junction Nitrogen Atom between the Six-membered Rings

For syntheses in which the newly formed ring is partially saturated, the chemistry involved in aromatization has been described in Section 8.37.3.5.

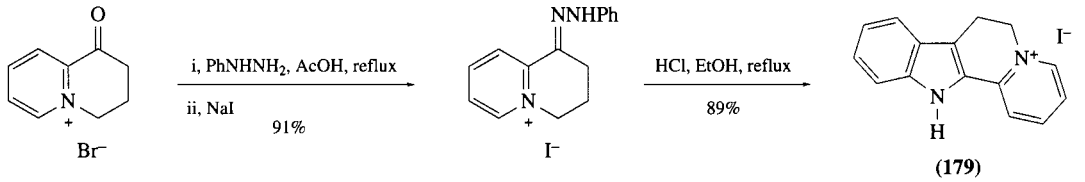


(176) (177) (178)

Scheme 28

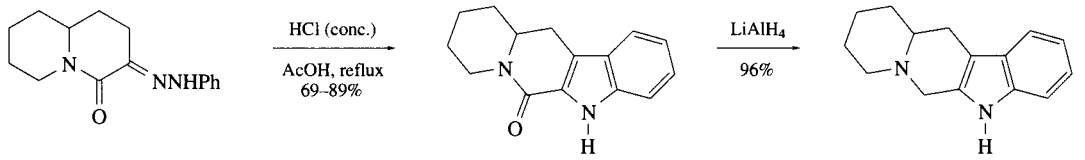
8.37.3.7.1 Annelation with the formation of the five-membered ring

The Fischer indole synthesis offers a straightforward approach to construct the indolo[2,3-*a*]quinolizine ring system. This method was popular in 1950s and a number of indolo[2,3-*a*]quinolizidine derivatives were prepared ⟨50MI 837-01, 50JCS1534, 52JA4960, 57JA3770, 58JCS2024, 58JCS2038, 58JOC435, 63JCS3440, 67CPB499, 73IJC621⟩. An example shown in Scheme 29 is the synthesis of 6,7-dihydroindolo[2,3-*a*]quinolizinium salt (**179**) ⟨58JCS1750⟩. Indolization of hydrazone (**180**) led to indolo[3,2-*b*]quinolizidin-6-one (**181**) (Scheme 30) ⟨72CPB1745⟩.



(179)

Scheme 29



(180) (181)

Scheme 30

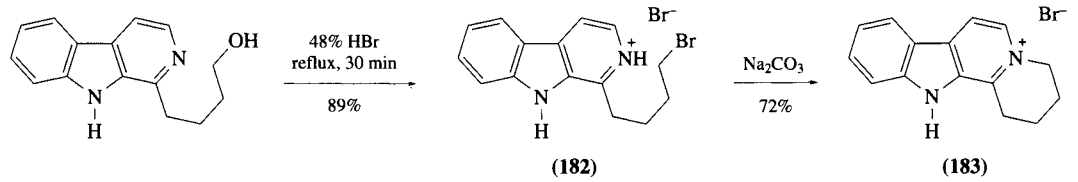
8.37.3.7.2 Annelation with the formation of the terminal six-membered ring

Since a few different preparative methods are available, the discussion of the syntheses will be organized according to the mode of bond formation involved in the construction of the terminal six-membered ring.

(i) Formation of one carbon—heteroatom bond

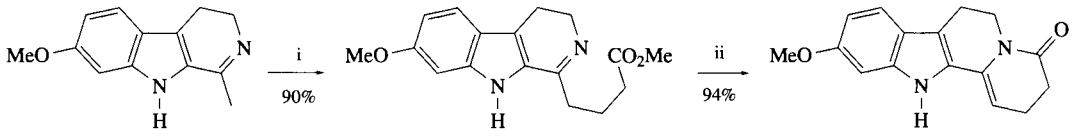
β-Carboline compound (**182**) cyclized smoothly with the action of one equivalent of sodium carbonate to give tetrahydroindolo[2,3-*a*]quinolizinium bromide in 72% yield ⟨52JCS650⟩. Lactam (**185**) was produced in excellent yield from the cyclocondensation of (**184**) ⟨72JCS(P1)731⟩. These

methods have been proved useful for the preparation of other indolo[2,3-*a*]quinolizine derivatives ⟨65RTC1183, 66JHC101, 66RTC744⟩.



(182) (183)

Scheme 31

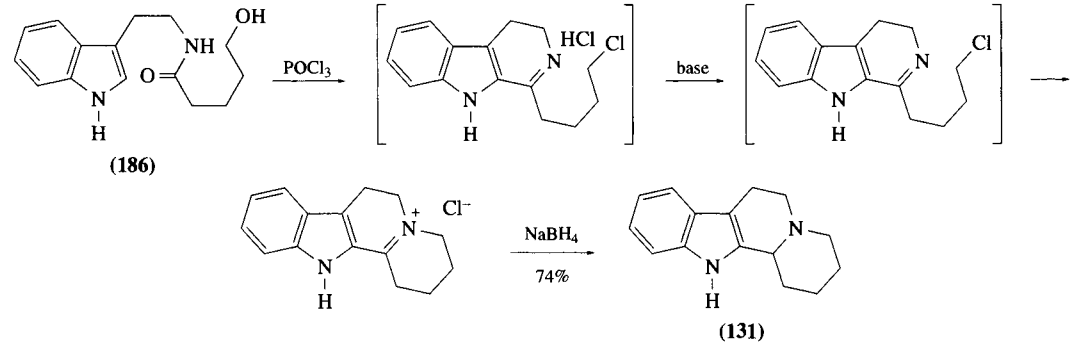


(184) (185)

i, $\diagdown\!\!\diagup$CO₂Me, 25 °C, 72 h; ii, MeOH, reflux

Scheme 32

In some convenient and efficient syntheses reported, annelation of the terminal six-membered ring with the formation of C—N bond was involved ⟨60AC(R)75, 68JHC799, 73OPP55, 84AJC367⟩. One example demonstrated in Scheme 33, is the synthesis of indolo[2,3-*a*]quinolizidine (**131**) which has been obtained in 74% overall yield from amide (**186**) ⟨75CPB304⟩.

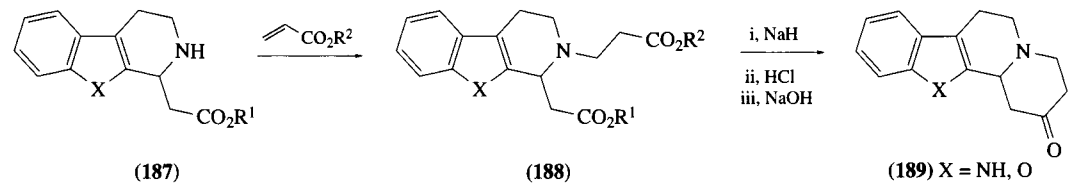


(186) (131)

Scheme 33

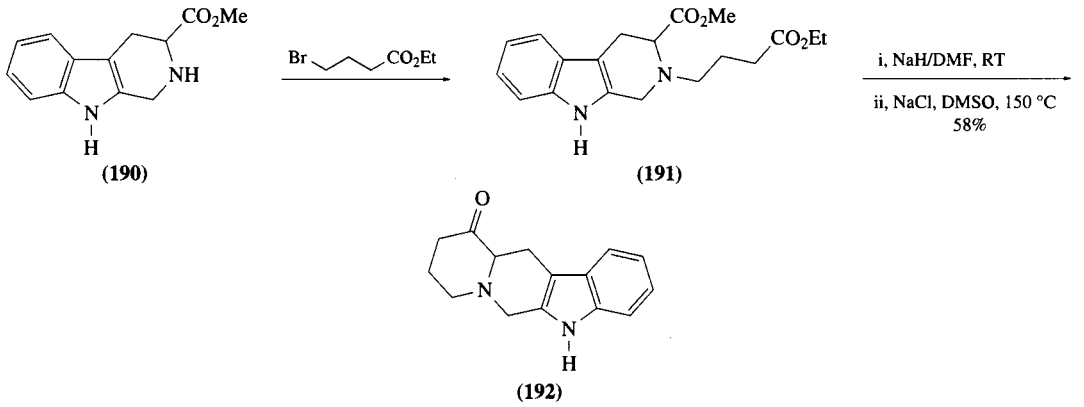
(ii) Formation of one bond γ to the nitrogen

Dieckmann condensation of diesters (**188**), which are derived from tetrahydro-β-carboline and tetrahydrobenzofuro[2,3-*c*]pyridine (**187**; X = NH, O), followed by the hydrolysis and decarboxylation provides another useful route to the condensed ring systems (**189**; X = NH, O) (Schemes 34 and 35) ⟨52JCS650, 58JCS2045, 59JA2251, 72CB2126, 88EUP0251714⟩. A linear tetracycle (**192**) has been obtained analogously from (**191**) ⟨50MI 837-02, 90JHC967⟩.



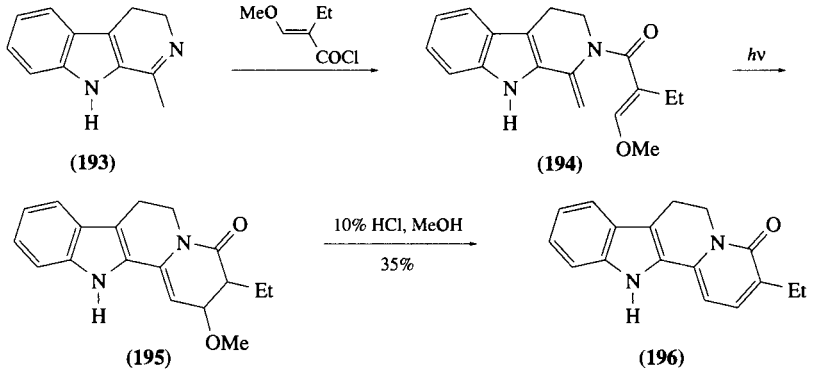
(187) (188) (189) X = NH, O

Scheme 34

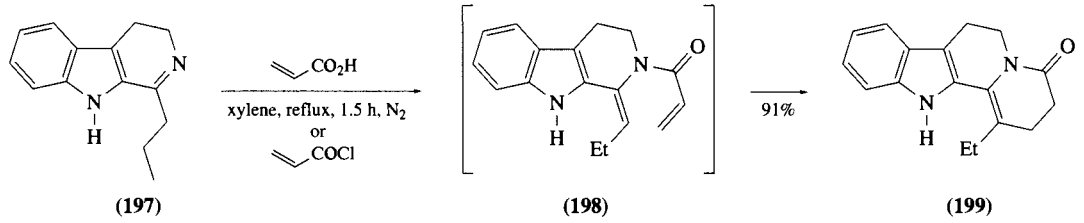


Scheme 35

Another approach to the indolo[2,3-*a*]quinolizine skeleton is the cyclization of enamide intermediates; thus, photocyclization of (**194**) and subsequent elimination of methanol from the cyclized product (**195**) afforded a 35% yield of (**196**) based on harmalane (**193**) ⟨84JCS(P1)2035⟩, and enamide intermediate (**198**) obtained from (**197**) underwent cyclization efficiently in refluxing xylene to give (**199**) in high yield ⟨80CC109⟩.



Scheme 36

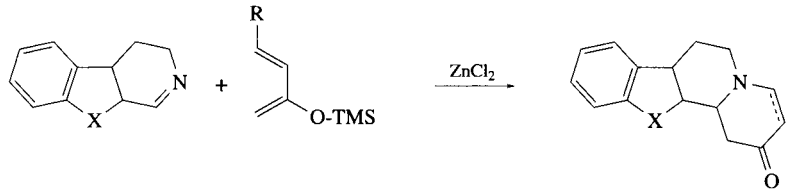


Scheme 37

(iii) Formation of two bonds from [4 + 2] atom fragments

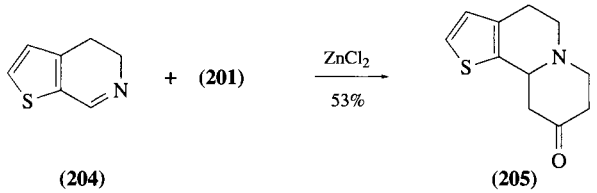
A general and powerful method to synthesize tricyclic heterocycles by constructing the terminal pyridine moiety is the hetero Diels–Alder reaction ⟨79H(12)949, 82T3087, 82TL3739⟩, for example compounds (**200**; X = NH, O, S), underwent zinc chloride-promoted cycloaddition with siloxy dienes (**201**; R = H) and (**202**; R = MeO) in acetonitrile to afford, respectively, the condensed ring products (**189**) (without C(3)=C(4) double bond) and (**203**) (with C(3)=C(4) double bond) in moderate yields (Equation (48)) ⟨85TL1277⟩. 9-Oxothieno[2,3-*a*]quinolizidine (**205**) has been prepared (53%) analogously from 4,5-dihydrothieno[2,3-*c*]pyridine (**204**) (Equation (49)) ⟨88JMC641⟩. The use of a

Lewis acid–proton acid combination such as $BF_3 \cdot OEt_2$–CF_3CO_2H was found to be highly effective for the activation of imines as heterodienophiles in Diels–Alder cycloaddition reactions, and under these conditions compound (**189**; X = O) was obtained in excellent yield ⟨85JMC1756, 87TL2103⟩.



(48)

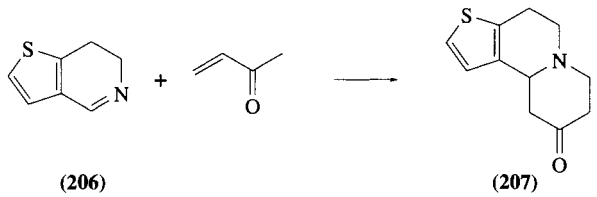
(**200**) (**201**) R = H, (**202**) R = OMe (**189**) without double bond, (**203**) with double bond



(49)

(**204**) (**205**)

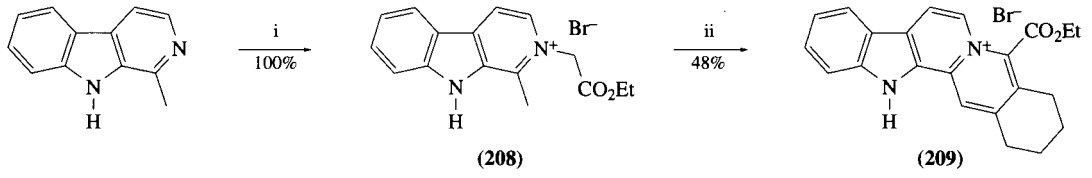
Compounds (**189**; X = O) and (**205**) (86%) have also been prepared by the treatment of (**200**) and (**204**) with methyl vinyl ketone, a convenient alternative synthetic route ⟨63ACH249, 69CB3959, 93PS17⟩. When 6,7-dihydrothieno[3,2-*c*]pyridine (**206**) reacted with methyl vinyl ketone, 9-oxo-thieno[3,2-*a*]quinolizidine (**207**) was formed in 70% yield (Equation (50)) ⟨86BSF(2)303⟩.



(50)

(**206**) (**207**)

In a synthetic study aimed at sempervirine, Potts and Mattingly ⟨68JOC3985⟩ reported a condensation reaction between (**208**) and 1,2-cyclohexanedione which led to pentacyclic ester bromide (**209**) (Scheme 38). Unfortunately, the more direct route to sempervirine involving condensation of harman methiodide with 1,2-cyclohexanedione failed.



(**208**) (**209**)

i, EtO_2CCH_2Br, PhH, reflux, 72 h; ii, cyclohexanedione, $Bu^n{}_2NH$, EtOH, reflux, 2 h

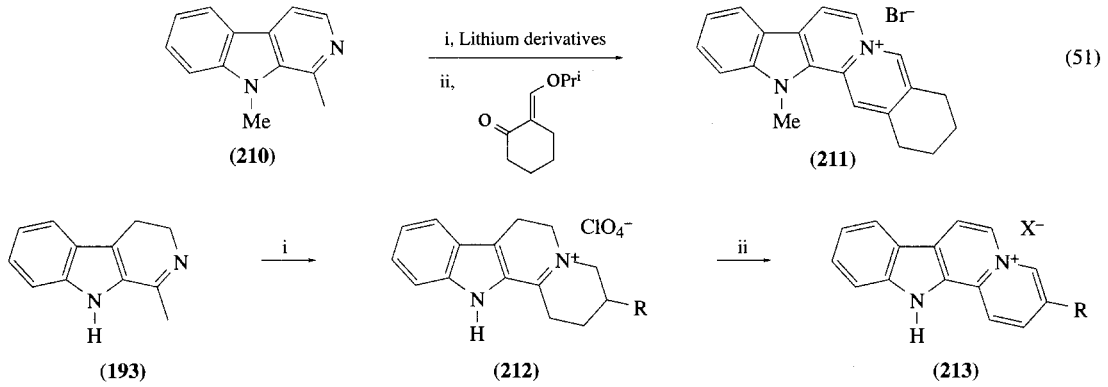
Scheme 38

(iv) Formation of two bonds from [3 + 3] atom fragments

Simultaneously with the publication of the structure of sempervirine ⟨49JA379(A)⟩, Woodward and McLamore ⟨49JA379(B)⟩ announced the synthesis of the *N*-methyl derivative of this alkaloid starting from *N*-methylharmane. Thus, the lithium derivative of *N*-methylharmane was condensed with isopropoxymethylene cyclohexanone leading to the smooth synthesis of methylsempervirinium salt (**211**). The same reaction procedures have been used for the synthesis of sempervirine ⟨53JA3361⟩ and 11-methoxysempervirine ⟨55JA5725⟩.

Another well-known method is to utilize harmalane (**193**) as a three-atom fragment. Due to its

1,3-bisnucleophilicity, harmalane reacts readily with 1,3-biselectrophiles such as α,β-unsaturated compounds ⟨72JCS(P1)731, 75ZN(B)653, 84H(22)233⟩ and 1,3-dihalo alkanes ⟨80CC860⟩ with the formation of six-membered ring. A very simple and highly efficient synthesis of indolo[2,3-*a*]quinolizine is depicted in Equation (51) and Scheme 39. The synthesis involved one-step formation of the tetracyclic immonium ion salts from condensation between (**193**) and 1,3-dibromopropane derivatives in the presence of $EtNPr^i_2$, followed by a dehydrogenation reaction ⟨80CC860⟩.



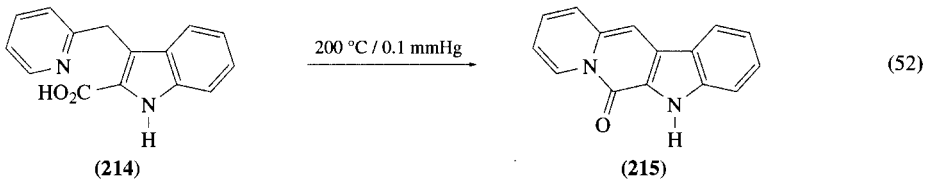
i, $BrCH_2CHRCH_2Br$, $EtNPr_2$, MeCN, reflux; ii, R = Et: Pd/C, 280 °C, 10 min; R = H: (a) Pd/C, (b) ddq

Scheme 39

8.37.3.7.3 Annelation with the formation of the middle ring

(i) Formation of one carbon—heteroatom bond

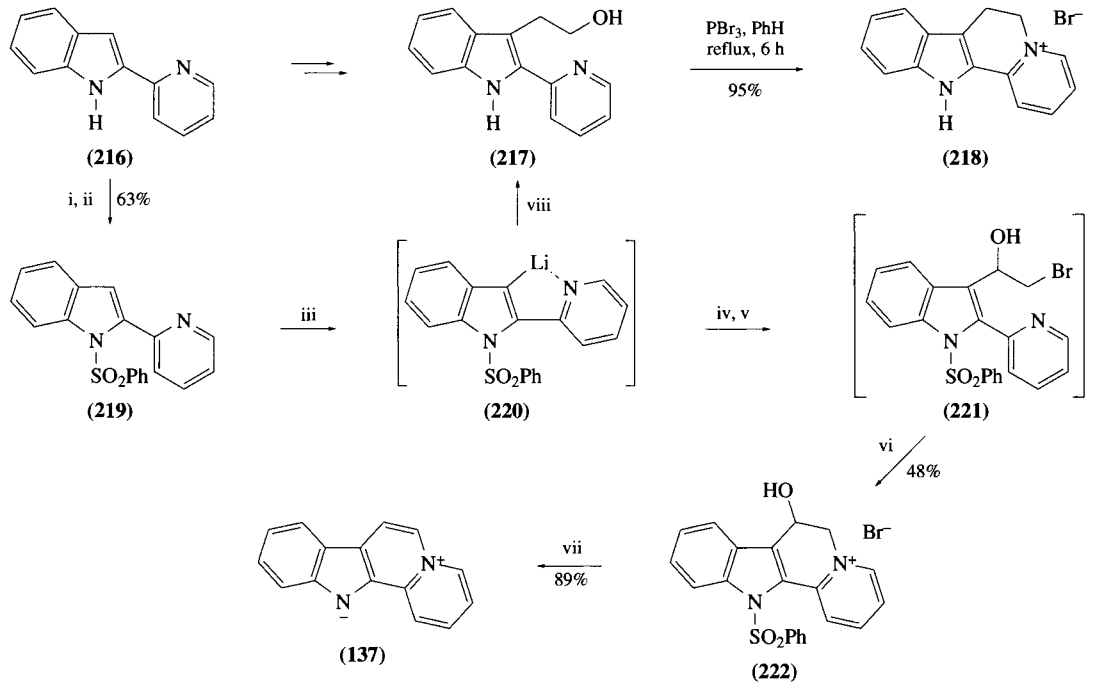
It has been reported that the linear tetracyclic compound (**215**) was obtained by heating 3-(2-pyridylmethyl)indole 2-carboxylic acid, although no yield was given in the paper ⟨54JCS2582⟩.



Cyclization of 3-hydroxymethyl-2-(2-pyridyl)indole (**217**) with the action of PBr_3 afforded dihydroindolo[2,3-*a*]quinolizinium salt (**218**) in high yield. The method, however, suffered from the tedious multistep preparation of the intermediate from 2-(2-pyridyl)indole (**216**) ⟨56CPB16⟩ or from 2-cyanopyridine derivatives ⟨63JCS3440⟩. The problems have been circumvented by Gribble and coworkers ⟨87TL5259, 88T3195⟩ who investigated a directed metalation reaction of *N*-protected 2-(2-pyridyl)indole. Treatment of (**219**) with *n*-butyllithium and quenching the resulting lithio species (**220**) with anhydrous bromoacetaldehyde provided indoloquinolizinium bromide (**222**). Hydrolysis of the *N*-phenylsulfonyl protecting group in (**222**) was accompanied by dehydration to give fully aromatic (**137**) directly (Scheme 40). This methodology has been applied successfully to synthesize other indoloquinolizine alkaloids such as flavopereirine, flavocarpine and sempervirine. It is equally applicable to the synthesis of 6,7-dihydroindoloquinolizine (**218**) when oxirane is employed to react with the lithio species (**220**), giving the alcohol intermediate (**217**) in acceptable yield ⟨87TL5259, 88T3195⟩.

(ii) Formation of one bond between five- and six-membered rings

Synthesis of indolo[2,3-*a*]quinolizine ring system can be carried out by forming the C(12a)—C(12b) bond, and in fact, the availability of tryptamine, tryptophyl halides and the appro-



i, NaH, THF, 0 °C, 1 h; ii, $PhSO_2Cl$, 0 °C, 2 h; iii, Bu^nLi, THF, −78 °C; iv, $BrCH_2CHO$, THF; v, AcOH; vi, work-up; vii, aq. NaOH, MeOH, reflux, 4 h; viii, oxirane

Scheme 40

priate pyridine derivatives has made this bond-forming strategy the most popular of all. The key point of this methodology is based on an intramolecular electrophilic attack upon the indole nucleus by a suitable immonium moiety.

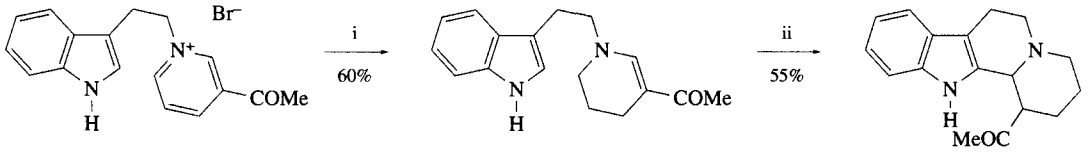
A widely performed procedure involves a partial reduction of pyridinium salts followed by an acid-induced cyclization, known as the "reductive cyclization" approach ⟨59E127, 62JA3732, 63JOC3066, 63TL1645, 64CB2463, 65JA1580, 65JA5461, 67JA6741, 68ACR78, 72JOC1833, 73JOC2831, 73SC241, 78ACS(B)77⟩. As demonstrated in Equation (53) and Schemes 41 to 43, partial reduction of pyridinium salts using $LiAlH_4$/THF, sodium dithionite, or catalytic hydrogenation gave enamine intermediates: Equation (53) ⟨63JOC3066, 73JOC2831⟩; Scheme (41) ⟨65JA1580⟩; Scheme 42 ⟨63TL1645, 78ACS(B)77⟩. Protonation of these enamines generated immonium ions that underwent cyclization to yield indolo[2,3-*a*]quinolizine ring products. The "reductive cyclization" route has been extended to the synthesis of the benzothieno[2,3-*a*]quinolizidine compound (**225**) from salt (**223**) via (**224**) (Scheme 43) ⟨70JCS(C)2269, 80JHC1355⟩.



(53)

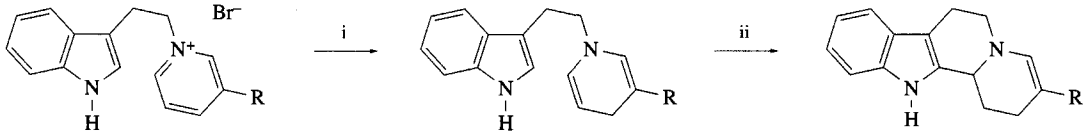
$R^1 = R^2 = H$; $R^1 = Bu^t$, $R^2 = H$; $R^1R^2 = (CH_2)_4$

In contrast to the "reductive cyclization," the indolo[2,3-*a*]quinolizidine structure can also be formed from *N*-β-(3-indolyl)ethylpiperidine derivatives by oxidizing the piperidine moiety to an immonium ion followed by spontaneous cyclization. Unfortunately, chemical yields obtained from this "oxidative cyclization" tactic were extremely low in most cases ⟨62JOC2283, 62JA4914⟩. An alternative was to form the piperidine *N*-oxide and then to cyclize it into indolo[2,3-*a*]quinolizidine using trifluoroacetic anhydride ⟨72CC930⟩ or ferrous sulfate ⟨72JOC1083⟩.



i, H_2, Pd/C, Et_3N, EtOH, 5.5 h; ii, 1 M HCl

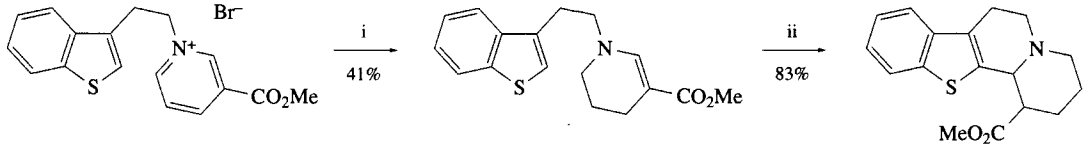
Scheme 41



R = PhCO, CN, COMe

i, sodium dithionite; ii, hydrochloric acid

Scheme 42

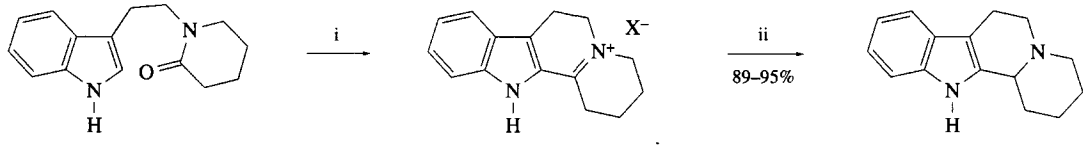


(223) **(224)** **(225)**

i,H_2/Pd, Et_3N, 5.5 h; ii, dry HCl, anhydrous EtOH

Scheme 43

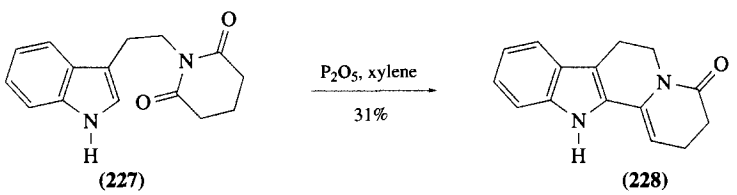
Bischler–Napieralski cyclization, another frequently used preparative method, provides a direct and efficient entry to indolo[2,3-*a*]quinolizidine compounds. For example, indolo[2,3-*a*]quinolizidine (**131**) was synthesized in excellent yield by the cyclization of *N*-(*β*-3-indolylethyl)valerolactam (**226**) with phosphorus oxychloride in refluxing benzene and reduction of the resulting immonium ion with sodium borohydride (Scheme 44) ⟨75CPB304, 77H(7)149⟩. A variety of indolo[2,3-*a*]quinolizidine alkaloids have been synthesized via Bischler–Napieralski cyclization reaction where both indole and lactam moieties of (**226**) are appropriately modified ⟨54JA949, 54JA950, 56JA2023, 57JA495, 57JA6426, 58BSF551, 79JA6404, 83IJC(B)531, 86H(24)1215, 88CPB3348, 89H(29)1037⟩. Cyclization of imide (**227**) did not occur with $POCl_3$, but tetracyclic compound (**228**) was formed in 31% yield when phosphorus pentoxide was used (Equation (54)) ⟨64JOC2771⟩. The indolo[3,2-*a*]quinolizine ring can also be constructed using Bischler–Napieralski cyclization ⟨66RTC744, 88JCR(S)218⟩; thus, treatment of pyridone (**229**) with phosphorus oxychloride led to 6,7-dihydroindolo[3,2-*a*]quinolizine (**230**) in good yield (Equation (55)) ⟨88JCR(M)1666, 88JCR(S)218⟩.



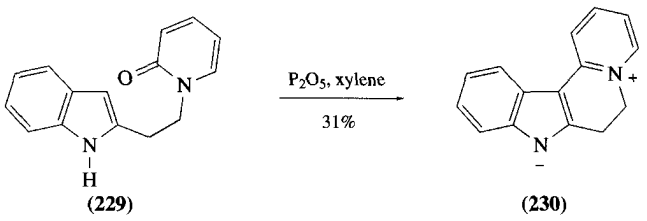
(226) **(131)**

i, $POCl_3$, benzene, reflux; ii, $NaBH_4$, MeOH

Scheme 44

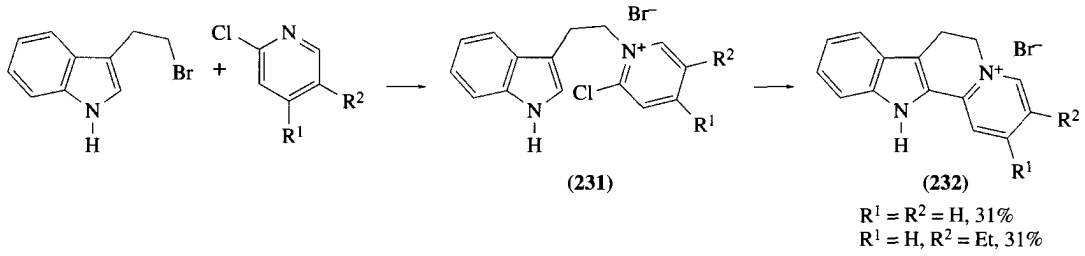


(227) **(228)** (54)



(55)

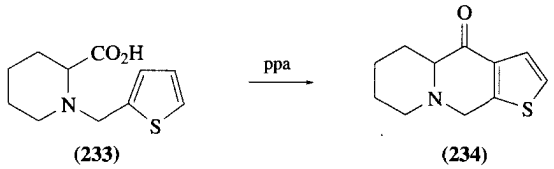
A more straightforward approach to 6,7-dihydroindolo[2,3-*a*]quinolizinium structures has been developed by condensing tryptophyl bromide and 2-halopyridines. Subsequent cyclization of 2-halopyridinium intermediates (**231**) gave the desired polycyclic products (**232**) ($R^1 = R^2 = H$, 31%; $R^1 = H$, $R^2 = Et$, 31%) (Scheme 45) ⟨61T5, 61T11⟩. The same approach was applied to the syntheses of flavocarpine and flavopereirine ⟨62JA3393⟩ and sempervirine ⟨68CPB549⟩.



Scheme 45

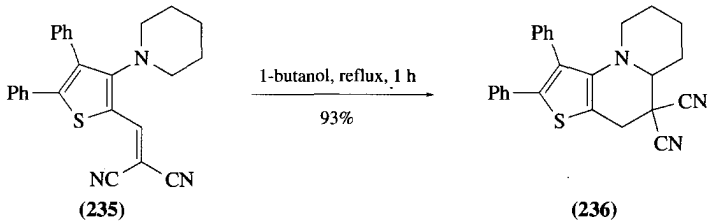
(iii) Formation of other C—C bonds

Cyclization of amino acid (**233**) by ppa furnished the linear tricyclic compound thieno[3,2-*b*]quinolizidinone (**234**) in 51% yield (Equation (56)). Thieno[2,3-*b*]quinolizidinone isomer and its benzenoid analogue are obtained similarly ⟨94JHC495⟩.



(56)

The "*tert*-amino effect" ⟨72AHC(14)211, 90RTC311⟩ provides an efficient method to the fused tricyclic heterocycles (see also Section 8.37.3.6.3), and therefore thermal cyclization of (**235**) led to thieno[2,3-*c*]quinolizidine (**236**) almost quantitatively (Equation (57)) ⟨90RTC481⟩.

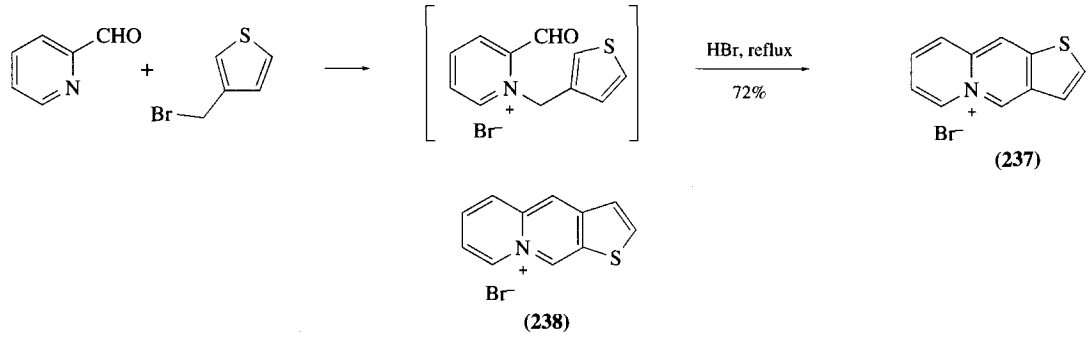


(57)

(iv) Formation of two bonds

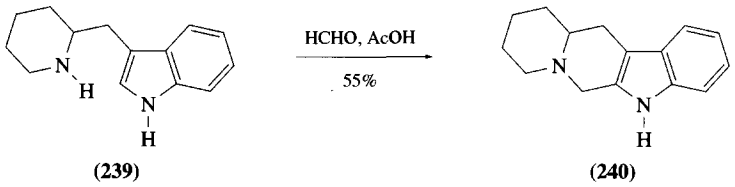
The synthesis of the thieno[2,3-*b*]quinolizinium ion (**237**) was effected in good yield from 2-formylpyridine and 3-thenyl bromide (Scheme 46). The same reaction of 2-thenyl chloride with 2-formylpyridine led to thieno[3,2-*b*]quinolizinium bromide (**238**) but in extremely low yield (4%).

These are the only known examples of parent aromatic heterocyclic systems having a ring junction nitrogen ⟨57JA4380⟩.



Scheme 46

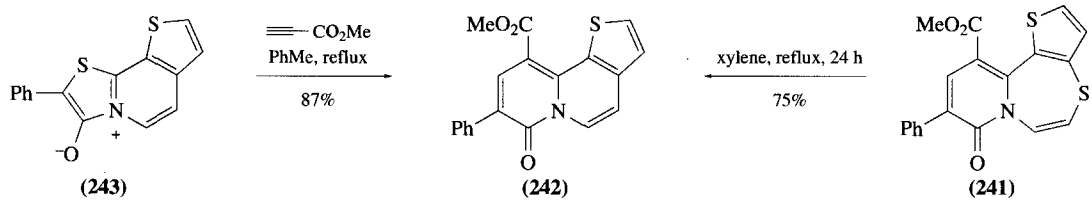
Indolo[3,2-*b*]quinolizidine (**240**) was obtained from the Pictet–Spengler ring closure of (**239**) (Equation (58)) ⟨57JA5686, 72CPB1745⟩. The indolo[2,3-*b*]quinolizidine ring can be prepared analogously ⟨62BRP891157⟩.



(58)

8.37.3.7.4 Miscellaneous methods

Few examples are known of the syntheses of tricyclic ring systems via ring transformations ⟨69T5319, 69T5329, 89SC1071⟩. Heating thiazepine (**241**) in xylene for 24 h led to thieno[2,3-*a*]quinolizine (**242**) in 75% yield (Scheme 47). Compound (**242**) has also been synthesized alternatively from the reaction of the mesoionic triazole derivative (**243**) with methyl propiolate, the reaction proceeding through cycloaddition and sulfur extrusion from the primary adduct ⟨90HCA763⟩.

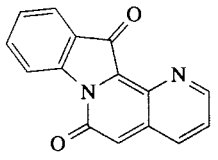


Scheme 47

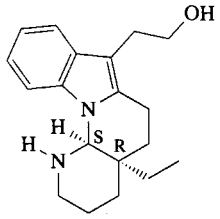
8.37.3.8 Important Compounds and Applications

As we have already shown in the previous sections, indolo[2,3-*a*]quinolizine (**137**) and indolo[2,3-*a*]quinolizidine (**131**) constitute the basic structures of a variety of indole alkaloids, and both are found in alkaloids from *Gonioma kamassi* ⟨65M909⟩ and *Dracontomelum magniferum* B1 ⟨66AJC1951⟩, respectively. Sempervirine, isolated from *Gelsemium sempervirens* ⟨48E24, 49JA379(A), 49NAT141⟩, is an example of a pentacyclic indole alkaloid. For detailed information with regard to the chemistry and physiology of the alkaloids having these structures, reviews appearing in *The Alkaloids* should be consulted ⟨B-52MI 837-01, B-65MI 837-01, B-68MI 837-01, B-86MI 837-02⟩. In addition, indolonaphthyridine structures have also been found in certain natural products, examples being the couroupitine A (**244**) from *Couroupita guianensis* ⟨74TL609⟩ and goniomitine (**245**) from the root bark of *Gonioma*

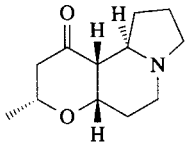
malagasy ⟨87TL2123, 88TL4563, 91CC462⟩. Elaeokanine E (**246**) is a tetrahydropyranoindolizidine alkaloid isolated from *Elaeocarpus kanienesis* ⟨72AJC817⟩.



(244)

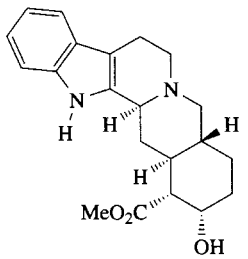


(245)

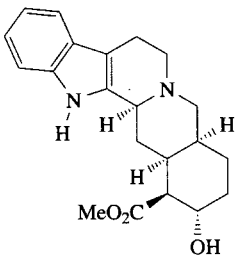


(246)

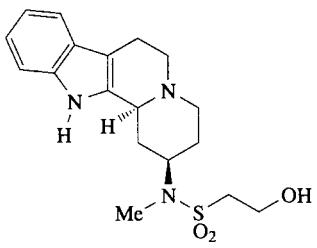
A study by Doxey and co-workers ⟨83BJP155⟩ has revealed that yohimbine (**247**) and rauwolscine (**248**) ⟨B-52MI 837-01, B-65MI 837-01, B-68MI 837-01, 82MI 837-02⟩ show selective antagonist activity against α_2-adrenoceptors in the vas deferens and central nervous system of the rat. Based in part on these and other observations, benzo[*b*]furo[2,3-*a*]quinolizidine compound (**249**) was designed and synthesized ⟨85JMC1756⟩. This substrate has been shown to be a potent and selective α_2-antagonist, with an affinity for the α_2-adrenoceptor greater than yohimbine and rauwolscine, and an α_2/α_1 selectivity greater than yohimbine and approximately the same as rauwolscine ⟨85JMC1756, 86MI 837-04, 88JMC641, 88MI 837-03⟩.



(247) yohimbine



(248) rauwolscine



(249) L-654,284

ACKNOWLEDGMENT

I wish to thank Professor Otto Meth-Cohn for his encouragement and suggestions for preparing the manuscript. Without his help, this chapter would not have been finished.

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8.38
Three Heterocyclic Rings Fused (6 : 5 : 6)

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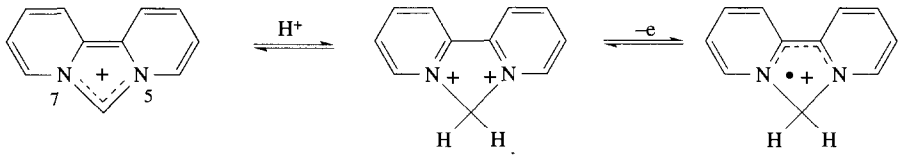
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8.38.1 SURVEY OF FUSED HETEROCYCLIC SYSTEMS (6:5:6) WITH RING JUNCTION HETEROATOMS

This is the first general review of fused systems composed of three heterocyclic rings (6 : 5 : 6) and containing at least one ring junction heteroatom. The reviewed original literature is to December 1994. There are 97 systems (6 : 5 : 6), shown in Table 1, containing one ring junction nitrogen atom. Analogues with one junction heteroatoms other than nitrogen have not been reported. The 21 systems (6 : 5 : 6), shown in Table 2, contain two ring junction nitrogen atoms, ring junction nitrogen and phosphorus atoms, and two ring junction phosphorus atoms. Tables 1 and 2 are organized into divisions according to the increasing number of ring heteroatoms of any kind. In each division the systems with nitrogen atoms are presented first followed by analogues with other heteroatoms in decreasing order of priority of the heteroatoms, for example oxygen then sulfur ⟨B-79MI 838-01⟩. In each particular division the systems are listed in order from the lowest to the highest set of position numbers of the ring heteroatoms in the tricyclic structures. A ring identifier (RID) designated by *Chemical Abstracts* is provided for each system. The first descriptor (1839) identifies the skeleton (6 : 5 : 6), and the next three-digit number describes heteroatoms and their positions in the tricyclic skeleton regardless of substituents and a degree of unsaturation. The ring identifiers are included to help retrieve any additional derivatives that will be known in the future. Finally, names of the parent systems and references to the parent compounds and derivatives are provided in Tables 1 and 2. In summary, these are intended as a quick reference to any of the 118 systems reviewed. It is hoped that this brief survey of ring systems (6 : 5 : 6) will assist the reader in retrieving more specific information presented in the subsequent Sections.

8.38.2 THEORETICAL METHODS

INDO and McLachlan-modified HMO calculations have been conducted to help interpret the electron spin resonance (ESR) spectrum of cation radical (**120**) ⟨78JPC1181⟩ which is generated by protonation of (**98**) in TFA followed by reduction with zinc of the resultant dication (**119**) (Scheme 1) ⟨63TL95⟩. The calculated energy level of the HOMO for (**120**) is of lower energy than that of the isoelectronic fluorene anion radical in both the INDO and HMO approximations. Similar calculations have been conducted to explain the ENDOR spectrum of (**120**) ⟨84CPL398⟩.

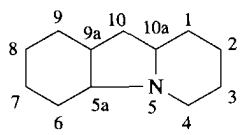


(**98**) (**119**) (**120**)

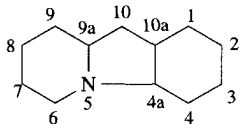
Scheme 1

Theoretical methods have been gaining importance in the analysis of regiochemistry. The approach relies on Hammond's postulate that transition states resemble the corresponding intermediates and, thus, should exhibit the same relative stabilities ⟨55JA334⟩. The selective alkylation of (**121**) at C-7 to give (**122**) has been explained in terms of a lower heat of formation of (**122**) in comparison to that of a C(8)—O-alkylated product, as calculated by an MNDO/2 method ⟨86JMC1099⟩. In a similar way the lowest calculated heat of formation for an adduct of $LiBH_4$ with C(2)=O of (**122**) in comparison to those of other adducts is consistent with the observed selective

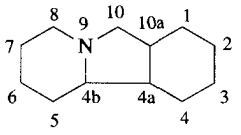
Table 1 Fused heterocyclic ring systems (6 : 5 : 6) with one ring junction nitrogen atom.



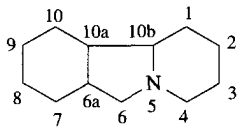
Type A



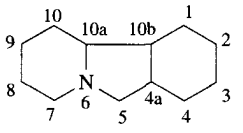
Type B



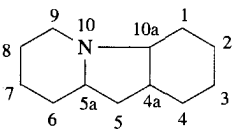
Type C



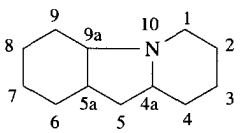
Type D



Type E



Type F



Type G

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(i) Two ring heteroatoms				
(1)	B	N-1, N-5	1839.246	Pyrido[2,3-*b*]indolizine ⟨72JA3649, 78AF1056⟩
(2)	E	N-1, N-6	1839.673	Pyrido[2,3-*a*]indolizine ⟨85JHC817, 90BCJ3047, 94TL5763⟩
(3)	C	N-1, N-9	1839.156	Pyrido[3,2-*a*]indolizine ⟨67BJ(105)663, 80JCR(S)18, 80ZN(B)490, 93ACS191⟩
(4)	F	N-1, N-10	1839.591	Pyrido[3,2-*b*]indolizine ⟨83ZOB422⟩
(5)	E	N-2, N-6	1839.529	Pyrido[3,4-*a*]indolizine ⟨80ZN(B)896⟩
(6)	C	N-2, N-9	1839.880	Pyrido[4,3-*a*]indolizine ⟨90CE665, 92TL7643⟩
(7)	B	O^+-1, N-5	1839.433	Pyrano[2,3-*b*]indolizin-1-ium ⟨74CB929, 76KGS1700, 79CL297, 80BCJ1115, 80JOC5100, 81JAP(K)8130979, 81JAP(K)81120685, 81JAP(K)81139486, 84BCJ548, 93AX(C)1230⟩
(8)	C	O-1, N-9	1839.630	2*H*-Pyrano[3,2-*a*]indolizine ⟨84BCJ548⟩
(9)	B	O-2, N-5	1839.892	1*H*-Pyrano[3,4-*b*]indolizine ⟨93JOC1144⟩
(10)	C	O-2, N-9	1839.153	1*H*-Pyrano[4,3-*a*]indolizine ⟨61JCS3497, 76ACS(B)512, 77JHC273⟩
(11)	C	S-1, N-9	1839.557	2*H*-Thiopyrano[3,2-*a*]indolizine ⟨82JOC369, 83JAP(K)8346091⟩
(ii) Three ring heteroatoms				
(12)	F	N-1, N-2, N-10	1839.313	Pyridazino[4,3-*b*]indolizine ⟨71JCS(C)2756⟩
(13)	B	N-1, N-3, N-5	1839.834	Pyrimido[4,5-*b*]indolizine ⟨90KFZ18, 91KGS852⟩
(14)	C	N-1, N-3, N-9	1839.835	Pyrimido[5,4-*a*]indolizine ⟨90KFZ18⟩
(15)	B	N-1, N-4, N-5	1839.902	Pyrazino[2,3-*b*]indolizine ⟨92KGS107⟩
(16)	D	N-1, N-5, N-7	1839.166	Pyrido[3′,2′: 3,4]pyrrolo[1,2-*a*]pyrimidine ⟨65BEP659530, 67USP3311629⟩
(17)	B	N-1, N-5, N-10	1839.262	Dipyrido[1,2-*a*: 2′,3′-*d*]imidazole ⟨83PJC1021, 90ZOR1141, 91AP(324)121, 91URP1641821, 91ZOR201, 91ZOR638, 92ZOB1903, 92ZOR2165⟩
(18)	F	N-1, N-5, N-10	1839.315	Dipyrido[1,2-*a*: 3′,2′-*d*]imidazole ⟨63JCS1666, 64JAP26731, 65JAP9160, 65NKZ839, 66JCS(C)80, 68T4581, 78CPB2924, 79CPB2532, 81JHC1565, 82CPB3046, 82JA7636, 83MI 838-01, 83TL1523, 84ACR403, 85JHC369, 86B5103, 86JHC425, 90PHA904, 92MI 838-01, 93MI 838-01, 93MI 838-02⟩
(19)	F	N-1, N-8, N-10	1839.359	Pyrido[3′,2′: 4,5]pyrrolo[1,2-*c*]pyrimidine ⟨74CB929, 94T3987, 94T3993⟩
(20)	C	N-1, N-9, N-10	1839.446	Dipyrido[1,2-*b*: 3′,2′-*d*]pyrazole ⟨77JAP(K)7736695, 79CL205, 80JCR(S)18, 87S484⟩
(21)	G	N-1, N-9, N-10	1839.941	Pyrido[3′,2′: 4,5]pyrrolo[1,2-*b*]pyridazine ⟨94JHC1561⟩
(22)	B	N-2, N-3, N-5	1839.245	Pyridazino[4,5-*b*]indolizine ⟨71MI 838-01, 75JCS(P1)1326, 88MI 838-01, 91USP4985560⟩

Table 1 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(23)	E	N-2, N-3, N6	1839.155	Pyridazino[4,5-*a*]indolizine ⟨71MI 838-01, 78JHC1303, 83H(20)1525, 88JHC1793, 92H(34)2239, 93CJC529⟩
(24)	B	N-2, N-5, N-10	1839.252	Dipyrido[1,2-*a*: 3′,4′-*d*]imidazole ⟨63JCS1666, 66JCS80⟩
(25)	F	N-2, N-5, N-10	1839.260	Dipyrido[1,2-*a*: 4′,3′-*d*]imidazole ⟨46JCS588, 92H(34)1491⟩
(26)	B	O-1, N-3, N-5	1839.866	2*H*-1,3-Oxazino[6,5-*b*]indolizine ⟨91BCJ3296, 92JAP(K)92270289⟩
(27)	E	N-1, O-5, N^+-6	1839.589	Isoxazolo[2,3-*a*: 4,5-*b*′]dipyridin-6-ium ⟨83T291, 86MI 838-01⟩
(28)	F	N-1, O-5, N^+-10	1839.568	Oxazolo[3,2-*a*: 4,5-*b*′]dipyridin-10-ium ⟨82H(18)101⟩
(29)	D	O-1, N-5, N-10	1839.852	2*H*-Pyrido[2′,3′: 3,4]pyrrolo[2,1-*b*][1,3]oxazine ⟨91BCJ1901⟩
(30)	C	O-2, N-9, N-10	1839.740	1*H*-Pyrano[3′,4′: 3,4]pyrazolo[1,5-*a*]pyridine ⟨87JAP(K)87267286, 92CPB631⟩
(31)	B	S-1, N-3, N-5	1839.864	2*H*-1,3-Thiazino[6,5-*b*]indolizine ⟨91BCJ3289, 92JAP(K)92270291⟩
(32)	F	N-1, S-5, N^+-10	1839.531	Thiazolo[3,2-*a*: 4,5-*b*′]dipyridin-10-ium 80TL2191, 81JCR(S)107⟩
(33)	B	N-1, N^+-5, S-10	1839.532	Thiazolo[3,2-*a*: 5,4-*b*′]dipyridin-5-ium ⟨80TL2191, 81JCR(S)107⟩
(34)	C	O-1, N-9, O-10	1839.560	2*H*,6*H*-Pyrano[3′,2′: 4,5]isoxazolo [2,3-*a*]pyridine ⟨82JOC230, 83JCS654, 90JCS(P1)2593⟩
(35)	E	O-2, O-5, N-6	1839.907	1*H*,3*H*-Pyrano[3′,4′: 4,5]isoxazolo[2,3-*a*]pyridine ⟨93T3857⟩
(36)	B	O-2, N-5, O-10	1839.671	1*H*,6*H*-Pyrano[4′,3′: 4,5]oxazolo[3,2-*a*]pyridine ⟨85BEP902060, 89USP4826964⟩
(iii) Four ring heteroatoms				
(37)	F	N-1, N-2, N-9, N-10	1839.324	Pyrrolo[1,5-*b*: 2,3-*c*′]dipyridazine ⟨63JCS5660, 66ACS2637, 68ACS1297, 76JHC1009, 88CI(L)109, 88JCS(P1)3097⟩
(38)	F	N-1, N-3, N-5, N-10	1839.317	Pyrido[1,2-*e*]purine ⟨61ZOB1906, 76MI 838-01, 81CB2844, 90JMC2073⟩
(39)	B	N-1, N-3, N-5, N-10	1839.263	Pyrido[2,1-*f*]purine ⟨69GEP1809013, 87KGS1551, 89MI 838-01, 89MI 838-02, 89MI 838-03, 92KFZ63, 92MI 838-02, 94JHC81⟩
(40)	C	N-1, N-3, N-7, N-9	1839.942	Pyrrolo[1,2-*c*: 4,3-*d*′]dipyrimidine ⟨94JHC1707⟩
(41)	C	N-1, N-3, N-9, N-10	1839.474	Pyrido[1′,2′: 1,5]pyrazolo[3,4-*d*]pyrimidine 77CPB2974, 81S910, 84JHC685, 89JCR(S)333⟩
(42)	B	N-1, N-4, N-5, N-8	1839.314	Pyrrolo[1,2-*a*: 4,5-*b*′]dipyrazine ⟨72RTC1175⟩
(43)	F	N-1, N-4, N-5, N-10	1839.322	Pyrido[1′,2′: 1,2]imidazo[4,5-*b*]pyrazine ⟨72CPB1834, 72JAP(K)7220197, 72JAP(K)7220199, 86JAP(K)86204185, 86JHC1419, 86JHC1741⟩
(44)	D	N-1, N-5, N-6, N-7	1839.171	Pyrido[2′,3′: 3,4]pyrazolo[1,5-*a*]pyrimidine ⟨65LA141, 77IJC(B)349, 78JHC1175, 81UKZ1085, 87MI 838-01, 90JCR(S)308, 91CCC1560⟩
(45)	D	N-1, N-5, N-6, N-9	1839.170	Pyrido[4′,3′: 3,4]pyrazolo[1,5-*a*]pyrimidine 59JA2452, 74T2791, 75ZN(B)778⟩
(46)	F	N-1, N-5, N-6, N-10	1839.811	Pyrido[3′,2′: 4,5]imidazo[1,2-*a*]pyrimidine ⟨90H(31)259⟩
(47)	B	N-1, N-5, N-9, N-10	1839.810	Pyrido[2′,3′: 4,5]imidazo[1,2-*a*]pyrimidine ⟨90H(31)259⟩
(48)	E	N-2, N-3, N-5, N-6	1839.503	Pyrido[1′,2′: 1,5]pyrazolo[3,4-*d*]pyridazine ⟨80JOC90⟩
(49)	B	N-2, N-3, N-5, N-10	1839.261	Pyrido[1′,2′: 1,2]imidazo[4,5-*d*]pyridazine ⟨68FES1141, 70USP3539582⟩
(50)	F	N-1, N-5, O-7, N-10	1839.316	2*H*-Pyrido[3′,2′: 4,5]imidazo[2,1-*c*][1,4]oxazine ⟨73TL4495, 77MI 838-01⟩
(51)	A	O-2, N-5, N-7, N-10	1839.888	1*H*-Pyrido[4′,3′: 4,5]imidazo[2,1-*c*][1,4]oxazine ⟨92H(34)1491⟩

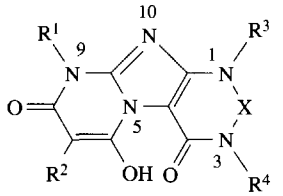
Table 1 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(52)	A	O-2, N-5, N-8, N-10	1839.253	1*H*-Pyrido[3′,4′: 4,5]imidazo[2,1-*c*][1,4]oxazine ⟨63JCS1666⟩
(53)	F	N-1, N-4, S-5, N^+-10	1839.836	Pyrido[2′,1′: 2,3]thiazolo[4,5-*b*]pyrazin-10-ium ⟨90KGS1276⟩
(54)	A	S-1, N-5, N-6, N-10	1839.376	2*H*-Pyrido[3′,2′: 4,5]imidazo[2,1-*b*][1,3]thiazine ⟨75GEP2429290, 76MIP12392, 81JAP(K)81123991⟩
(55)	A	N-1, N-5, N-8, S-10	1839.437	2*H*-Pyrido[4′,3′: 4,5]thiazolo[3,2-*a*]pyrimidine ⟨76IJC(B)759⟩
(56)	A	S-1, N-5, N-9, N-10	1839.558	2*H*-Pyrido[2′,3′: 4,5]imidazo[2,1-*b*][1,3]thiazine ⟨81JAP(K)81123992, 83AP(316)985⟩
(57)	B	N-1, N-5, N-9, S-10	1839.341	6*H*-Pyrido[3′,2′: 4,5]thiazolo[3,2-*a*]pyrimidine ⟨73IJC744, 73JHC769⟩
(58)	F	O-1, O-5, N-6, N-10	1839.325	2*H*,7*H*-Pyrano[2′,3′: 4,5]oxazolo[3,2-*a*]pyrimidine ⟨71JOC4105, 75JOC2372, 78JPR157, 81CJC468, 85CPB3689⟩
(59)	E	S-1, N-4, N-6, S-9	1839.182	2*H*,7*H*-Pyrrolo[2,1-*c*: 3,4-*b*′]bis[1,4]thiazine ⟨61CB442, 63JCS3736, 91MI 838-01⟩
(60)	A	N-1, N-5, S-8, S-10	1839.436	2*H*,7*H*-Thiopyrano[4′,3′: 4,5]thiazolo[3,2-*a*]pyrimidine ⟨76IJC(B)759⟩
(61)	B	O-2, N-5, O-8, O-10	1839.655	1*H*-Pyrano[4′,3′: 4,5]oxazolo[2,3-*c*][1,4]oxazine ⟨85BEP902060, 86JMC1225, 89USP4826964⟩
(*iv*) *Five ring heteroatoms*				
(62)	D	N-1, N-2, N-5, N-6, N-7	1839.450	Pyrido[2′,3′: 3,4]pyrazolo[5,1-*c*][1,2,4]triazine ⟨77H(6)681, 77S556, 78JHC1175, 91G209, 91IJC(B)878, 91MI 838-02, 93CCC1198⟩
(63)	C	N-1, N-2, N-5, N-9, N-10	1839.853	Pyrimido[1′,2′: 1,5]pyrazolo[3,4-*c*]pyridazine ⟨91CCC1560, 91H(32)895⟩
(64)	D	N-1, N-3, N-5, N-6, N-7	1839.554	Pyrido[2′,3′: 3,4]pyrazolo[1,5-*a*]-1,3,5-triazine ⟨81GEP3001498, 90MI 838-01⟩
(65)	B	N-1, N-3, N-5, N-6, N-10	1839.294	Pyridazino[6,1-*f*]purine ⟨69GEP1809013⟩
(66)	A	N-1, N-3, N-5, N-6, N-10	1839.462	Pyrido[3′,2′: 4,5]imidazo[1,2-*a*]-1,3,5-triazine ⟨77ZC262⟩
(67)	F	N-1, N-3, N-5, N-6, N-10	1839.395	Pyrimido[1,2-*e*]purine ⟨75CPB1696, 76JAP(K)7606993, 91CPB270⟩
(68)	F	N-1, N-3, N-5, N-7, N-10	1839.318	Pyrazino[1,2-*e*]purine ⟨67KFZ16, 67URP196876⟩
(69)	B	N-1, N-3, N-5, N-8, N-10	1839.264	Pyrazino[2,1-*f*]purine ⟨60GEP1086707, 69GEP1809013, 94JHC81⟩
(70)	C	N-1, N-3, N-5, N-9, N-10	1839.736	Pyrazolo[1,5-*a*: 3,4-*d*′]dipyrimidine ⟨88JCR(S)46, 89CZ181, 89JCR(S)333, 90JAP(K)90289518, 92MI 838-03⟩
(71)	B	N-1, N-3, N-5, N-9, N-10	1839.265	Pyrimido[2,1-*f*]purine ⟨62MI 838-01, 67RZC907, 68MI 838-01, 72FRP2132582, 73FRP2157726, 73MI 838-01, 75CPB1696, 79S581, 80KPS626, 80MI 838-01, 80MIP358599, 81KGS1102, 84EUP107165, 86AP(319)566, 86H(24)2179, 86JMC1099, 86MI 838-01, 87AP(320)1004, 87PHA371, 88JOC3265, 88UKZ1084, 89AP(322)447, 89JMC1118, 89LA1251, 89MI 838-04, 89S681, 89USP4816458, 90H(31)1549, 91AX(C)1902, 91MI 838-03, 92MI 838-04, 94JHC81⟩
(72)	F	N-1, N-4, N-5, N-6, N-10	1839.677	Pyrazino[2′,3′: 4,5]imidazo[1,2-*a*]pyrimidine ⟨86JMC1099⟩
(73)	F	N-1, N-2, N-4, O-5, N-10	1839.865	7*H*-Pyrido[2′,1′: 2,3]oxazolo[5,4-*e*]-1,2,4-triazine ⟨91MI 838-04⟩
(74)	F	N-1, N-3, N-5, O-6, N-10	1839.609	7*H*-[1,3]Oxazino[3,2-*e*]purine ⟨83CCC1910, 86CCC459⟩
(75)	F	N-1, N-3, N-5, O-7, N-10	1839.319	2*H*-[1,4]Oxazino[4,3-*e*]purine ⟨66KGS192⟩
(76)	B	N-1, N-3, N-5, O-8, N-10	1839.854	1*H*-[1,4]Oxazino[3,4-*f*]purine ⟨91S625⟩
(77)	F	N-1, N-3, N-5, O-8, N-10	1839.759	9*H*-[1,3]Oxazino[3,4-*e*]purine ⟨89MI 838-05⟩
(78)	B	N-1, N-3, N-5, O-9, N-10	1839.267	6*H*-[1,3]Oxazino[2,3-*f*]purine ⟨65MI 838-01, 71AP(304)117, 71MI 838-02, 79BRP2006765, 87AP(320)999⟩
(79)	B	N-1, N-3, N-5, N-9, O-10	1839.546	6*H*-Oxazolo[3,2-*a*: 5,4-*d*′]dipyrimidine, ⟨81MI 838-01⟩

Table 1 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(80)	A	S-1, N-2, N-5, N-6, N-10	1839.737	2*H*-Pyrido[3′,2′: 4,5]imidazo[1,2-*e*]-1,2,5-thiadiazine ⟨87FRP2597478⟩
(81)	A	S-1, N-2, N-5, N-8, N-10	1839.738	2*H*-Pyrido[3′,4′: 4,5]imidazo[1,2-*e*]-1,2,5-thiadiazine ⟨87FRP2597478⟩
(82)	F	N-1, N-3, N-5, S-6, N-10	1839.321	7*H*-[1,3]Thiazino[3,2-*e*]purine ⟨72JOC1464, 75GEP2429290, 81JAP(K)81123991, 88SC1299⟩
(83)	F	N-1, N-3, S-5, N-6, N-10	1839.516	7*H*-Thiazolo[3,2-*a*: 4,5-*d*′]dipyrimidine ⟨79IJC(B)346, 92CCC1565, 92PS(70)67⟩
(84)	F	N-1, N-3, N-5, S-7, N-10	1839.320	2*H*-[1,4]Thiazino[4,3-*e*]purine ⟨68KGS433⟩
(85)	B	N-1, N-3, N-5, S-8, N-10	1839.855	1*H*-[1,4]Thiazino[3,4-*f*]purine ⟨91S625⟩
(86)	A	N-1, N-3, N-5, N-9, S-10	1839.444	2*H*-Pyrido[3′,2′: 4,5]thiazolo[3,2-*a*]-1,3,5-triazine ⟨77MI 838-02⟩
(87)	B	N-1, N-3, N-5, S-9, N-10	1839.269	6*H*-[1,3]Thiazino[2,3-*f*]purine ⟨59JOC1410, 62MI 838-02, 72JOC1464, 75MI 838-01, 79BEP871195, 80FRP2438658, 81JAP(K)81123992, 88SC1299, 90KGS967⟩
(88)	F	N-1, N-4, S-5, N-6, N-10	1839.721	7*H*-Pyrazino[2′,3′: 4,5]thiazolo[3,2-*a*]pyrimidine ⟨87H(26)689⟩
(89)	F	N-1, N-3, O-5, O-6, N-10	1839.423	5a*H*,7*H*-Pyrimido[4′,5′: 4,5]oxazolo[2,3-*b*][1,3]oxazine ⟨76CPB2461⟩
(90)	F	N-1, O-3, S-5, N-6, N-10	1839.889	2*H*,7*H*-Pyrimido[2′,1′: 2,3]thiazolo[4,5-*d*][1,3]oxazine ⟨92CCC1565⟩
(*v*) *Six ring heteroatoms*				
(91)	C	N-1, N-2, N-3, N-5, N-9, N-10	1839.784	Pyrimido[1′,2′: 1,5]pyrazolo[3,4-*d*]-1,2,3-triazine ⟨89CZ181⟩
(92)	D	N-1, N-2, N-5, N-6, N-7, N-8	1839.464	Pyridazino[3′,4′: 3,4]pyrazolo[5,1-*c*]-[1,2,4]triazine ⟨77S556, 81JHC675, 91H(32)901⟩
(93)	D	N-1, N-2, N-5, N-6, N-7, N-9	1839.867	Pyrimido[4′,5′: 3,4]pyrazolo[5,1-*c*]-[1,2,4]triazine ⟨92JCS(P1)239⟩
(94)	A	N-1, N-2, N-5, N-6, N-8, N-10	1839.679	[1,2,4]Triazino[4,3-*e*]purine ⟨85JCS(P1)2347⟩
(95)	A	N-1, N-2, N-5, N-7, N-9, N-10	1839.266	[1,2,4]Triazino[3,4-*f*]purine ⟨56BSF888, 61GEP1119279, 69MI 838-01, 74KGS1696, 74UKZ215, 75MI 838-02, 75MI 838-03, 79ZOB879, 81MI 838-02, 85MI 838-01, 86KFZ187, 88CI(L)785, 91S625⟩
(96)	B	N-1, N-3, N-5, N-6, N-9, N-10	1839.733	[1,2,4]Triazino[3,2-*f*]purine ⟨87CPB4031, 87KGS1398, 88JHC791, 88UKZ531⟩
(97)	A	O-1, N-2, N-5, N-7, N-9, N-10	1839.268	2*H*-1,2,5-Oxadiazino[6,5-*f*]purine ⟨56BSF888⟩

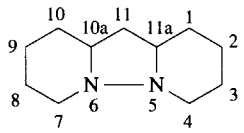
reduction of (**122**) to (**123**) ⟨88JOC3265⟩. A similar analysis has successfully been applied to intermolecular cyclizations leading to systems (6 : 5 : 6) including (**121**) and (**122**) ⟨86JMC1099⟩.



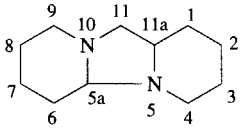
(**121**) R^2 = H, X = CO
(**122**) R^2 = 1°-alkyl, X = CO
(**123**) R^2 = 1°-alkyl, X = CH_2

A more common approach to the analysis of cyclization reactions is by a frontier molecular orbital (FMO) theory which postulates that a preferred transition state involves a low energy-gap interaction between the HOMO and LUMO of the reactants with a favorable charge distribution

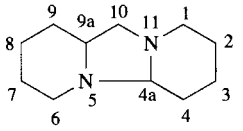
Table 2 Fused heterocyclic systems (6 : 5 : 6) with two ring junction heteroatoms.



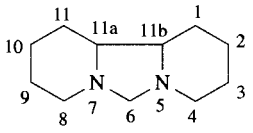
Type H



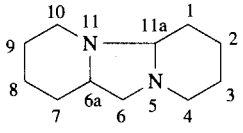
Type I



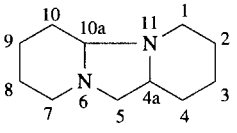
Type J



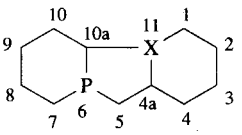
Type K



Type L



Type M



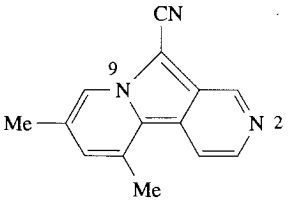
Type N

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(i) Two ring nitrogen atoms				
(98)	K	N^+-5, N-7	1839.190	Dipyrido[1,2-*c*: 2′,1′-*e*]imidazol-5-ium ⟨63TL95, 64JMC644, 65AJC1819, 68AJC1023, 68T4411, 68T6625, 69JC250, 72KGS954, 78HCA1622, 78JPC1181, 84CPL(109)398, 90JCR(S)20, 90MRC1035⟩
(99)	I	N^+5, N-10	1839.326	Dipyrido[1,2-*a*: 1′,2′-*c*]imidazol-5-ium ⟨59JCS2040, 63CPB694, 68TL905, 70ACS397, 76CB3646, 77LA1692, 85JOC4855, 87JCS(P1)2585, 87JOC5046, 89TL5137, 91CC494, 93EUP538837, 93MI 838-03⟩
(ii) Three ring heteroatoms				
(100)	L	N-1, N^+-5, N-11	1839.741	Pyrido[1′,2′: 3,4]imidazo[1,2-*a*]pyrimidin-5-ium ⟨87JCS(P1)2585⟩
(101)	J	N-1, N^+-5, N-11	1839.327	Pyrido[1′,2′: 3,4]imidazo[1,2-*b*]pyridazin-5-ium ⟨71JCS(C)2756⟩
(102)	L	N-2, N^+-5, N-11	1839.743	Pyrido[1′,2′: 3,4]imidazo[1,2-*a*]pyrazin-5-ium ⟨87JCS(P1)2585⟩
(103)	J	N-2, N^+-5, N-11	1839.742	Pyrido[1′,2′: 3,4]imidazo[1,2-*c*]pyrimidin-5-ium ⟨87JCS(P1)2585⟩
(104)	K	O-2, N-5, N-7	1839.613	1*H*,6*H*-Pyrido[1′,2′: 3,4]imidazo[5,1-*c*][1,4]oxazine ⟨83JCS(P1)2857⟩
(105)	N	N-5, P-6, N-11	1839.697	7*H*-Phosphorino[1′,2′: 2,3][1,4,2]diazophospholo[4,5-*a*]pyridine ⟨86PS(28)289⟩
(106)	K	N-5, Si-6, N-7	1839.222	6*H*-[1,3,2]Diazasilolo[1,5-*a*: 3,4-*a*′]dipyridine ⟨73ZOB806, 90JOM47, 92JOM(385)51, 93JOM(454)35⟩
(107)	K	N-5, B-6, N-7	1839.187	6*H*-[1,3,2]Diazoborolo[1,5-*a*: 3,4-*a*′]dipyridine ⟨88T1053, 89H(31)359, 93ZN(B)561⟩
(108)	N	S-5, P-6, P-11	1839.824	1*H*,7*H*-Biphosphorino[1,2-*b*: 1′,2′-*d*][1,2,4]thiadiphosphole ⟨90HAC37⟩
(iii) Four ring heteroatoms				
(109)	H	N-1, N-5, N-6, N-10	1839.398	2*H*-Pyrazolo[1,5-*a*: 2,3-*a*′]dipyrimidine ⟨75HCA1944, 88LA819⟩
(110)	L	N-1, N^+-5, N-6, N-11	1839.328	Pyrido[2′,1′: 3,4][1,2,4]triazolo[1,5-*a*]pyrimidin-5-ium ⟨71KGS1433⟩
(111)	H	N-1, N-5, N-6, N-11	1839.332	2*H*-Pyrido[1′,2′: 2,3][1,2,4]triazolo[1,5-*a*]pyrimidine ⟨72CB794⟩
(112)	K	N-1, N-5, N-7, N-11	1839.774	6*H*-Imidazo[1,5-*a*: 3,4-*a*′]dipyrimidine ⟨89JOC4771, 90JOC3704, 91JOC4308, 92JOC3901⟩
(113)	I	N-1, N^+-5, N-10, N-11	1839.575	Pyrido[1′,2′: 1,5][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ium ⟨82UKZ647⟩
(114)	L	N-1, N^+5-, N-10, N-11	1839.356	Pyrimido[2′,1′: 2,3]imidazo[1,5-*b*]pyridazin-5-ium ⟨74KGS846⟩

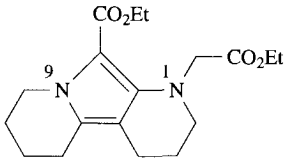
Table 2 (continued).

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Chem. Abstr. ring identifier*	*Name of the parent system and references*
(iv) Five ring heteroatoms				
(115)	L	N-1, N^+-5, N-6, N-7, N-11	1839.329	[1,2,4]Triazolo[1,5-*a*: 4,3-*a'*]dipyrimidin-5-ium ⟨71UKZ1044, 80UKZ835⟩
(116)	M	N-1, N-5, N^+-6, N-10, N-11	1839.369	Pyrimido[1′,2′: 1,5][1,2,4]triazolo[4,3-*b*]pyridazin-6-ium ⟨74KGS843⟩
(v) Six ring heteroatoms				
(117)	I	N-1, N-3, N^+-5, N-6, N-10, N-11	1839.538	Pyrimido[1′,2′: 1,5][1,2,4]triazolo[4,3-*a*]-1,3,5-triazin-5-ium ⟨80UKZ1092⟩
(118)	M	N-1, N-4, N-5, N^+-6, N-10, N-11	1839.343	Pyrimido[1′,2′: 1,5][1,2,4]triazolo[4,3-*b*][1,2,4]triazin-6-ium ⟨73UKZ1040⟩

in the transition state. The exclusive formation of (**124**) by intermolecular cyclization that involves the construction of the central pyrrole ring has been analyzed by using HMO, PM3, MNDO, and STO-3G approximations ⟨92CE665, 92TL7643⟩. The results of AM1 calculations are consistent with a low energy-transition state of an intermolecular cyclization reaction in which the pyrrole ring of (**125**) is formed ⟨93ACS191⟩.



(**124**)



(**125**)

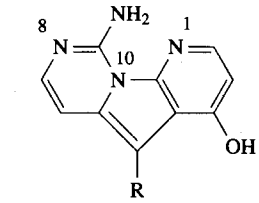
8.38.3 EXPERIMENTAL STRUCTURAL METHODS

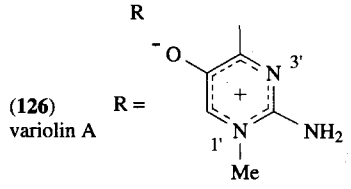
8.38.3.1 X-ray Diffraction

The structures of variolin A (**126**) and variolin B (**127**), the alkaloids isolated from the Antarctic sponge *Kirkpatrickia varialosa*, have been determined ⟨94T3987, 94T3993⟩. Both molecules contain intramolecular hydrogen bonds between C(9)—NH and N-1 and between C(4)—OH and N-3′. The C(5′)—O bond length of 1.345 Å and the N(1′)—Me bond at 1.492 Å in (**126**) are consistent with the unusual zwitterionic character of the pyrimidine substituent.

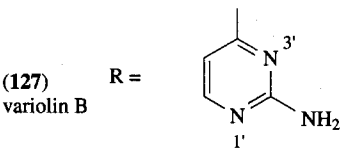
The alkaloid anosmine (**128**) was isolated from the orchids *Dendrobium anosmum* and *Dedrobium parishii* ⟨68TL905⟩. The suggested molecular structure was confirmed by x-ray crystallographic studies ⟨70ACS397⟩. The imidazolium cation and the adjacent atoms C-1, C-4, C-6, and C-9 are all close to a plane. The two six-membered rings of (**128**) are in a twisted-chair conformation.

In many cases, the x-ray diffraction analyses of synthetic products were required because spectral methods and chemical transformations gave ambiguous results. The structures determined include compounds (**122**; $R^2 = H$) ⟨86H(24)2179⟩ and its dihydrodeoxy derivative ⟨91AX(C)1902⟩, two analogues of (**122**) ⟨86JMC1099⟩, (**123**; $R^2 = Pr^n$) ⟨88JOC3265⟩ and a dioxo derivative of the parent system (**71**) of pharmacological interest ⟨86JMC1099⟩, compound (**124**) ⟨92TL7643⟩ and an additional derivative of its parent system (**6**) ⟨92CE665⟩, a betaine (**129**) ⟨81JCR(S)107⟩, a pyranoindolizine (**130**; $R^1 = Ac$, $R^2 = Me$, $R^3 = H$) ⟨93AX(C)1230⟩, thiazino-indolizines (**131**) and (**132**) ⟨91BCJ3289⟩, a diazaborolane (**133**) ⟨93ZN(B)561⟩, and a thiadiphospholane (**134**) ⟨90HAC37⟩. The stable molecule of (**134**) has an unusually long C(10a)—P(11) bond of 1.881 Å. Additional structures solved are

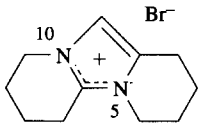




(**126**) variolin A R =

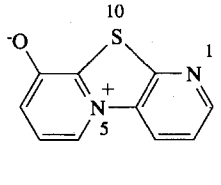


(**127**) variolin B R =

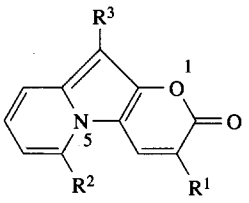


(**128**)

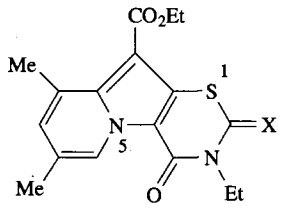
derivatives of the following systems listed in Tables 1 and 2: (**37**) ⟨68ACS1297⟩, (**99**) ⟨87JOC5046⟩, and (**112**) ⟨92JOC3901⟩.



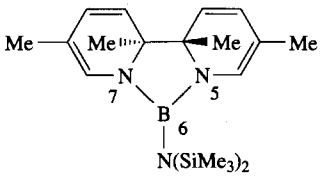
(**129**)



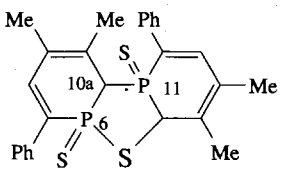
(**130**)



(**131**) X = O
(**132**) X = S



(**133**)



(**134**)

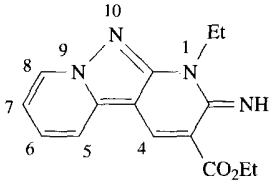
An important conclusion from the analysis of compounds discussed above is that all systems containing ring heteroatoms and sp^2-hybridized ring carbon atoms only are virtually planar. This analysis is valid not only for the cationic system of (**129**) but also for non-cationic systems with ring junction nitrogen atoms and containing additional ring heteroatoms, such as (**121**), (**122**), (**124**), (**126**), (**127**), (**130**), (**131**), and (**132**).

8.38.3.2 Molecular Spectra

In many cases the spectral data of fused ring systems (6 : 5 : 6) shows no unifying features. Detailed analysis of ^{1}H NMR, ^{13}C NMR, IR, electronic absorption and emission, and mass spectra is beyond the scope of this chapter. Original reports collected in Tables 1 and 2 should be consulted for data related to a particular class of compounds. The more general or interesting features are discussed in subsequent sections.

8.38.3.2.1 Proton NMR spectroscopy

The (6 : 5 : 6) systems are analogues of biaryls with a one-atom bridge linking positions α and α' to the torsional bond between the two six-membered subunits. Consequently, two features which are known to cause deshielding of protons adjacent to the torsional bond in biaryls, namely a steric compression effect and a neighboring-ring current effect, are also operative in the ^{1}H NMR spectra of fused aromatic (6 : 5 : 6) derivatives. The spectrum of compound (**135**) is illustrative: δ 8.32 (H-4), δ 7.60 (H-5), δ 7.37 (H-6), δ 6.90 (H-7) and δ 8.41 (H-8) ⟨80JCR(S)18⟩. As can be seen, the chemical shift for H-5 is greater than that for H-7 although the two protons are in the same pyridine ring and positioned similarly with the respect to N-9. It should be noted, however, that these two effects are normally weaker than deshielding of an α-proton by a ring nitrogen atom ⟨92ZOR2165⟩, including a ring junction nitrogen atom, as illustrated by the lowest field chemical shift for H-8.



(**135**)

Chemical shift assignment in the ^{1}H NMR spectra is conveniently aided by the use of lanthanoid shift reagents, provided the electron-rich complexation site of a molecule by the metal ion can be predicted. This technique has been used for a betaine (**129**) and analogues ⟨81JCR(S)107, 82H(18)101⟩.

Coupling constants for protons are similar to those of the corresponding one-ring aromatic derivatives. A low value is generally observed for coupling of protons α and β to a ring heteroatom including ring junction nitrogen atom ⟨71KGS1433, 80TL2191, 81JCR(S)107⟩.

The analysis of coupling constants is a powerful tool for conformational studies of saturated systems. Compounds investigated are derivatives of systems (**35**) ⟨93T3857⟩, (**98**) ⟨68T4411, 68T6625, 90JCR(S)20, 90MRC1035⟩, and (**112**) ⟨91JOC4308, 92JOC3901⟩.

8.38.3.2.2 Carbon-13 NMR spectroscopy

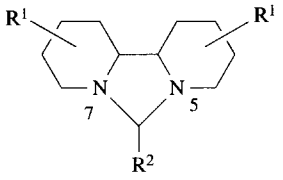
Although ^{13}C NMR is being used routinely for structural determination of derivatives of (6 : 5 : 6) systems, few complete assignments of carbon resonances have been made. The complete assignments in the spectra of the following classes of compounds have been made on the basis of models of structurally related compounds, decoupling experiments, isotopic enrichment, or calculation: (**18**) ⟨83MI 838-01⟩, (**19**) ⟨94T3987, 94T3993⟩, (**23**) ⟨88JHC1793⟩, (**32**) ⟨80TL2191⟩, (**71**) ⟨89LA1251, 94JHC81⟩, (**98**) ⟨90JCR(S)20, 90MRC1035⟩, (**99**) ⟨89TL5137, 91CC494, 93MI 838-03⟩, (**106**) ⟨90JOM(385)47, 93JOM(454)35⟩, and (**112**) ⟨92JOC3901⟩.

8.38.3.2.3 NMR spectroscopy of other elements

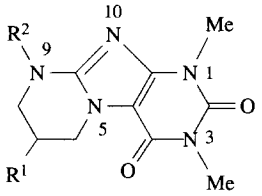
In spite of the large number of known (6 : 5 : 6) systems with ring nitrogen atoms, few reports deal with ^{15}N NMR. Biosynthesis of anosmine (**128**) has been studied by using ^{15}N tracer experiments ⟨91CC494⟩. Several derivatives of a diazaborole (**107**) have been characterized by ^{15}N NMR and ^{11}B NMR ⟨88T1053, 89H(28)359⟩. Silicon-29 NMR spectra of several diazasiloles (**106**) have been reported ⟨90JOM47, 92JOM51⟩.

8.38.3.2.4 IR spectroscopy

The appearance of a set of strong bands in the 2800–2600 cm^{-1} region for quinolizidines in which the lone pair of electrons on nitrogen is *anti* to at least two axial hydrogens on the adjacent carbon atoms is known as the Bohlmann effect ⟨58CB2157⟩. This criterion has been used in the configurational and conformational assignments of perhydrodipyrido[1,2-*c*: 2′,1′-*e*]imidazoles (**136**; R^1, R^2 = H, Me) ⟨68T4411, 68T6625, 90JCR(S)20⟩. The spectra of compounds (**137**; R^1 = H, R^2 = alkyl) have been analyzed in detail ⟨67RZC907⟩.



(136)



(137)

8.38.3.2.5 Electronic absorption and fluorescence spectroscopy

Virtually all fully conjugated ring systems (6 : 5 : 6) show UV absorption above 350 nm ⟨59JCS2040, 63CPB694, 65NKZ839, 81JHC1565, 90KGS1276, 92ZOB1903, 92ZOR2165⟩ and in many instances the absorption of substituted derivatives, such as (**138**) ⟨72JA3649⟩, (**139**) ⟨85JOC4855⟩, and (**140**; R = H, Ph) ⟨88UKZ531⟩ is extended into the visible region. Notably, compound (**141**) has an sp^3-hybridized silicon atom in the ring structure and shows a strong absorption in the visible region ⟨90JOM(385)47⟩.

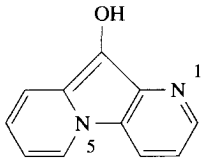
Many dyes are composed of a heterocyclic (6 : 5 : 6) system substituted with a 4-(dimethylamino)styryl group ⟨71UKZ1044, 73UKZ1040, 74KGS843, 76KGS1700, 80UKZ835, 81UKZ1085⟩, as exemplified by (**142**; λ_{max}^{MeOH} = 519 nm, ε = 40 000 $M^{-1}cm^{-1}$) ⟨82UKZ647⟩. The symmetric trimethine dye (**143**) ⟨81UKZ1085⟩ shows the electronic absorption in the near-infrared region (λ_{max}^{EtOH} = 705 nm, ε = 106 000 $M^{-1}cm^{-1}$). Additional examples of similar polymethine dyes are known, albeit their quantitative absorption data has not been reported up to 1995 ⟨65LA(682)141, 71UKZ1044⟩.

Polar compounds of a heterocyclic (6 : 5 : 6) system display a negative solvatochromism, the hypsochromic shift of the absorption maximum in solvents of increased polarity ⟨80UKZ835, 92ZOB1903⟩. This effect is especially large for betaine (**139**) ⟨85JOC4855⟩.

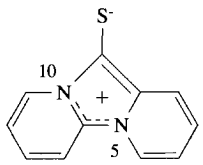
The recent commercial availability of inexpensive laser diodes emitting a single wavelength in the visible and near-infrared regions has stimulated studies of fluorescence of the discussed classes of compounds. A strong fluorescence of pyranoindolizines (**130**; R^1 = CO_2Et, R^2 = H, R^3 = H, Me, Ph) has been noted ⟨80JOC5100⟩. In general, the fluorescence quantum yield increases with an increased rigidity of the molecule, which minimizes a radiationless loss of energy. The Stokes shift also depends on structural features ⟨92ZOB1903, 92ZOR2165⟩ and can be as high as 120 nm for molecules with proton transfer in the excited state ⟨88UKZ531⟩.

8.38.3.2.6 Mass spectrometry

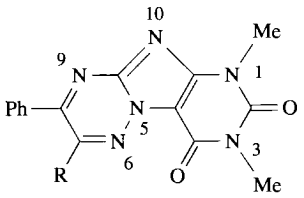
A unifying feature of the fragmentation pattern of pyrimidopurines (**71**) ⟨86MI 838-01, 88UKZ1084⟩ including (**137**; R^1 = OH, R^2 = Ph) ⟨81KGS1102⟩, triazinopurines (**96**) exemplified by (**140**; R = H) ⟨88UKZ531⟩, and thiazinopurines (**87**) such as (**144**; R = H, Me) ⟨90KGS967⟩ is a high stability of the central imidazole ring in the initial fragmentation steps. A similar, albeit tentative, conclusion can be reached from the analysis of mass spectra of dipyridoimidazole (**18**) and a number of substituted derivatives ⟨86JHC425⟩. As expected, the fragmentation of the molecular ion of (**145**) is dominated by successive losses of substituents ⟨81MI 838-01⟩. A major fragmentation pathway of pyridoindolizines (**138**) ⟨72JA3649⟩ and (**146**) ⟨67BJ(105)663⟩ involves expulsion of carbon monoxide.



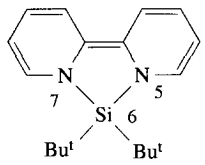
(138)



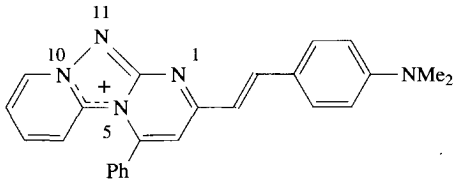
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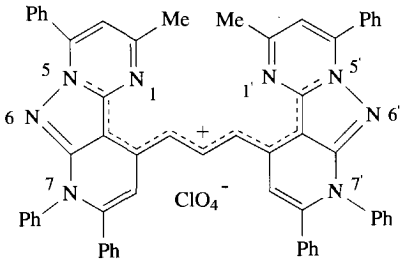
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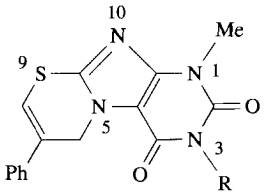
(141)



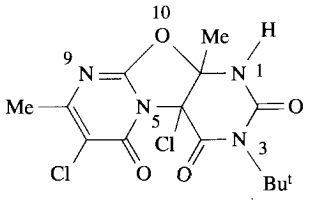
(142)



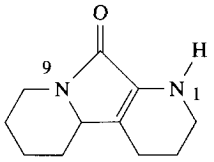
(143)



(144)



(145)



(146)

8.38.4 THERMODYNAMIC ASPECTS

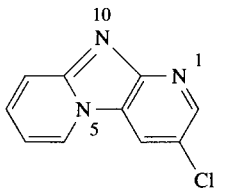
Configurational and conformational studies of hydrogenated derivatives of (**35**), (**98**), and (**112**) by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy have been mentioned in Section 8.38.3. Diastereomers of (**136**; $R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^1 = Me$, $R^2 = H$; $R^1 = H$, $R^2 = 4\text{-}NO_2C_6H_4$) can be separated by preparative gas–liquid chromatography on a Carbowax column and by standard column chromatography on alumina ⟨69JC250, 90MRC1035⟩ or silica gel ⟨90JCR(S)20⟩. Isomers of shortest retention time are those with the nitrogen lone electron pairs on the opposite sides of the molecule and axial substituents ⟨69JC250⟩.

A strong preference of molecules (**121**), (**122**), and (**123**) to exist in an enol form has been explained in terms of an intramolecular hydrogen bonding between C(6)—OH and C(4)=O ⟨88JOC3265⟩. Interestingly, the results of the calculations of heats of formation have suggested that the enol form is more stable than the corresponding keto form, even without taking into account the hydrogen bonding ⟨86JMC1099⟩.

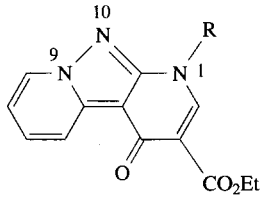
8.38.5 REACTIVITY OF FULLY CONJUGATED RINGS

8.38.5.1 Electrophilic Attack at Nitrogen

Protonation and methylation with methyl iodide of a pyridoindolizine (**138**) takes place at N-1 ⟨72JA3649⟩. Upon titration with acid, compound (**147**) undergoes protonation at N-10 and then at N-1 to form a dication ⟨92ZOR2165⟩. Methylation of (**147**) with methyl iodide produces apparently a mixture of N(1)Me and N(10)Me derivatives in a ratio of 4 : 3. The mixture has not been separated ⟨91ZOR638⟩. By contrast, both methylation and ethylation of a dipyridoimidazole (**148**; R = H) are highly chemoselective yielding the respective product (**148**; R = Me, Et) almost quantitatively ⟨77JAP(K)7717497, 77JAP(K)7736695⟩. (See ⟨89JCR(S)333⟩ for a related alkylation of a derivative of (**70**).)

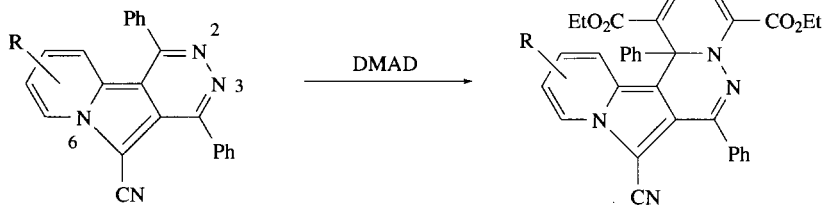


(**147**)



(**148**)

The reaction of pyridazinoindolizines (**149**; R = H, 8-Me, 9-Me, 10-Me, 9-Ph, 9-Bz) with DMAD yields the corresponding 1 : 2 adduct (**150**) the formation of which involves a Michael-type addition ⟨92H(34)2239, 93CJC529⟩, but not a 1,3-dipolar cycloaddition to positions five and seven of (**149**) as erroneously suggested previously (Equation (1)) ⟨83H(20)1525, 88JHC1793⟩. The observed regioselectivity has been explained in terms of a higher nucleophilicity of N-2 than N-3 in (**149**).

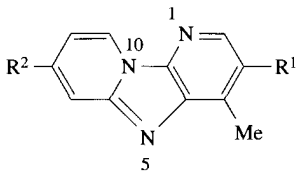


(149) (150) (1)

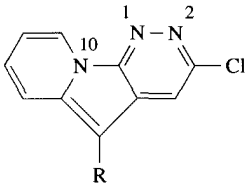
8.38.5.2 Electrophilic Attack at Carbon

The (6 : 5 : 6) systems discussed in this Section are combinations of fully conjugated π-electron excessive and π-electron-deficient heteroaromatic rings. They readily undergo electrophilic substitution reactions, which, as a rule, are highly regioselective.

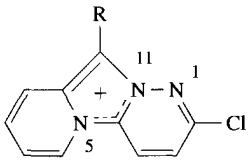
Dipyridoimidazoles (**151**; R^1 = H, R^2 = H, Me) undergo nitration upon treatment with nitric acid to give the corresponding product (**151**; $R^1 = NO_2$) ⟨81JHC1565⟩. Bromination of a pyridazinoindolizine (**152**; R = H) with bromine in pyridine yields (**152**; R = Br) ⟨71JCS(C)2756⟩. The substitution of bromine (R = Br) for hydrogen (R = H) in imidazolium derivatives (**153**) and its 6-Me homologue ⟨71JCS(C)2756⟩ ((**154**) and (**155**): ⟨87JCS(P1)2585⟩) is accomplished by treatment with bromine in acetic acid. In a similar fashion, bromination, acetylation, benzoylation, methylation, and Michael-type addition of nucleophilic cation (**98**) (Table 2) all take place at position 6 ⟨63TL95, 65AJC1819⟩. Proton exchange at position 6 of (**98**) in acidic solution has already been mentioned in Section 8.38.2. A similar exchange for (**156**) at position 10 has been noted ⟨87JCS(P1)2585⟩.



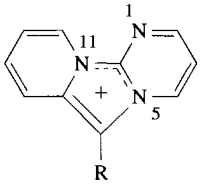
(151)



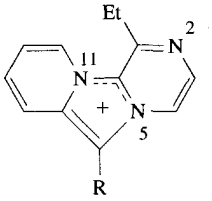
(152)



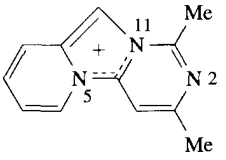
(153)



(154)



(155)



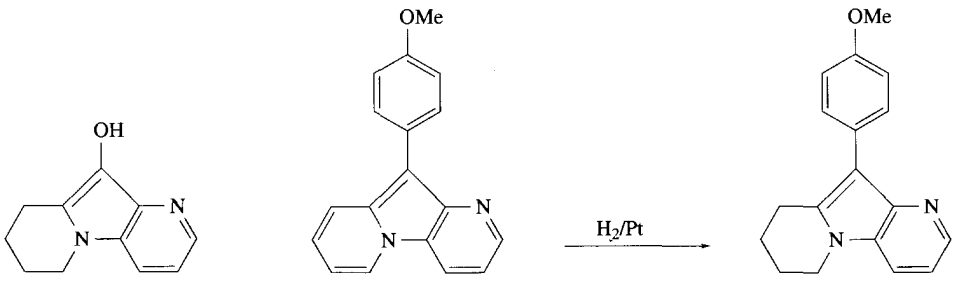
(156)

8.38.5.3 Nucleophilic Attack at Carbon

Two reactions that cause destruction of a parent compound have been reported. The action of hydroxide ion on a dipyridoimidazolium cation (**98**) in the presence of air produces 2,2′-bipyridine ⟨63TL95, 65AJC1819⟩. The hydroxide ion undergoes addition at the position one of the cation (**156**) followed by opening of the pyrimidine ring in the resultant adduct to give 3-[2-(acetamido)propen-1-yl]imidazo[1,5-*a*]pyridine ⟨87JCS(P1)2585⟩.

8.38.5.4 Reduction

A regioselective reduction of a carbonyl group in (**122**) by metal hydrides has been discussed in Section 8.38.2. The high stability of the central imidazole ring toward hydride reduction, as in (**122**), has also been noted for several derivatives of (**96**) ⟨88JHC791⟩. Four reports describe a selective partial hydrogenation of fully conjugated (6 : 5 : 6) systems. The alkaloid anosmine (**128**) has been obtained by hydrogenation of a dipyridoimidazolium bromide (**99**) over a platinum catalyst ⟨68TL905⟩. Only the fused pyridine moiety with a ring junction nitrogen atom is reduced in pyridoindolizines (**138**) ⟨72JA3649⟩ and (**158**) ⟨78AF1056⟩ to give (**157**) and (**159**), respectively, under similar conditions (Equation (2)). A pyridine ring of the system (**44**) is selectively hydrogenated in the presence of a palladium catalyst ⟨78JHC1175⟩.

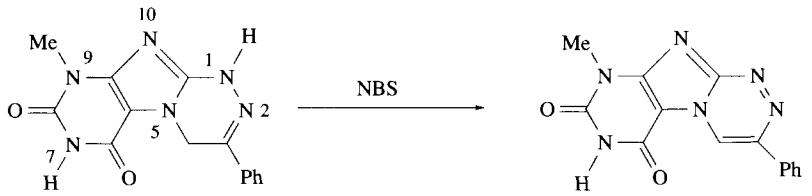


(157) (158) (159) (2)

8.38.6 REACTIVITY OF NONCONJUGATED RINGS

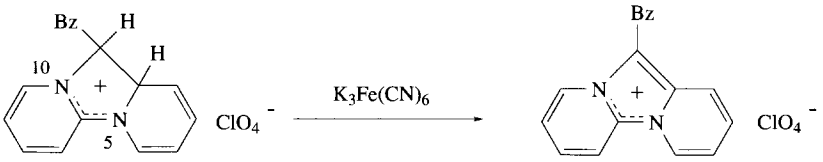
8.38.6.1 Aromatization

Oxidation of two dihydro derivatives, (**160**) ⟨81MI838-02⟩ and (**161**) ⟨77LA1692⟩, have been reported (Equations (3) and (4)).



(3)

(160)

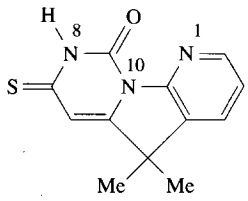


(4)

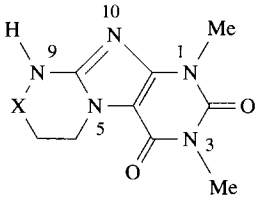
(161)

8.38.6.2 Electrophilic Attack at Nitrogen

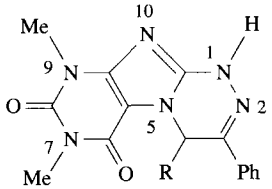
Compound (**162**) is apparently methylated at N-8 upon treatment with diazomethane ⟨74CB929⟩. Acetylation, nitrosation ⟨68MI 838-01⟩, and alkylation ⟨92MI 838-04⟩ of (**163**; X = CH_2), acetylation ⟨86AP(319)566, 87AP(320)1004⟩ of (**163**; X = CHMe), and alkylation ⟨89AP(322)447, 89LA1251, 91MI 838-03⟩ of (**163**; X = CO) all take place at the N-9 atom. Compounds (**164**; R = H) ⟨56BSF888⟩ and (**164**; R = Ph) ⟨69MI 838-01⟩ are acetylated at N-1.



(162)



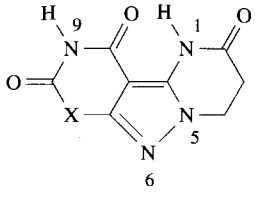
(163)



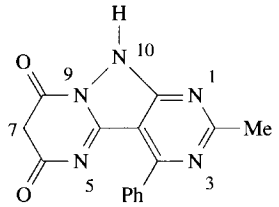
(164)

8.38.6.3 Electrophilic Attack at Carbon

The treatment of (**165**; X = CH_2) with benzenediazonium chloride or benzaldehyde produces the respective coupling product (**165**; X = CHNNPh) and condensation product (**165**; X = CCHPh) ⟨74T2791⟩. A similar condensation reaction of (**166**) with *p*-bromobenzaldehyde takes place at C-7 ⟨92MI 838-03⟩.



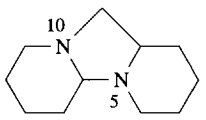
(165)



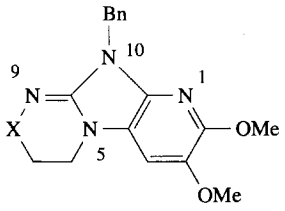
(166)

8.38.6.4 Reduction

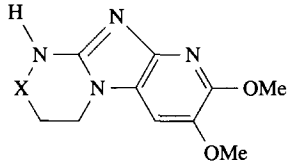
The alkaloid anosmine (**128**) is inert toward catalytic hydrogenation over a platinum catalyst but readily undergoes a reaction in the presence of Raney nickel and hydroxide ion, or with LAH to give a fully saturated tricyclic diamine (**167**) of unknown stereochemistry ⟨68TL905⟩. Removal of a benzyl group from (**168**; X = CO) by hydrogenation over a palladium catalyst produces (**169**; X = CO) while reduction with diborane yields (**168**; X = CH_2). A subsequent catalytic hydrogenation of (**168**; X = CH_2) gives (**169**; X = CH_2) ⟨90H(31)259⟩.



(**167**)



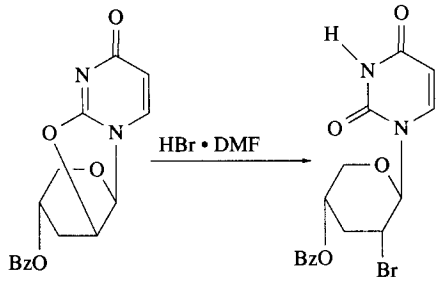
(**168**)



(**169**)

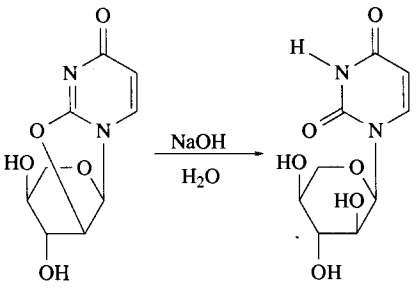
8.38.6.5 Ring Opening

Cyclic nucleosides, such as (**170**) and (**171**) are derivatives of the parent system (**58**) (Equations (5) and (6)). They undergo a stereospecific opening of the central ring upon treatment with acid in an aprotic solvent ⟨78JPR157, 81CJC468, 85CPB3689⟩ or with hydroxide ion in aqueous solution ⟨71JOC4105, 75JOC2372⟩. A reductive ring opening of (**172**) is also stereospecific (Equation (7)) ⟨82JOC230⟩.



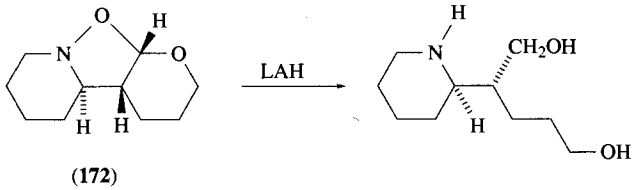
(**170**)

(5)



(**171**)

(6)



(**172**)

(7)

8.38.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

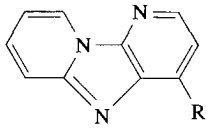
8.38.7.1 Nucleophilic Displacement

Substituted compounds of this class undergo many reactions that are typical for their mono and bicyclic analogues. Examples are replacement of an amide carbonyl group or a vinyl analogue, such as in 4(1*H*)-pyridone, by a thiocarbonyl group by treatment with P_2S_5 ⟨81MI 838-02⟩ and by chlorine in a reaction with $POCl_3$ ⟨61ZOB1906, 68KGS433, 81JHC1565, 90KFZ18, 91USP4985560, 92KFZ63⟩. A chlorine substituent in the product of the latter reaction can be displaced by oxygen- ⟨68KGS433⟩, sulfur- ⟨61ZOB1906, 68KGS433, 92KFZ63⟩, or nitrogen-centered nucleophiles ⟨68KGS433, 90KFZ18, 91USP4985560⟩. Surprisingly, the chloro substituent in compound (**152**; R = H) is highly resistant to nucleophilic displacement ⟨71JCS(C)2756⟩. Conjugation that involves a lone electron pair of the ring junction N-10 atom and which increases partial negative charges at the N-1 and C-2 atoms may be responsible for the observed lack of reactivity of (**152**).

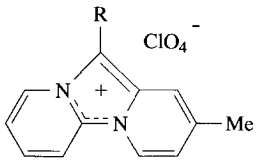
8.38.7.2 Replacement by Hydrogen

Reduction of a carbonyl group in (**122**) to a methylene has been mentioned in Section 8.38.2. A more general approach to deoxygenation of an amide carbonyl group or its vinyl analogue in a ring structure involves a preparation of a chloro derivative followed by displacement of the chlorine by hydrazine, as discussed above, and then treatment of the resultant hydrazino derivative with $CuSO_4$ in aqueous AcOH. The last step is illustrated by the preparation of (**173**; R = H) from (**173**; R = $NHNH_2$) ⟨81JHC1565⟩.

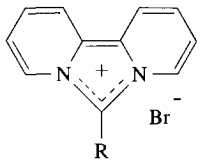
In several instances a substituent is removed by treatment with acid or base. When refluxed in hydrobromic acid, the mesoionic dipyridoimidazolium derivative (**139**) undergoes decomposition to the parent cation (**99**) and elemental sulfur ⟨85JOC4855⟩. The treatment of (**174**; R = Bz) with acid yields (**174**; R = H) ⟨76CB3646⟩. Removal of the acyl group from (**175**; R = Ac, Bz) to give the parent cation (**175**; R = H) (**98** in Table 2) is accomplished readily under acidic or basic conditions ⟨65AJC1819⟩.



(**173**)



(**174**)



(**175**)

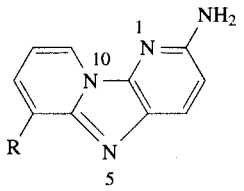
8.38.7.3 Modification

A methyl group at the position α or γ to a ring junction quaternary nitrogen atom in a (6:5:6) system undergoes a condensation reaction with a carbonyl function or an equivalent. This important reaction for synthesis of polymethine dyes has been discussed in Section 8.38.3, and structures of the representative dyes (**142**) and (**143**) are given for illustration.

As a general rule, a thioamide function which constitutes part of a ring system is alkylated at the sulfur atom by a reaction with a primary alkyl halide in the presence of a base ⟨61ZOB1906, 81MI 838-02, 84JHC685, 92CCC1565⟩. A mesoionic compound (**139**) is also alkylated at the sulfur atom ⟨85JOC4855⟩.

Two potent mutacarcinogens (**176**; R = Me) and (**176**; R = H), abbreviated in the biochemical literature as Glu-P-1 and Glu-P-2, respectively, have been isolated from a glutamic acid pyrolysate. The induction of mutagenesis and carcinogenesis is due to covalent binding of the amino group of these compounds to a C-8 atom of guanine in DNA ⟨79CPB2532⟩. Accordingly, the chemistry of the

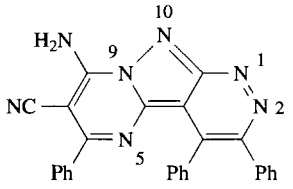
amino group in (**176**), namely direct alkylation ⟨86B5103⟩, acylation ⟨83TL1523⟩, tosylation, alkylation of the tosyl derivatives ⟨82CPB3046⟩, and oxidation to a nitro group ⟨82JA7636⟩ has received much attention ⟨84ACR403⟩.



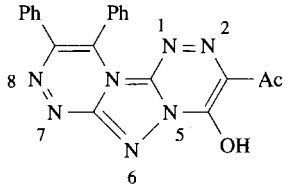
(**176**)

8.38.7.4 Cyclocondensation

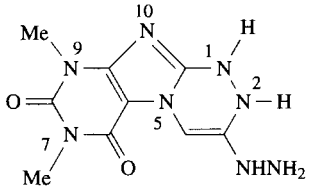
An additional heterocyclic ring fused to a (6 : 5 : 6) system can be constructed by a cyclocondensation reaction of an appropriately substituted tricyclic derivative with an external reagent. The NH_2–CN functionality of (**177**) was transformed into a pyrimidine by the reaction with formamide ⟨91H(32)895⟩, and cyclocondensation of the Ac–OH functionality in (**178**) with phenylhydrazine gave a pyrazole ⟨91H(32)901⟩. A hydrazino derivative (**179**) was condensed with a carboxylic acid to give a 1,2,4-triazole in the reaction that involves an N-2 atom of (**179**) ⟨88CI(L)785⟩.



(**177**)



(**178**)



(**179**)

8.38.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Reactions of substituents attached to ring heteroatoms of the (6 : 5 : 6) systems have not been reported up to 1995.

8.38.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

8.38.9.1 General Remarks

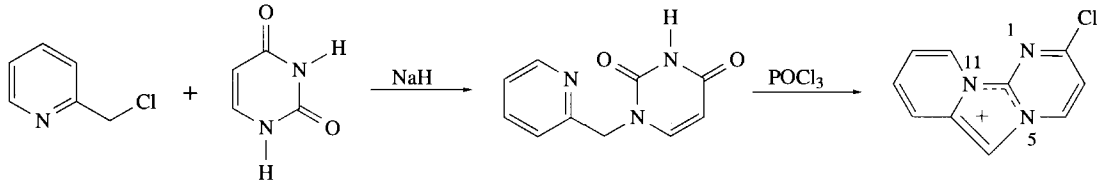
Many versatile approaches to the construction of fused heterocyclic systems (6 : 5 : 6) with ring junction heteroatoms have been reported. More general reactions which can be used for synthesis of derivatives of several tricyclic systems, and transformations which have potential for use in the preparation of a series of substituted compounds, are discussed in this section. References to a particular system (Tables 1 and 2) should be consulted for additional synthetic methods that are limited in scope and, in many instances, applicable to the preparation of a single derivative.

Formation of the five-membered ring is presented first because it is a conceptually simple approach. It should be noted, however, that the addition of a fused six-membered ring to a bicyclic component offers much more versatility in the construction of a (6 : 5 : 6) system. Each subsection below starts with intramolecular cyclization of an isolated intermediate product. Reactions which follow are one-pot intermolecular cyclizations.

8.38.9.2 Formation of the Five-membered Ring

8.38.9.2.1 Intramolecular cyclization

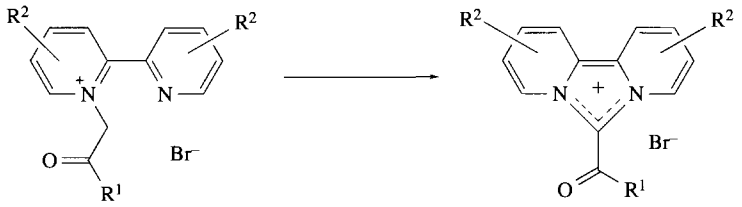
A general method for the construction of (6 : 5 : 6) systems containing a pyridoimidazolium cation is a $POCl_3$-mediated cyclization of readily available 2-pyridylmethyl-substituted lactams, as illustrated by the preparation and then cyclization of (**180**) to (**181**) (Scheme 2), a derivative of the parent system (**100**) ⟨87JCS(P1)2585⟩. By using an appropriate starting lactam this methodology provides an easy access to other derivatives of (**100**) as well as systems (**37**), (**96**) ⟨71JCS(C)2756⟩, (**99**), (**102**), and (**103**) ⟨87JCS(P1)2585⟩.



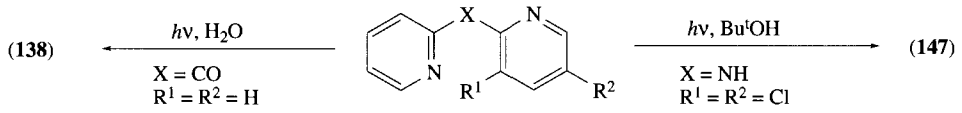
(**180**) (**181**)

Scheme 2

The dipyridoimidazolium system (**98**) substituted with an acyl group at the six position (**183**; R^1 = alkyl, aryl, R^2 = H, Me) is conveniently constructed by cyclization of the corresponding salt (**182**) with bromine in pyridine or *p*-toluenesulfonyl chloride in pyridine (Equation (8)). The salts (**182**) are obtained in high yields by treatment of 2,2′-bipyridine and its 4,4′- and 5,5′-dimethyl homologues with aliphatic or aromatic bromomethyl ketones ⟨68AJC1023⟩. A facile preparation of (**138**) ⟨72JA3649⟩ and (**147**) ⟨90ZOR1141, 91URP1641821, 91ZOR638⟩ involves photocyclization of the respective substrates (**184**; X = CO) and (**184**; X = NH) by irradiation with a high-pressure mercury lamp (Scheme 3).



(**182**) (**183**) (8)



(**138**) (**184**) (**147**)

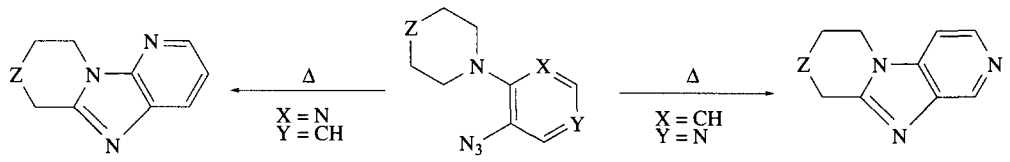
Scheme 3

Thermolysis of azides (**186**) yields the respective products (**185**; Z = CH_2, O) and (**187**; Z = CH_2, O) (Scheme 4) ⟨63JCS1666, 66JCS(C)80⟩ which are derivatives of the respective parent systems (**18**), (**50**), (**24**), and (**52**). Compound (**185**; Z = CH_2) has also been obtained by reductive cyclization of 3-nitro-2-piperidinopyridine with $TiCl_3$ ⟨68T4581⟩.

Intramolecular cyclization of appropriately substituted nucleosides is a general approach to the preparation of cyclic nucleosides, such as (**170**) and (**171**), which are derivatives of the parent system (**58**) ⟨71JOC4105, 75JOC2372, 78JPR157, 81CJC468, 85CPB3689⟩.

8.38.9.2.2 Synthesis from [4 + 1] fragments

Reactions presented below involve cyclization of an unfused biheterocycle at two ring nitrogen atoms adjacent to the torsional bond by an electrophilic reagent.

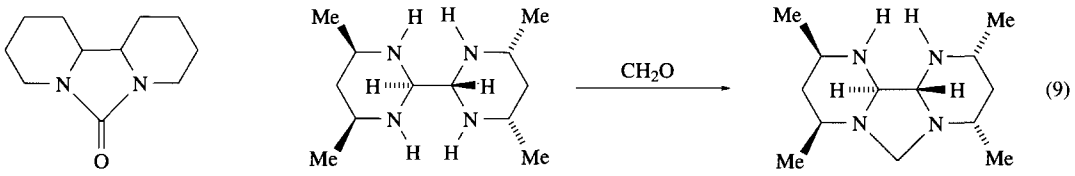


(185) (186) (187)

Scheme 4

The treatment of 2,2′-bipyridine with diiodomethane yields a dipyridoimidazolium salt (**98**), and a similar reaction with benzylidene chloride gives a 6-phenyl derivative of (**98**) ⟨63TL95, 65AJC1819⟩. Alkyl substituted 2,2′-bipyridines react in a similar way with these two reagents but other alkylidene halides are inert.

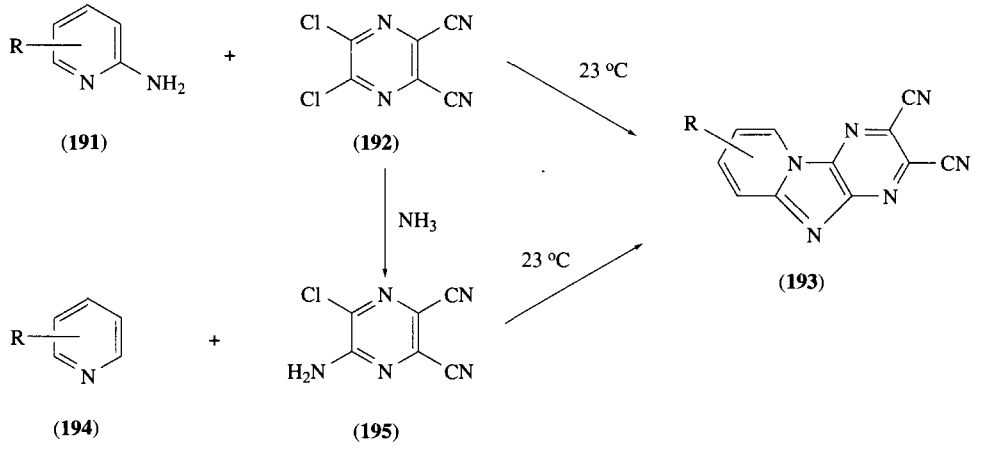
Aliphatic and aromatic aldehydes undergo a reaction with various 2,2′-bipiperidines to give the corresponding perhydrodipyridoimidazoles (**136**; R^1 = H, Me, R^2 = H, alkyl, Ar) ⟨64JMC644, 68T4411, 68T6625, 78HCA1622⟩. The treatment of 2,2′-bipiperidine with phosgene yields (**188**) ⟨64JMC644, 72KGS954⟩. A perhydro-2,2′-bipyrimidine (**189**) is cyclized with formaldehyde to give a tricyclic product (**190**) (Equation (9)) with retention of stereochemistry of the bicyclic component ⟨91JOC4308, 92JOC3901⟩.



(188) (189) (190) (9)

8.38.9.2.3 Synthesis from [3 + 2] fragments

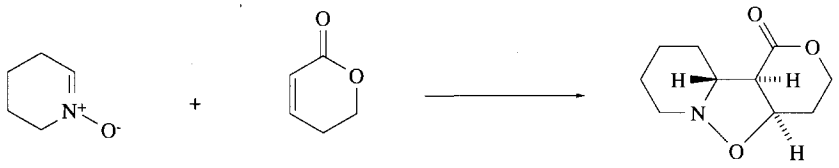
Pyridoimidazopyrazines (**43**) were obtained for the first time by a complicated route from 2-aminopyrazine-4-oxide ⟨72CPB1834, 72JAP(K)7220197, 72JAP(K)7220199⟩. In a more recent method, in the mid-1980s, various 2-aminopyridines (**191**) were allowed to react with readily available 2,3-dichloro-5,6-dicyanopyrazine (**192**) under mild conditions to give (**193**), derivatives of the parent system (**43**), in high yields (Scheme 5) ⟨86JHC1419⟩. A large number of compounds (**193**) substituted with a variety of groups at the 6, 7, 8, or 9 positions have been obtained by a modification which involves treatment of (**192**) with ammonia to give (**195**) followed by a reaction with various pyridines (**194**) ⟨86JAP(K)86204185, 86JHC1741⟩. A related synthesis of a pyridothiazolopyrazinium salt (**53**) involves a reaction of 2-thiopyridine with 2,3-dichloropyrazine ⟨90KGS1276⟩.



(191) (192) (193) (194) (195)

Scheme 5

Additional general reactions are the synthesis of 11-acyldipyridoimidazolium salts such as (**174**; R = Ac, Bz) by condensation of 1-acylmethyl-2-chloropyridinium salts with pyridine and substituted pyridines under mild conditions ⟨76CB3646, 77LA1692⟩, and a 1,3-dipolar cycloaddition of a nitrone (**196**) with heterocyclic alkenes. A derivative (**198**) of the parent system (**35**) has been obtained by the reaction of (**196**) with 5,6-dihydro-2-pyranone (**197**) (Equation (10)) ⟨93T3857⟩. A similar reaction occurs with 2,3-dihydropyran yields (**172**), a perhydro derivative of the parent system (**34**) ⟨82JOC230, 90JCS(P1)2593⟩.

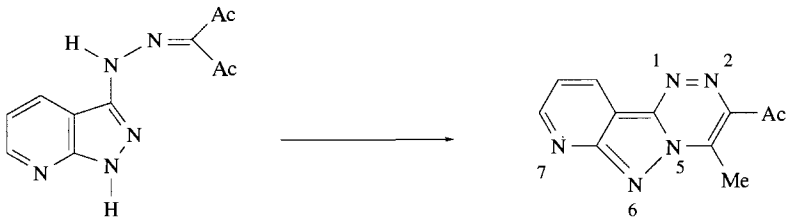


(196) (197) (198) (10)

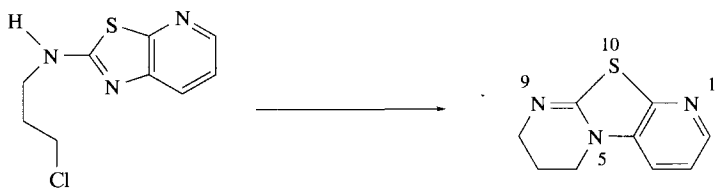
8.38.9.3 Formation of the Six-membered Ring

8.38.9.3.1 Intramolecular cyclization

Intramolecular cyclization reactions involving a nucleophilic ring nitrogen atom of a five-membered ring of a fused (6 : 5) bicyclic component have been applied to the construction of fused (6 : 5 : 6) systems. Upon cyclization this nitrogen atom becomes a ring junction atom. Examples of an intramolecular nucleophilic attack at an sp^2- and sp^3-hybridized carbon atom of an adjacent substituent are known. The first type of cyclization, as illustrated by the cyclization of (**199**) to (**200**) (Equation (11)) ⟨77H(6)681⟩, has been used in the synthesis of additional derivatives of the parent system (**62**) ⟨78JHC1175, 91G209, 91JC(B)878, 91MI 838-02, 93CCC1198⟩ as well as (**64**) ⟨90MI 838-01⟩, (**70**) ⟨89JCR(S)333⟩, and (**87**) ⟨59JOC1410⟩. An intramolecular nucleophilic substitution reaction is exemplified by the cyclization of (**201**) to (**202**) (Equation (12)) ⟨73IJC744⟩. This approach has been used in the construction of the tricyclic skeleton of (**29**) ⟨91BCJ1901⟩, (**47**) ⟨90H(31)259⟩, (**67**), and (**71**) ⟨75CPB1696, 76JAP(K)7606993⟩.



(199) (200) (11)

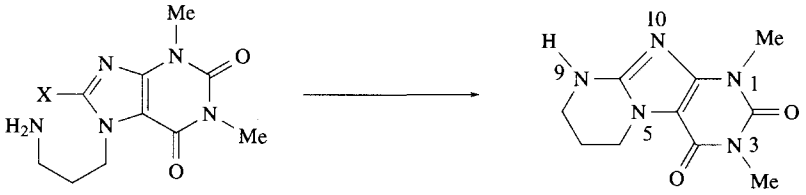


(201) (202) (12)

Similar cyclizations of an electrophilic substituent and a ring carbon atom of the five-membered ring of a fused bicyclic component are rare. This approach has been used in the preparation of derivatives of (**2**) ⟨85JHC817⟩ and (**18**) ⟨81JHC1565⟩.

A general approach to the synthesis of *f*-fused purines is an intramolecular displacement of a halogen in an 8-halopurine by a nucleophilic group attached to N-7 of the purine. This approach has been used in the preparation of (**204**) from (**203**) (Equation (13)) ⟨79S581⟩, other derivatives

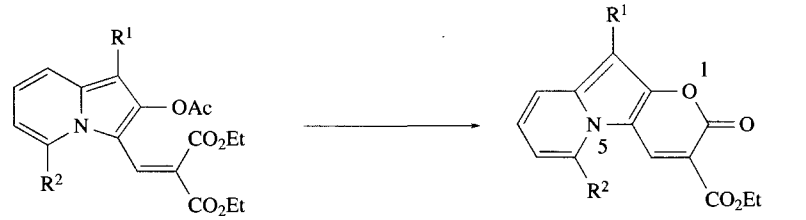
of the parent system (**71**) ⟨80KPS626, 86AP(319)566, 87AP(320)1004⟩ and derivatives of systems (**78**) ⟨71AP(304)117, 71MI 838-02, 87AP(320)999⟩, (**87**) ⟨62MI 838-02⟩, and (**95**) ⟨85MI 838-01⟩.



(13)

(**203**) (**204**)

By far the most numerous examples of the intramolecular cyclization are for reactions between two substituents attached to a five-membered ring of the fused (6 : 5) system, which do not involve displacement of the substituent from the five-membered ring. This approach is illustrated by cyclization of (**205**; R^1 = H, Me, Et, Ph, R^2 = H, Me) to (**206**) (Equation (14)) ⟨84BCJ548⟩. Substituted systems obtained by this type of cyclization are (**7**), (**8**) ⟨84BCJ548⟩, (**10**) ⟨76ACS(B)512⟩, (**11**) ⟨82JOC369, 83JAP(K)8346091⟩, (**20**) ⟨80JCR(S)18⟩, (**30**) ⟨92CPB631⟩, (**45**) ⟨59JA2452, 74T2791, 75ZN(B)778⟩, (**46**) ⟨90H(31)259⟩, (**49**) ⟨70USP3539582⟩, (**71**) ⟨87PHA371, 89S681, 90H(31)1549⟩, (**87**) ⟨88SC1299, 90KGS967⟩, (**95**) ⟨75MI 838-03, 91S625⟩, and (**96**) ⟨88JHC791⟩. Additional studies are needed to substantiate the claim that a derivative of the system (**56**) is formed by a Michael addition of 2-thioimidazo[4,5-*b*]pyridine to acrylonitrile or ethyl acrylate followed by cyclization ⟨83AP(316)985⟩.

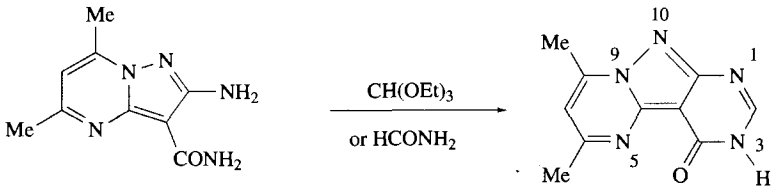


(14)

(**205**) (**206**)

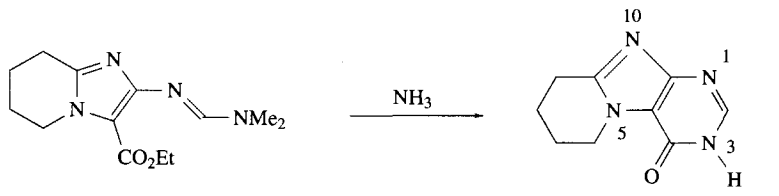
8.38.9.3.2 Synthesis from [5 + 1] fragments

Two major approaches are cyclization of a 1,5-dinucleophile with an electrophile and ring closure of a 1,5-dielectrophile with a nucleophile. The first reaction type is illustrated by the synthesis of (**208**) from (**207**) (Equation (15)) ⟨89CZ181⟩. This approach has been used in the construction of systems (**38**) ⟨61ZOB1906⟩, (**41**) ⟨81S910⟩, (**68**) ⟨67KFZ16⟩, (**75**) ⟨66KGS192⟩, (**83**) ⟨92KFZ63⟩, (**84**) ⟨68KGS433⟩, and (**91**) ⟨89CZ181⟩. In addition to the preparation of (**210**) from (**209**) (Equation (16)) ⟨92KFZ63⟩ a large number of derivatives of (**71**) have been obtained by the second method ⟨62MI 838-01, 80MI 838-01, 81KGS1102, 87PHA371, 89LA1251⟩.



(15)

(**207**) (**208**)

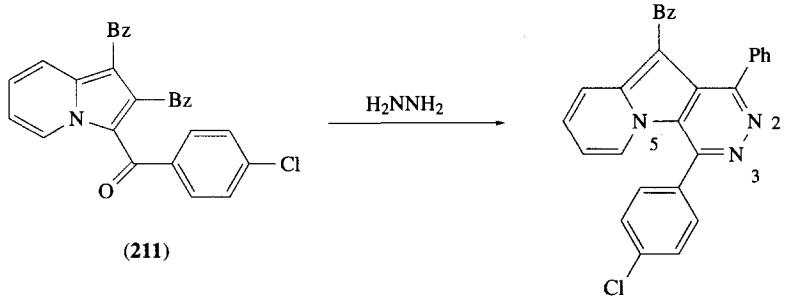


(16)

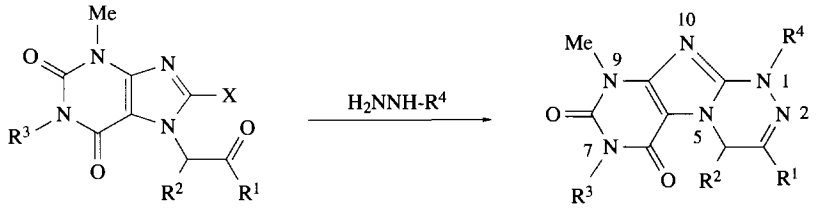
(**209**) (**210**)

8.38.9.3.3 Synthesis from [4 + 2] fragments

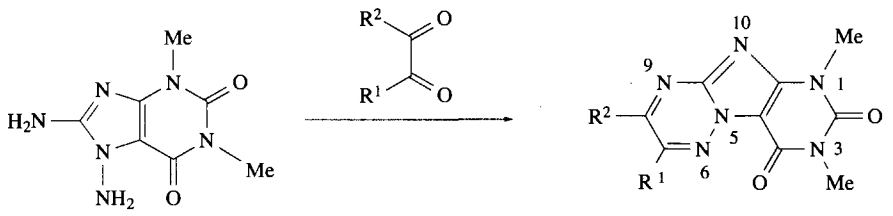
The classical route to pyrazines by the reaction of a 1,4-dicarbonyl compound with hydrazine provides a convenient entry into substituted systems (**22**) ⟨91USP4985560⟩, (**23**) ⟨78JHC1303, 83H(20)1525, 88JHC1793⟩, and (**48**) ⟨80JOC90⟩. In particular, the reaction of (**211**) with hydrazine is regioselective yielding a single isomer (**212**) (Equation (17)) ⟨75JCS(P1)1326⟩. Two related approaches have been used in the synthesis of *f*-fused xanthines. Thus, cyclization of (**213**; X = Br, Cl) with hydrazine or a substituted hydrazine gives (**214**; R^1, R^2, R^4 = H, Me, Ph, R^3 = H, Me) (Equation (18)) ⟨69MI 838-01, 75MI 838-02, 81MI 838-02, 85MI 838-01, 86KFZ187⟩ and a reaction of a diamine (**215**) with a 1,2-dicarbonyl compound yields (**216**; R^1 = R^2 = H, Me, Ph) (Equation (19)) ⟨87KGS1398⟩. One isomer of the apparent structure (**216**; R^1 = Me, R^2 = H; R^1 = Ph, R^2 = H) is obtained exclusively if the corresponding keto aldehyde is used for cyclization ⟨88JHC791⟩. Contradictory results have been obtained in another study ⟨88UKZ531⟩.



(211) (212) (17)

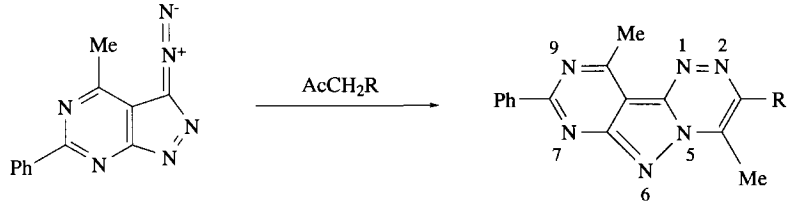


(213) (214) (18)



(215) (216) (19)

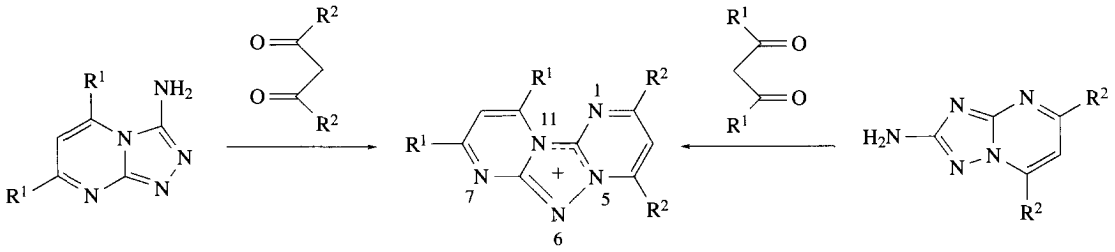
An interesting preparation of (**218**; R = Ac, CO_2Et) is by a reaction of a diazo compound (**217**) with pentane-2,4-dione or ethyl acetoacetate (Equation (20)) ⟨92JCS(P1)239⟩. Related routes to systems (**62**) ⟨77S556⟩ and (**92**) ⟨77S556, 81JHC675, 91H(32)901⟩ have been reported.



(217) (218) (20)

8.38.9.3.4 Synthesis from [3 + 3] fragments

Cyclocondensation of aminoazoles with 1,3-dicarbonyl compounds, equivalents, or similar 1,3-dielectrophilic reagents is a versatile synthetic route to fused heterocyclic compounds. Upon cyclization, the ring nitrogen atom adjacent to the amino group in the bicyclic azole derivative normally becomes a ring junction atom in the tricyclic product, as shown by the transformation of (**219**) to (**220**; R^1 = Me, Ph, R^2 = Me, Ph) (Scheme 6). The synthesis of the same product (**220**) from (**221**) illustrates a general rule that the ring closure involves the more nucleophilic ring nitrogen atom of the azole substrate ⟨71UKZ1044, 80UKZ835⟩. This type of cyclocondensation provides an efficient entry into the following systems: (**44**) ⟨77IJC(B)349, 81UKZ1085, 87MI 838-01, 91CCC1560⟩, (**57**) ⟨73JHC769⟩, (**63**) ⟨91H(32)895⟩, (**67**) ⟨91CPB270⟩, (**70**) ⟨88JCR(S)46, 92MI 838-03⟩, (**71**) ⟨86JMC1099, 87PHA371, 89LA1251, 89MI 838-04, 94JHC81⟩, (**109**) ⟨75HCA1944, 88LA819⟩, (**110**) ⟨71KGS1433⟩, (**113**) ⟨82UKZ647⟩, and (**117**) ⟨80UKZ1092⟩. Substituted systems (**18**) ⟨81JHC1565⟩, (**44**) ⟨65LA(682)141⟩, and (**114**) ⟨74KGS846⟩ have been obtained by cyclocondensation that involves a ring carbon atom adjacent to the amino group of the aminoazole substrate. In a related synthetic entry into the system (**7**) enolate ion of 2(3*H*)-indolizinone is reacted with a 1,2-dielectrophilic reagent ⟨76KGS1700, 80JOC5100⟩.

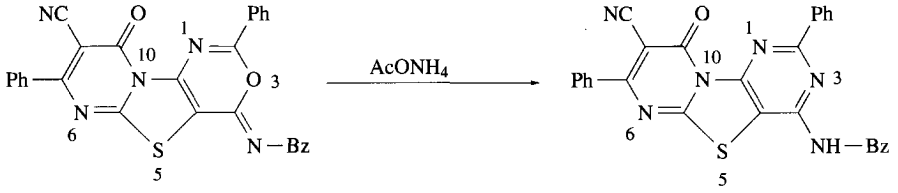


(**219**) (**220**) (**221**)

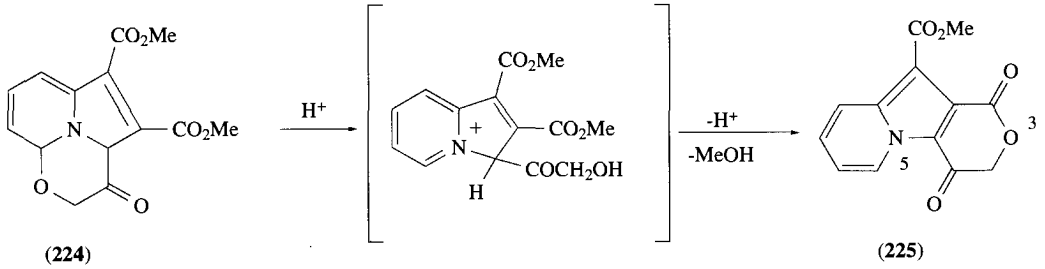
Scheme 6

8.38.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Ring transformation reactions of intermediate products have often been postulated in the literature to explain the formation of a heterocyclic fused system (6 : 5 : 6). Only two reports describe ring transformation of a well-characterized substrate. These are syntheses of (**223**) from (**222**) in the presence of $AcONH_4$ (Equation (21)) ⟨92CCC1565⟩ and acid-catalyzed rearrangement of (**224**) producing (**225**) (Scheme 7) ⟨93JOC1144⟩.



(**222**) (**223**) (21)



(**224**) (**225**)

Scheme 7

8.38.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

The following Section 8.38.12 and the Section 8.38.9 on synthesis should be consulted to retrieve desired information on the preparation of important classes of compounds. A more detailed review is not justified in the light of the many systems (6 : 5 : 6) described.

8.38.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Compounds with fused heterocyclic systems (6 : 5 : 6) exhibit diverse biological activities. Virtually all patents listed in Tables 1 and 2 describe drugs or potential drugs. Many derivatives of systems (**39**), (**71**), (**72**), (**78**), (**95**), and (**96**) with an *f*-fused xanthine subunit are drugs that act on the central nervous system ⟨86KFZ187, 89MI 838-04, 91MI 838-03, 92MI 838-04⟩, are antiviral agents ⟨92KFZ63⟩, and anti-inflammatory agents ⟨79BRP2006765, 86JMC1099, 87CPB4031, 88CI(L)785, 88JOC3265, 89JMC1118, 89LA1251⟩. Tuberculostatic activity has been noted for many derivatives of (**17**) and (**18**) ⟨90PHA904, 91AP(324)121⟩. All references to the system (**58**) in Table 1 refer to synthesis of nucleoside antibiotics and analogues. In a similar way, all known derivatives at (**61**) have been synthesized as potential anticancer agents.

The chemistry of potent carcinogens (**176**) ⟨78CPB2924⟩ (known as Glu-P-1 and Glu-P-2) is discussed in Section 8.38.7.3. Studies in the early 1990s have been devoted to an understanding of the molecular basis of carcinogenesis induced by these compounds ⟨92MI 838-01, 93MI 838-01, 93MI 838-02⟩. Related reports describe the formation of a derivative of the system (**39**) resulting from a reaction of a guanine base in DNA with *N*-nitrosopyrrolidine, a potent carcinogen ⟨89MI 838-01, 89MI 838-02, 89MI 838-03, 92MI 838-02⟩.

The chemistry and spectral properties of dyes have been discussed in Sections 8.38.3.2 and 8.38.7.3. Intense research is underway to develop practical fluorescent labels and probes for bioanalytical applications ⟨90JCR(S)308⟩. The near-infrared fluorescing dyes are primary candidates for the development because of a negligible background interference from a biological medium in the near-infrared region. A large number of potential substrates for synthesis of polymethine near-infrared dyes can be found in the references listed in Section 8.38.3.2.

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8.39
Three Heterocyclic Rings Fused (6 : 6 : 6)

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8.39.1 SURVEY OF SYSTEMS

This is the first attempt to review all fused heterocyclic systems (6 : 6 : 6) containing at least one ring junction heteroatom. There are three classes of these systems, namely heterocyclic analogues of anthracene, phenanthrene, and phenalene, which are surveyed in Tables 1–3 respectively. Please

consult Section 8.38.1 of the preceding chapter regarding the organization of the Tables and additional information concerning the tabulated material. The survey is an integral part of the sections that follow; brevity was necessary in order to review the large number of systems (6 : 6 : 6).

8.39.2 THEORETICAL METHODS

INDO/S CI computations have been conducted to predict sites of protonation and explain the absorption and emission spectra of a derivative of (**15**) ⟨85MI 839-01, 86ZN(A)661⟩. Semiempirical MNDO computations predict little charge delocalization in the pyrimidinediium system (**38**) and a similar dication derived from (**39**) ⟨86CJC1711⟩. Hückel–McLachlan calculations have been used to explain the ability of a tetrazine (**53**) to form charge–transfer complexes and to help interpret PE and ESR spectra ⟨87HCA1661, 94HCA86⟩. The AM1 Hamiltonian more accurately predicts a stable conformation of (**72**) than the MNDO method ⟨89CB1989⟩. The electronic structure of azaphenalenes (**152**), (**170**)–(**172**), and (**181**)–(**183**) has been studied extensively by using HAM/3 semiempirical, STO-3G *ab initio* and other approximations ⟨69JCS(A)1754, 80JA6068, 84JA2805, 84CCA991, 85JA3884, 86JA17, 94JHC929⟩. The HAM/3 computations predict the greatest HOMO and total electron density of (**152**) at positions 1, 3, 4, 6, 7, and 9 ⟨85JA3884⟩.

Neither the parent systems (**40**), (**70**), (**73**)–(**75**) (Table 1), (**142**), (**151**) (Table 2), (**181**), (**198**) (Table 3) nor their derivatives are known. These systems, however, have generated a considerable theoretical interest and have been examined by theoretical calculations. Numerous predictions have been made for presently unknown compounds. The features of interest are the aromaticity of boron–nitrogen heterocycles (**40**), (**70**), (**75**), (**142**), (**151**), (**202**) ⟨67CJC2059, 71CCC1248, 84RRC613⟩ and nitrogen heterocycles (**164**), (**167**), (**173**) ⟨93JIC693, 94JHC929⟩ and the potential conductivity or superconductivity of systems (**73**), (**74**), (**184**) ⟨87IC3797, 92JPC5184, 93JPC4974⟩.

8.39.3 EXPERIMENTAL STRUCTURAL METHODS

8.39.3.1 X-ray Diffraction

The conjugated systems (**53**) ⟨86HCA1521⟩, (**101**) ⟨91MI 839-01⟩, (**114**) ⟨91TL4473⟩, (**171**) ⟨84MI 839-07⟩, and (**183**) ⟨82JA5497⟩ are virtually planar in the solid state. The cation (**84**) is only approximately planar ⟨71CC426⟩, and a heterocyclic skeleton of the 2,2,3a,5,5,6a,8,8,9a-nonachloro substituted system (**198**) is not planar at all ⟨72JCS(D)623, 73CJC520⟩. The molecular structures of noncyclically conjugated derivatives of (**31**) ⟨90JOC467⟩, (**39**) ⟨85JCS(P2)433⟩, (**54**) ⟨91JA5910, 92JA6017⟩, (**139**) ⟨85CC311, 88TL1573⟩, (**144**) ⟨83JA2350⟩, and (**187**) ⟨82TL2891, 83H(20)579, 83H(20)1891⟩ have been solved. X-ray diffraction analysis has also been used to study the conformation of perhydro derivatives of (**55**) ⟨78JCS(P2)818⟩, (**67**) ⟨80JCS(P2)1733⟩, (**69**) ⟨85AX(C)122, 87AX(C)170⟩, (**152**) ⟨84JOC2217, 92TL1281⟩, (**191**) ⟨89HCA1125⟩, (**192**) ⟨88JOM(341)109⟩, and (**199**) ⟨84AG301⟩ in crystal.

8.39.3.2 Molecular Spectra

8.39.3.2.1 NMR spectroscopy

The fully conjugated systems (6 : 6 : 6) of Table 2 are analogues of biaryls with a two-atom bridge linking positions α and α' to the torsional bond. The effect of this structure feature on ^{1}H NMR spectra is similar to that discussed in subsection Section 8.38.3.2 for the (6 : 5 : 6) systems.

The chemical shifts for protons of pyrido[2,1,6-*de*]quinolizine (**152**) ($\delta = 2.1$–3.6) are among the highest fields reported for protons joined to trigonal carbon atoms. This high degree of shielding is evidence of a paramagnetic ring current in the 12π-peripheral ⟨94JHC929⟩.

The integral application of ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy has been a highly successful approach in conformational studies of saturated compounds, such as derivatives of (**39**) ⟨72TL1437⟩, (**68**) ⟨84ZOR510⟩, (**69**) ⟨89PS(41)235⟩, (**72**) ⟨79JCS(P2)1133⟩, (**82**) ⟨94T9909⟩, (**98**) ⟨92T349⟩, (**143**) ⟨81TL1711⟩, (**189**) ⟨81TL2217, 91T1013⟩, and (**191**) ⟨80TL3635, 81TL4365⟩.

8.39.3.2.2 Electronic absorption and fluorescence spectroscopy

Detailed spectroscopic and photophysical studies of the following systems or derivatives have been reported: (**15**) ⟨83JOC2476, 87JCS(F2)1475, 90ZN(A)999⟩, (**25**) ⟨83CC183, 83JOC2481⟩, (**39**) ⟨82JPC2049⟩, (**101**) ⟨89JCS(P2)1691⟩, (**152**) ⟨86JA17⟩, and (**183**) ⟨84JPC4324⟩.

8.39.3.2.3 ESR spectroscopy

Systems (**53**) ⟨94HCA86⟩, (**62**) ⟨91CB2781⟩, (**152**) ⟨73JA6702⟩, and a 6,7-dihydroderivative of (**139**), diquat, ⟨93JPC7800⟩ are easily oxidized to stable cation radicals. The ESR spectrum of the unstable anion radical resulting from reduction of (**152**) has been obtained ⟨73JA6702⟩.

8.39.4 THERMODYNAMIC ASPECTS

The concept of topological resonance energy was introduced to provide a relative measure of aromaticity ⟨77JA1692⟩. In a newer approach, the absolute hardness, or HOMO–LUMO gap, as the measure of aromaticity is defined to be in the ionization potential of the species minus its electron affinity. The parameters of the absolute hardness and a related relative hardness for (**152**) are consistent with the high reactivity of this compound ⟨89JA7371⟩.

8.39.5 REACTIVITY

The reactions of heterocyclic compounds composed of fused systems (6 : 6 : 6), such as electrophilic and nucleophilic attack at a ring or a substituent and partial reduction, are often highly selective. Unfortunately, there are few unifying features among the reactivities of the three different classes of systems, and a detailed treatment of the reactivity is beyond the scope of this concise chapter. All references to the chemistry of a particular parent compound and derivatives are given in Tables 1–3.

8.39.6 SYNTHESIS

8.39.6.1 General Remarks

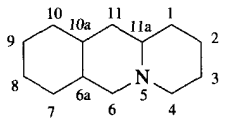
All synthesis references are printed in boldface in Tables 1–3. The many synthetic methods reported have been classified below into several general approaches according to a one-pot construction of one, two, and three fused rings, and ring transformation of a fused ring system substrate. The references listed in Tables 1–3 are not duplicated here if a particular ring system (6 : 6 : 6) has been constructed using one approach only. It should be noted that the particular approach according to this classification may involve different types of chemistry.

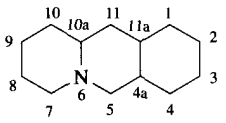
8.39.6.2 Hetero Analogues of Anthracene (Table 1)

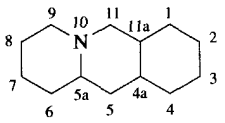
8.39.6.2.1 Formation of the central ring

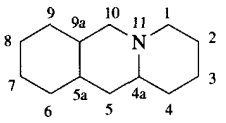
The most widely used method involves an intermolecular cyclization of two one-ring components substituted with appropriate functional groups. This approach provides an efficient synthetic entry to (**1**), (**6**), (**7**) ⟨78CB2297, 86ZC290, 91LA1215⟩, (**8**), (**9**), (**11**) ⟨86CB1070⟩, (**12**), (**15**) ⟨81TL449, 83JHC575, 83JOC2476⟩, (**16**) ⟨72CB743, 86ZC290⟩, (**20**), (**24**), (**25**), (**28**), (**30**), (**32**), (**34**), (**35**), (**39**), (**49**), (**51**)–(**56**), (**58**), (**62**), (**63**), (**65**)–(**68**), and (**71**). An intramolecular cyclization of a substrate composed of two six-membered heterocycles and bridged by a one-atom unit has been applied to the synthesis of derivatives of (**5**), (**15**) ⟨75JHC477, 85JHC173, 94JHC81⟩, (**17**), (**26**), (**27**), (**38**), (**43**), (**45**), (**46**), and (**69**).

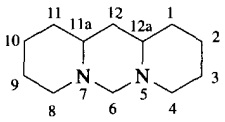
Table 1 Fused heterocyclic systems (6 : 6 : 6) with *Chemical Abstracts* ring identifier (2508) for the tricyclic skeleton. (References in bold refer to synthesis.)

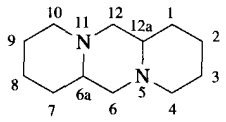

Type I

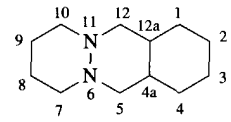

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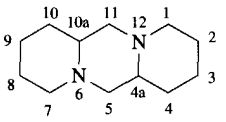

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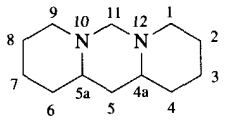

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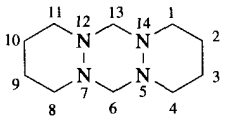

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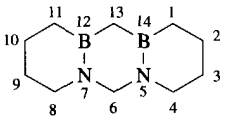

Type VI


Type VII


Type VIII


Type IX

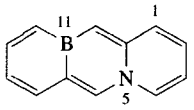
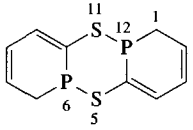

Type X


Type XI

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
A One ring junction nitrogen atom					
A.1 Two ring heteroatoms					
(1)	II	*N*1, *N*6	2508.86	2*H*-Pyrido[1,2-*g*]-1,6-naphthyridine	**57MI 839-01**, 81CJC106
(2)	II	*O*1, *N*6	2508.99	2*H*,5*H*-Pyrano[2,3-*b*]quinolizine	**72LA(761)25**, **80M93**, **83M485**
(3)	III	*O*2, *N*10	2508.855	1*H*,3*H*-Pyrano[4,3-*b*]quinolizine	**94H(38)81**
A.2 Three ring heteroatoms					
(4)	II	*N*1, *N*3, *N*6	2508.88	2*H*-Pyrimido[4,5-*b*]quinolizine	**70YZ127**
(5)	I	*N*1, *N*5, *N*10	2508.759	2*H*-Pyrimido[1,2-*g*]naphthyridine	**89MIP8905809**, **90JHC189**
(6)	III	*N*1, *N*5, *N*10	2508.675	1*H*-Dipyrido[1,2-*a*:3′,2′-*d*]pyrimidine	**86ZC290**
(7)	II	*N*1, *N*6, *N*11	2508.144	2*H*-Dipyrido[1,2-*a*:2′,3′-*d*]pyrimidine	**71JHC637**, **71JOC2192**, **78CB2297**, **86ZC290**, **91LA1215**, **92JHC25**
(8)	III	*N*2, *N*5, *N*10	2508.693	1*H*-Dipyrido[1,2-*a*:4′,3′-*d*]pyrimidine	**87JCS(P1)909**, **87JHC1473**, **87MI 839-01**, **87MI 839-02**, **87T1157**, **88MI 839-01**, 93OMS(28)18
(9)	II	*N*2, *N*6, *N*11	2508.674	2*H*-Dipyrido[1,2-*a*:3,4′-*d*]pyrimidine	**86ZC290**
(10)	I	*N*1, *N*5, *O*8	2508.753	2*H*,6*H*-Pyrano[4′,3′:4,5]pyrido[1,2-*a*]pyrimidine	**89LA1241**
(11)	II	*O*1, *N*6, *N*11	2508.149	2*H*,5*H*-Pyrano[2,3-*d*]pyrido[1,2-*a*]pyrimidine	**86CB1070**, **90ZC98**, **93MIP9323398**
(12)	III	*O*2, *N*5, *N*10	2508.715	1*H*,3*H*-Pyrano[4,3-*d*]pyrido[1,2-a]pyrimidine	**87JHC1557**
(13)	I	*O*1, *N*5, *O*8	2508.754	2*H*,6*H*,7*H*-Pyrano[4′,3′:4,5]pyrido[2,1-*b*][1,3]oxazine	**89LA1241**
(14)	I	*S*1, *N*5, *O*8	2508.752	2*H*,6*H*,7*H*-Pyrano[4′,3′:4,5]pyrido[2,1-*b*][1,3]thiazine	**89LA1241**

A.3 *Four ring heteroatoms*					
(15)	II	*N*1, *N*3, N^+6, *N*11	2508.146	Pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-6-ium	**74USP3836533**, **75JHC477**, **81TL449**, **83JHC575**, **83JOC2476**, **85JHC173**, 85MI 839-01, 86JPC5820, 86ZN(A)661, 87JCS(F2)1475, **88JHC959**, 90ZN(A)999, **94JHC81**
(16)	III	*N*1, *N*4, *N*5, *N*10	2508.215	1*H*-Pyrido[2,1-*b*]pteridine	**72CB743**, **86ZC290**, **92MI 839-01**
(17)	I	*N*1, *N*5, *N*10, *N*11	2508.631	2*H*-Pyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidine	**85JHC193**, **86MIP8606375**, **93CCC1130**
(18)	III	*N*1, *O*4, *N*5, *N*10	2508.814	1*H*,7*H*-Pyrido[1′,2′ : 1,2]pyrimido[4,5-*b*][1,4]oxazine	**91IJC(B)839**
(19)	II	*N*1, *N*6, *O*7, *N*11	2508.698	Pyrido[2′,3′ : 4,5]pyrimido[1,2-*b*][1,2]oxazine	**87JHC175**, 91JHC2071
(20)	I	*N*1, *N*5, *N*10, *S*11	2508.377	2*H*,6*H*-Pyrido[3,2-*e*]pyrimido[2,1-*b*][1,3]thiazine	**73JIC358**
(21)	II	*N*1, *N*6, *S*9, *N*11	2508.145	Pyrido[2′,3′ : 4,5]pyrimido[2,1-*c*][1,4]thiazine	**73CPB770**
(22)	I	*S*1, *N*5, *S*8, *N*11	2508.657	2*H*,6*H*,7*H*-Thiopyrano[4′,3′ : 4,5]pyrimido[2,1-*b*][1,3]thiazine	**85MI 839-02**
A.4 *Five ring heteroatoms*					
(23)	II	*N*1, *N*2, *N*5, *N*6, *N*11	2508.736	2*H*-Pyridazino[3,4-*e*]pyrido[1,2-*b*][1,2,4]triazine	**89CB1935**, **90CB1415**, **91CB1477**, 92JAP(K)04015644
(24)	II	*N*1, *N*3, *N*5, *N*6, *N*11	2508.524	2*H*-Pyrido[1,2-*b*]pyrimido[4,5-*e*][1,2,4]triazine	**79DIS(B)5678**
(25)	II	*N*1, *N*3, *N*6, *N*8, *N*11	2508.406	2*H*-Dipyrimido[1,6-*a* : 4′,5′-*d*]pyrimidine	**74CPB2086**, **83CC183**, **83JOC2481**, 86JPC5820, 87ZN(A)485, 90ZN(A)999
(26)	I	*N*1, *N*3, *N*6, *N*9, *N*11	2508.860	2*H*-Pyrazino[1,2-*a*]pyrimido[4,5-*d*]pyrimidine	**94JHC81**
(27)	III	*N*1, *N*4, *N*5, *N*6, *N*10	2508.216	1*H*-Pyrimido[2,1-*b*]pteridine	**86MIP8606375**, **93CCC1130**
(28)	II	*N*1, *N*3, *N*6, *N*8, *O*11	2508.535	2*H*,7*H*-Dipyrimido[6,1-*b* : 5′,4′-*e*][1,3]oxazine	**80KGS992**
(29)	I	*N*1, *N*3, *N*5, *N*10, *S*11	2508.625	2*H*,6*H*-Pyrido[3′,2′ : 5,6][1,3]thiazino-[3,2-*a*]-1,3,5-triazine	**85FES65**
(30)	II	*N*1, *N*3, *S*5, *N*6, *N*11	2508.299	Pyrido[1,2-*b*]pyrimido[4,5-*e*][1,2,4]thiadiazine	**69GEP(O)1809013**
(31)	II	*N*1, *N*3, *N*6, *S*9, *N*11	2508.147	Pyrimido[4′,5′ : 4,5]pyrimido[2,1-*c*][1,4]thiazine	**66MI 839-01**, **67CPB1178**, **67CPB1183**, **67JAP05000302**, **67JAP42005665**, **67JAP42009834**, **67JAP42020070**, **67JAP42025916**, **68CPB1773**, **68JAP43005397**, **68JAP43010631**, **68JAP43019553**, **68JAP43019958**, **68JAP43019959**, **69JAP44030276**, **72YZ27**, **73CPB770**, **74MI 839-01**, **75MI 839-01**, **90JOC467**
(32)	II	*N*1, *N*3, *N*6, *N*10, *S*11	2508.448	2*H*,7*H*-Dipyrimido[2,1-*b* : 5′,4′-*e*][1,3]thiazine	**76IJC(B)759**
(33)	III	*N*1, *N*4, *N*5, *S*6, *N*10	2508.450	1*H*,7*H*-[1,3]Triazino[2,3-*b*]pteridine	**77ACS(B)167**, **78CB971**, **93HCA431**
A.5 *Six ring heteroatoms*					
(34)	II	*N*1, *N*3, *S*5, *N*6, *N*7, *N*11	2508.301	Pyridazino[1,6-*b*]pyrimido[4,5-*e*][1,2,4]thiadiazine	**69GEP(O)1809013**
(35)	II	*N*1, *N*3, *S*5, *N*6, *N*9, *N*11	2508.300	Pyrazino[1,2-*b*]pyrimido[4,5-*e*][1,2,4]thiadiazine	**69GEP(O)1809013**
(36)	IV	*N*1, *S*3, *N*5, *N*6, *N*8, *N*11	2508.148	Pyrimido[4′,5′ : 4,5]pyrimido[1,2-*d*][1,3,4]thiadiazine	**70CPB1201**, **70GEP(O)1954275**, 72JAP47050120
(37)	IV	*P*1, *O*2, *N*4, *N*5, *N*6, *N*11	2508.801	1*H*,3*H*-Pyrido[2′,3′ : 4,5]pyrimido[1,2-*c*][1,3,5,2]oxa-diazaphosphorine	**89MI 839-01**
B *Two ring junction heteroatoms*					
B.1 *Two ring heteroatoms*					
(38)	V	N^+5, N^+7	2508.341	Dipyrido[1,2-*c* : 2′,1′-*f*]pyrimidinediium	69JC250, 69MI 839-01, **70T3369**, **73JOC1098**, 74OMR(6)253, 76JCS(P2)418, 86CJC1711, 88SM371

Table 1 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
(39)	VI	*N*5, *N*11	2508.342	Dipyrido[1,2-*a*:1′,2′-*d*]pyrazine	67EGP55860, 70G421, 70JCS(D)482, **72CCC4060**, 72TL1437, 73CCC1940, 73CCC1957, 74CPB157, **78JCR(S)224**, 81MI 839-01, 82JPC2049, **84MI 839-01**, 85JCS(P2)433, **85JOC2910**, 86CJC1711
(40)			2508.2	Borino[1,2-*d*]pyrido[1,2-*a*][1,4]azaborine	71CCC1248
B.2 *Three ring heteroatoms*					
(41)	VII	*N*1, *N*6, *N*11	2508.87	Pyridazino[1,2-*a*]pyrido[2,3-*d*]pyridazine	**70AQ561**, **73JCS(P1)26**
(42)	VII	*N*2, *N*6, *N*11	2508.66	Pyridazino[1,2-*a*]pyrido[3,4-*d*]pyridazine	**70AQ561**
(43)	V	N^+5, *N*7, *N*12	2508.350	2*H*-Dipyrido[1,2-*a*:2′,1′-*d*][1,3,5] triazin-5-ium	69MI 839-01, **73JOC1098**, 74OMR(6)253, 82SM31, **86H(24)1893**, 86JPC5820, **86S402**, **86USP4594413**, 88ZOB1685, 89ZOR1354
(44)	IX	*S*1, *N*10, *N*12	2508.849	11*H*-Pyrido[1′,2′:3,4]pyrimido[1,6-*b*][1,2] thiazine	**93SL551**
(45)	V	N^+5, N^+7, *S*12	2508.366	2*H*-Dipyrido[2,1-*b*:1′,2′-*e*][1,3,5] thiadiazinediium	67NAT381, **68T2697**
(46)	V	N^+5, N^+7, *Se*12	2508.474	2*H*-Dipyrido[2,1-*b*:1′,2′-*e*][1,3,5] selenadiazinediium	**78ZN(B)118**
B.3 *Four ring heteroatoms*					
(47)	VII	*N*1, *N*4, *N*6, *N*11	2508.205	Pyrazino[2,3-*d*]pyridazino[1,2-*a*] pyridazine	**70AQ561**
(48)	VI	*N*1, *N*5, *N*7, *N*11	2508.799	Pyrazino[1,2-*a*:4,5-*a*′]dipyrimidine	**90JCR(S)304**
(49)	VIII	*N*1, *N*6, *N*7, *N*12	2508.343	Pyrazino[1,2-*b*:4,5-*b*′]dipyrimidine	**71JCS(C)526**, **71RRC1107**, **73MI 839-01**
(50)	VII	*N*2, *N*3, *N*6, *N*11	2508.67	Dipyridazino[1,2-*a*:4′,5′-*d*]pyridazine	**68JCS(C)2857**, **75JHC95**
(51)	VI	*N*2, *N*5, *N*8, *N*11	2508.601	Dipyrazino[1,2-*a*:1′,2′-*d*]pyrazine	**84DIS(B)202**, **85JMC1228**, **89USP4871736**, 93MIP9323075
(52)	VIII	*N*2, *N*6, *N*8, *N*12	2508.522	Pyrazino[1,2-*c*:4,5-*c*′]dipyrimidine	**80MI 839-01**, 81RRC879, **94JHC1707**
(53)	VI	*N*5, *N*6, *N*11, *N*12	2508.357	Dipyrido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazine	**67CB2467**, **73JOC4259**, **75JPR561**, **77ZOR948**, **86HCA1521**, 86HCA1531, 87HCA1661, 88JAP(K)63229455, 90HCA81, 94HCA86
(54)	VI	*O*2, N^+5, *O*8, N^+11	2508.779	Pyrazino[2,1-*c*:5,4-*c*′]bis[1,4]oxazinediium	**89USP4871736**, **91JA5910**, **92JA6017**
(55)	VIII	*O*5, *N*6, *O*11, *N*12	2508.365	1*H*,7*H*-Dipyrido[1,2-*b*:1′,2′-*e*][1,4,2,5] dioxadiazine	**72LA(759)183**, 78JCS(P2)818, **82M339**, **92OS(70)265**
(56)	VI	*S*2, *N*5, *S*8, *N*11	2508.510	1*H*,6*H*-Pyrazino[2,1-*c*:5,4-*c*′]bis[1,4]thiazine	**79KGS1211**, **87MI 839-03**
(57)			2508.784	1*H*,7*H*-Bisphosphorino[1,2-*b*:1′,2′-*e*][1,4,2,5]dithiadiphosphorine	**90HAC37**

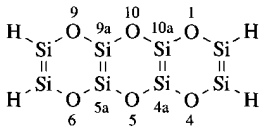
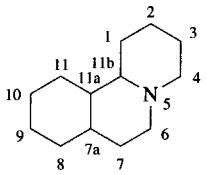
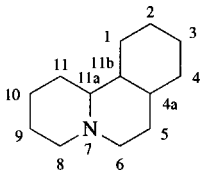
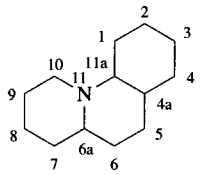
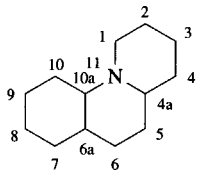
B.4 *Five ring heteroatoms*					
(58)	IX	*N*2, *N*5, *N*8, N^+10, *N*12	2508.662	1*H*-Dipyrimido[1,6-*a*:6′,1′-*d*][1,3,5]triazin-10-ium	**85CI(L)797, 86H(24)1893, 86USP4594413**
(59)	VIII	*N*1, *O*4, *N*5, N^+6, *N*12	2508.692	1*H*,8*H*-Pyrido[1′,2′:1,6][1,2,4]triazino[3,4-*b*][1,3,4]oxadiazin-6-ium	**86JCR(S)460**
(60)	VIII	*N*1, *S*4, *N*5, N^+6, *N*12	2508.626	1*H*,8*H*-Pyrido[1′,2′:1,6][1,2,4]triazino[3,4-*b*][1,3,4]thiadiazin-6-ium	**84S697**
B.5 *Six ring heteroatoms*					
(61)	V	*N*1, *N*3, *N*5, *N*7, *N*9, *N*11	2508.457	2*H*,6*H*-Pyrimido[1,6-*a*:3,4-*a*′]bis[1,3,5]triazine	**77CR(C)25, 80EJM341**
(62)	VI	*N*1, *N*5, *N*6, *N*7, *N*11, *N*12	2508.443	Dipyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazine	**76RTC282, 89EGP272303, 91CB2781**
(63)	VIII	*N*2, *N*5, *N*6, *N*8, *N*11, *N*12	2508.442	Dipyrimido[1,6-*b*:1′,6′-*e*][1,2,4,5]tetrazine	**76M1241, 90ZC133**
(64)	VIII	*N*2, *O*5, *N*6, *N*8, *O*11, *N*12	2508.425	1*H*,7*H*-Dipyrimido[1,6-*b*:1′,6′-*e*][1,4,2,5]dioxadiazine	**75CB3387**
(65)	VI	*O*2, *N*5, *N*6, *O*8, *N*11, *N*12	2508.358	1*H*,6*H*-Bis[1,4]oxazino[4,3-*b*:4′,3′-*e*][1,2,4,5]tetrazine	**65JA393**
B.6 *Eight ring nitrogen atoms*					
(66)	VI	*N*1, *N*2, *N*5, *N*6, *N*7, *N*8, *N*11, *N*12	2508.364	Bis[1,2,4]triazino[4,3-*b*:4′,3′-*e*][1,2,4,5]tetrazine	**67CB2585, 87S1134**
C. *Four ring junction heteroatoms*					
C.1 *Four ring heteroatoms*					
(67)	X	*N*5, *N*7, *N*12, *N*14	2508.370	6*H*,13*H*-Dipyridazino[1,2-*a*:1′,2′-*d*][1,2,4,5]tetrazine	**63JOC1144**, 72JA3138, 74JA576, 74JCS(P2)948, 76JA5748, 78LA1505, 79CB853, 80JCS(P2)91, 80JCS(P2)1733, 87MI 839-04
C.2 *Six ring heteroatoms*					
(68)	X	*O*2, *N*5, *N*7, *O*9, *N*12, *N*14	2508.596	1*H*,6*H*,8*H*,13*H*-Bis[1,3,4]oxadiazino[3,4-*a*:3′,4′-*d*][1,2,4,5]tetrazine	**84ZOR510**
(69)	X	*N*5, *P*6, *N*7, *N*12, *P*13, *N*14	2508.612	6*H*,13*H*-Dipyridazino[1,2-*a*:1′,2′-*d*][1,2,4,5,3,6]tetrazadiphosphorine	85AX(C)122, 87AX(C)170, **89PS(41)235**
(70)	XI	*N*5, *B*6, *N*7, *B*12, *N*13, *B*14	2508.4	6*H*,13*H*-Bis[1,2]azaborino[1,2-*a*:2′,1′-*d*][1,3,5]triazatriborine	71CCC1248
C.3 *Eight ring heteroatoms*					
(71)	X	*N*2, *N*3, *N*5, *N*7, *N*9, *N*10, *N*12, *N*14	2508.700	6*H*,13*H*-Bis[1,2,4,5]tetrazino[1,2-*a*:1′,2′-*d*][1,2,4,5]tetrazine	**88CB815**
(72)	X	*O*2, *O*3, *N*5, *N*7, *O*9, *O*10, *N*12, *N*14	2508.371	1*H*,4*H*,6*H*,8*H*,11*H*,13*H*-[1,2,4,5]Tetrazino[1,2-*d*:4,5-*d*]bis[1,2,4,5]dioxadiazine	**60LA(635)73**, 79JCS(P2)1133, 89CB1989
C.4 *Fourteen ring heteroatoms*					
(73)	X	*O*1, *N*2, *N*3, *O*4, *N*5, *O*6, *N*7, *O*8, *N*9, *N*10, *O*11, *N*12, *O*13, *N*14	2508.820	Bis[1,4,2,3,5,6]dioxatetrazino[2,3-*b*:2′,3′-*e*][1,4,2,3,5,6]dioxatetrazine	92JPC5184
(74)	X	*S*1, *N*2, *N*3, *S*4, *N*5, *S*6, *N*7, *S*8, *N*9, *N*10, *S*11, *N*12, *S*13, *N*14	2508.835	Bis[1,4,2,3,5,6]dithiatetrazino[2,3-*b*:[1,4,2,3,5,6]dithiatetrazine	93JPC4974
(75)	XI	*N*1, *B*2, *N*3, *B*4, *N*5, *B*6, *N*7, *B*8, *N*9, *B*10, *N*11, *B*12, *N*13, *B*14	2508.5	6*H*,13*H*-Bis[1,3,5,2,4,6]triazatriborino[1,2-*a*:2′,1′-*d*][1,3,5,2,4,6]triazatriborine	84RRC613
(76)			2508.372	1,4,5,6,9,10-Hexaoxa-2,3,4*a*,5*a*,7,8*a*,9*a*,10*a*-octasilaanthracene	**63MI 839-01**

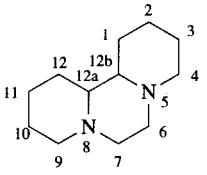
Table 2 Fused heterocyclic systems (6 : 6 : 6) with *Chemical Abstracts* ring identifier (2404) for the tricyclic skeleton. (References in bold refer to synthesis.)

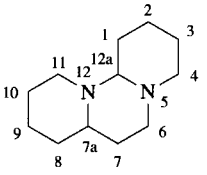

Type XII

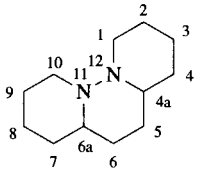

Type XIII


Type XIV


Type XV


Type XVI


Type XVII


Type XVIII

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
A One ring junction nitrogen atom					
A.1 Two ring heteroatoms					
(77)	XIII	*N*1, *N*7	2404.656	1*H*-Pyrido[1,2-*h*]-1,7-naphthyridine	**85EUP154142**, 87EUP216247, **87USP4690928**, 87USP4710504, **88JMC641**
(78)	XIV	*N*1, N^+11	2404.328	Pyrido[1,2-*a*][1,8]naphthyridin-11-ium	**78H(9)1717**, **B-79MI 839-01**, **80CPB220**, **80FES1052**, **81CPB2526**, **84MI 839-02**, **89UKZ839**, **92S798**, **93T2691**
(79)	XIII	*N*2, *N*7	2404.233	1*H*-Pyrido[2,1-*a*][2,7]naphthyridine	**67ACS580**
(80)	XIV	*N*2, *N*11	2404.692	2*H*-Pyrido[1,2-*a*][1,7]naphthyridine	**86UKZ506**
(81)	XIV	*N*3, *N*11	2404.290	2*H*-Pyrido[1,2-*a*][1,6]naphthyridine	**71USP3557100**, **86MI 839-01**, **86UKZ506**
(82)	XIII	*N*4, *N*7	2404.234	1*H*-Pyrido[2,1-*f*][1,6]naphthyridine	**67ACS580**, 67NAT381, 68AX(A)252, **70CPB124**, 72MI 839-01, 81CJC106, **94T9909**
(83)	XIII	*O*4, *N*7	2404.235	1*H*,6*H*-Pyrano[3,2-*a*]quinolizine	**72LA(761)25**, **83M349**
A.2 Three ring heteroatoms					
(84)	XIII	*N*1, *N*2, N^+7	2404.274	Pyridazino[3,4-*a*]quinolizin-7-ium	**71CC426**, **73AJC389**
(85)	XIV	*N*1, *N*2, *N*11	2404.687	2*H*-Pyridazino[4,3-*c*]quinolizine	**86MI 839-01**
(86)	XIV	*N*1, *N*3, *N*11	2404.532	2*H*-Pyrimido[5,4-*c*]quinolizine	**80CL817**
(87)	XIV	*N*1, *N*5, *N*11	2404.827	2*H*-Dipyrido[1,2-*a* : 3′,2′-*e*]pyrazine	**91S982**, **92JHC529**
(88)	XIV	*N*1, *N*6, *N*11	2404.330	2*H*-Dipyrido[1,2-*a* : 3′,2′-*e*]pyrimidine	**83M1197**, **85EJM61**, **86H(24)3075**, **86JHC509**, **87MIP554364**
(89)	XIV	*N*1, *N*7, *N*11	2404.329	2*H*-Pyrimido[1,2-*a*][1,8]naphthyridine	**66G1443**, **67G1262**, **67G1274**, **69G677**, **71GI29**, **71JCS(C)2985**, **72G253**, **77JCS(P1)789**, **90JHC881**
(90)	XIV	*N*1, *N*8, *N*11	2404.849	2*H*-Pyrazino[1,2-*a*][1,8]naphthyridine	**92S798**, **93H(36)1337**

(91)	XIV	*N*2, *N*4, *N*11	2404.738	2*H*-Pyrimido[4,5-*c*]quinolizine	**88MI 839-02**
(92)	XIV	*N*3, *N*5, *N*11	2404.844	2*H*-Dipyrido[1,2-*a*:3′,4′-*e*]pyrazine	**92JHC529**
(93)	XIV	*N*3, *N*7, *N*11	2404.359	2*H*-Pyrimido[1,2-*a*][1,6]naphthyridine	**74JHC151**
(94)	XIV	*N*4, *N*5, *N*11	2404.639	2*H*-Dipyrido[1,2-*a*:2′,3′-*e*]pyrazine	**85IJC(B)182, 89MI 839-02, 94FES259**
(95)	XV	*N*4, *N*7, *N*11	2404.482	1*H*-Pyrimido[1,2-*a*][1,5]naphthyridine	**78PJC1395**
(96)	XIV	*N*1, *O*8, *N*11	2404.850	[1,4]Oxazino[4,3-*a*][1,8]naphthyridine	**92S798**
(97)	XIV	*N*4, *O*5, *N*11	2404.764	Dipyrido[2,3-*b*:1′,2′-*d*][1,4]oxazine	**90JAP(K)02096580**
(98)	XIV	*O*1, *N*9, *N*11	2404.832	2*H*,5*H*-Pyrano[3′,2′:5,6]pyrido[1,2-*c*]pyrimidine	**92T349**
(99)	XIV	*N*1, *S*8, *N*11	2404.851	[1,4]Thiazino[4,3-*a*][1,8]naphthyridine	**92S798**
A.3 Four ring heteroatoms					
(100)	XIV	*N*1, *N*2, *N*6, *N*11	2404.718	2*H*-Pyrido[2′,1′:2,3]pyrimido[4,5-*c*]pyridazine	**88CB2049**
(101)	XIV	*N*1, *N*3, *N*5, *N*11	2404.714	2*H*-Pyrido[2,1-*h*]pteridine	**87T3955, 89JCS(P2)1691, 89MIP148975, 90CJC2164, 91JA1756**, 91MI 839-01, **91MI 839-02, 92MI 839-02**
(102)	XIV	*N*1, *N*3, *N*6, *N*11	2404.533	2*H*-Pyrido[1,2-*a*]pyrimido[5,4-*e*]pyrimidine	**80CL817, 85JHC173, 87KGS677**
(103)	XIII	*N*1, *N*4, *N*7, *N*10	2404.275	1*H*-Pyrido[1,2-*a*:3,4-*b*′]dipyrazine	**64MI 839-01**
(104)	XII	*N*1, N^+5, *N*6, *N*8	2404.246	Pyrido[3,2-*d*]pyrimido[1,2-*b*]pyridazin-5-ium	**71JOC2457, 85MI 839-03**
(105)	XII	*N*1, *N*5, *N*6, *N*9	2404.689	2*H*-Pyrido[4,3-*d*]pyrimido[1,2-*b*]pyridazine	**85MI 839-03**
(106)	XII	*N*1, *N*5, *N*6, *N*10	2404.690	2*H*-Pyrido[3,4-*d*]pyrimido[1,2-*b*]pyridazine	**85MI 839-03**
(107)	XII	*N*1, *N*5, *N*6, *N*11	2404.691	2*H*-Pyrido[2,3-*d*]pyrimido[1.2-*b*]pyridazine	**85MI 839-03**
(108)	XII	*N*1, *N*5, *N*7, *N*8	2404.471	2*H*-Pyrido[3,2-*e*]pyrimido[1,2-*c*]pyrimidine	**78JHC877**
(109)	XII	*N*1, *N*5, *N*7, *N*9	2404.564	2*H*-Pyrido[4,3-*e*]pyrimido[1,2-*c*]pyrimidine	**82EUP46446**
(110)	XIV	*N*1, *N*5, *N*7, *N*11	2404.608	2*H*-Pyrido[3′,2′:5,6]pyrazino[1,2-*a*]pyrimidine	**83IJC(B)1233, 88EUP257508**
(111)	XIV	*N*1, *N*5, *N*8, *N*11	2404.484	2*H*-Pyrazino[1,2-*a*]pyrido[3,2-*e*]pyrazine	**79USP4138564**
(112)	XIV	*N*1, *N*6, *N*7, *N*11	2404.678	2*H*-Pyrido[3,2-*e*]pyrimido[1,2-*a*]pyrimidine	**86JHC509, 87MIP554363**
(113)	XV	*N*1, *N*7, *N*8, *N*11	2404.553	1*H*-Pyrido[1,6-*b*:3,2-*c*′]dipyridazine	**81JA7011**
(114)	XIII	*N*2, *N*4, *N*5, *N*7	2404.769	1*H*-Pyrido[1,2-*c*]pyrimido[5,4-*e*]pyrimidine	**90MI 839-01, 91TL4473, 93JOC6976**
(115)	XIV	*N*2, *N*5, *N*7, *N*11	2404.717	2*H*-Pyrido[4′,3′:5,6]pyrazino[1,2-*a*]pyrimidine	**88EUP257508**
(116)	XIV	*N*2, *N*5, *N*8, *N*11	2404.485	2*H*-Pyrazino[1,2-*a*]pyrido[4,3-*e*]pyrazine	**79USP4138564**
(117)	XIV	*N*3, *N*5, *N*7, *N*11	2404.716	2*H*-Pyrido[3′,4′:5,6]pyrazino[1,2-*a*]pyrimidine	**88EUP257508**, 93BRP2257360, 93MI 839-01
(118)	XV	*N*3, *N*6, *N*7, *N*11	2404.486	1*H*-Pyrazino[1,2-*a*]pyrido[2,3-*e*]pyrazine	**79USP4138564**
(119)	XIV	*N*1, *O*6, *N*8, *N*11	2404.751	2*H*,8*H*-Pyrazino[2,1-*b*]pyrido[2,3-*d*][1,3]oxazine	**89MI 839-03**
(120)	XIV	*N*2, *N*3, *O*8, *N*11	2404.887	Pyridazino[4′,5′:5,6]pyrido[2,1-*c*][1,4]oxazine	**94H(37)171**
(121)	XIV	*N*1, *S*6, *N*7, *N*11	2404.546	2*H*,8*H*-Pyrido[2,3-*d*]pyrimido[2,1-*b*][1,3]thiazine	**81JHC495**
A.4 Five ring heteroatoms					
(122)	XII	*N*1, *N*2, *N*5, *N*6, *N*8	2404.247	2*H*-Pyrido[2′,3′,:4,5]pyridazino[6,1-*c*][1,2,4]triazine	**70M303**
(123)	XII	*N*1, *N*2, *N*5, *N*6, *N*11	2404.276	2*H*-Pyrido[3′,2′:4,5]pyridazino[6,1-*c*][1,2,4]triazine	**70M303**
(124)	XIV	*N*1, *N*3, *N*5, *N*7, *N*11	2404.607	2*H*-Pyrimido[2,1-*h*]pteridine	**83IJC(B)1233**
(125)	XIII	*N*1, *N*3, *N*6, *N*7, *N*11	2404.753	1*H*-Dipyrimido[1,2-*b*:4′,5′-*d*]pyridazine	**89T4485**
(126)	XIII	*N*1, *N*4, *N*5, *N*7, *N*11	2404.828	1*H*-Pyrimido[1,2-*c*]pteridine	**91CCC2288**
(127)	XII	*N*1, *N*5, *N*6, *N*8, *N*10	2404.752	2*H*-Dipyrimido[1,2-*b*:5′,4′-*d*]pyridazine	**89T4485**
(128)	XIV	*N*1, *N*6, *N*7, *N*8, *N*11	2404.679	2*H*-Pyrido[3′,2′,:5,6]pyrimido[2,1-*c*][1,2,4]triazine	**86JHC509, 90AF1349**
(129)	XIV	*N*2, *N*4, *N*5, *N*8, *N*11	2404.506	2*H*-Pyrazino[1,2-*f*]pteridine	**82JMC161**
(130)	XIV	*N*2, *N*4, *N*5, *N*9, *N*11	2404.355	2*H*-Pyrimido[1,6-*f*]pteridine	**74GEP(O)2330984**, 75B3338, **81JMC1086**, 83B1005, **84MI 839-03, 87B522**
(131)	XIV	*N*1, *N*4, *N*6, *S*7, *N*11	2404.447	2*H*,8*H*-[1,3]thiazino[3,2-*a*]pteridine	**77ACS(B)167**
(132)	XV	*N*3, *N*4, *S*6, *N*7, *N*11	2404.505	Pyrido[3′,2′,:5,6][1,4]thiazino[3,4-*c*][1,2,4]triazine	**79URP638068, 93KGS559**
(133)	XIV	*N*1, *N*3, *O*6, *O*7, *N*11	2404.393	2*H*,6*aH*,8*H*-[1,3]Oxazino[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazine	**75USP3860596**

Table 2 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
***A.5** Six ring heteroatoms*					
(134)	XIII	*N*1, *N*3, *N*5, *N*6, *N*7, *N*11	2404.622	1*H*-Dipyrimido[1,2-*c*:4′,5′-*e*][1,2,3]triazine	**84JCS(P1)1475**
(135)	XIV	*N*2, *N*3, *N*4, *N*6, *N*7, *N*11	2404.673	2*H*-Pyrimido[2′,1′,:2,3]pyrimido[5,4-*d*][1,2,3]triazine	**86JCS(P1)711**
(136)	XIV	*N*2, *N*4, *S*5, *N*7, *N*8, *N*11	2404.504	Pyrimido[5′,4′:5,6][1,4]thiazino[3,4-*c*][1,2,4]triazine	**93KGS559**
***A.6** Seven ring heteroatoms*					
(137)	XII	*N*1, *N*2, *N*5, *N*6, *N*7, *N*9, *N*11	2404.674	2*H*-Pyrimido[4,5-*e*][1,2,4]triazino[4,3-*c*][1,2,3]triazine	**86JCS(P1)711**
(138)	XIV	*N*1, *N*2, *N*5, *N*6, *N*7, *N*10, *N*11	2404.864	2*H*-Pyridazino[3,4-*e*][1,2,4]triazino[3,2-*c*][1,2,4]triazine	**93MI 839-02**
***B** Two ring junction atoms*					
***B.1** Two ring heteroatoms*					
(139)	XVI	N^+5, N^+8	2404.285	Dipyrido[1,2-*a*:2′,1′-*c*]pyrazinediium	*General chemistry*: 67AJC1213, **68AJC2951**, **68JCS(C)926**, 68T4411, 68T5433, 68TL2599, 69CCC2037, 69E1247, 69JA3822, **69JCS(C)610**, 69T4781, 70JCS(D)494, **71JHC29**, 72AX(B)1244, 72AX(B)3065, **72JCS(P1)138**, **72JHC1165**, 72JMR(8)207, 73JCS(P2)80, **74CPB157**, **74JHC303**, 76JA1711, **76ZN(B)115**, **77AJC657**, 77JCS(P2)445, 78JCS(F1)665, 78JPC1181, 82AJC1341, **82JCS(P1)125**, 83JA2350, 84ANC1030, **84H(22)803**, **84LA1731**, 85BBA(810)385, **85JOC2910**, 86CJC1711, **86CL2139**, 86JC265, 86TAL745, 87CJC2425, **87JA2876**, **87JOC521**, 87MI 839-05, 88CL373, 88JA8232, 88JOC4745, **88TL1569**, 89AG462, **89CB1023**, **89GEP(O)3717071**, **89JA5782**, 90CL493, 90MI 839-02, **90URP1594175**, 91BCJ1821, 91CPB956, 91EUP431547, **91JOC4678**, 91MI 839-03, 91MI 839-04, **91SM1819**, 92MI 839-03, **92TL1771**, 93JC271, **93JPC7800**, **94CC51**, 94JC217, 94MI 839-01 *Applications*: 67AJC1195, 67NAT381, 68NAT1067, 69NAT464, 70MI 839-01, 71MI 839-01, 72CI(L)195, 72MI 839-02, 72MI 839-03, 73JA3411, 73LA324, 75GEP(O)2500409, 75MI 839-02, 75MI 839-03, 76JCS(F1)2416, 77CJC2601, 77MI 839-01, 78IC1827, 78JA5790, 78JPC2662, 79JCS(F1)1912, 79JEC283, 79MI 839-02, B-79MI 839-03, 80CPL(74)314, 80JMOC539, 80JPC2762, 80MI 839-02, 80MI 839-03, B-80MI 839-04, 81JA4727, 81JA7270, 81JMOC261, 81JOC1255, 82IJ117, 82IJ147, 82JA2683, 82JA3618, 82JA7519, 82JEC211, 82MI 839-01, 82MI 839-02, 83CC1140, 83IC1672, 83JA5617, 83JCS(F1)1135, 83MI 839-01, 83NJC15, 84ANC866, 84JCS(F1)2255, 84JCS(F1)2693, 84JPC2009, 84JPC5845, 84MI 839-04, 84TL2867,

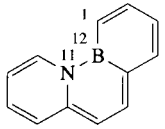
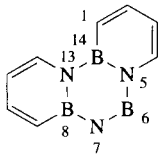
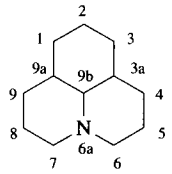
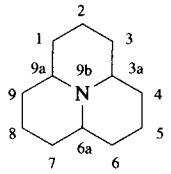
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(140)	XVII	*N*5, N^+12	2404.331	2*H*-Dipyrido[1,2-*a*:1′,2′-*c*]pyrimidin-5-ium	**70LA(737)1**, 71IJQ221, **76S201**, **93BCJ1222**
(141)	XVIII	N^+11, N^+12	2404.333	Dipyrido[1,2-*b*:2′,1′-*f*]pyridazinediium	71GEP(O)2017343
(142)			2404.2	Borino[1,2-*b*]pyrido[2,1-*f*][1,2] azaborine	71CCC1248
B.2 *Four ring heteroatoms*					
(143)	XVI	*N*1, *N*5, *N*8, *N*12	2404.545	Pyrazino[1,2-*a*:4,3-*a*′]dipyrimidine	**81TL1711**, 84EUP113582, **88MI 839-04**, 89MI 839-05, **90JCR(S)304**, **92JCS(P1)561**, **93JOC5753**
(144)	XVI	*N*2, *N*5, *N*8, *N*11	2404.548	Dipyrazino[1,2-*a*:2′,1′-*c*]pyrazine	**81JMC1329**, 83JA2350, 83MI 839-02, **85JMC1111**, **92USP5130426**, 93MIP9323075
(145)	XVI	*N*5, *N*6, *N*7, *N*8	2404.334	Dipyrido[1,2-*d*:2′,1′-*f*][1,2,3,4]tetrazine	**73AG50**, **74GEP(O)2327545**, **78HCA1622**, **94CB2073**
(146)	XVII	*S*1, *N*5, *S*8, *N*12	2404.488	2*H*,6*H*,9*H*,12*aH*-Pyrimido[2,1-*b*:4,3-*b*′]bis[1,3]thiazine	**79LA334**
B.3 *Six ring nitrogen atoms*					
(147)	XVII	*N*1, *N*3, *N*5, *N*8, *N*10, *N*12	2404.453	2*H*,6*H*-Pyrimido[1,2-*a*:3,4-*a*′]bis[1,3,5]triazine	**77CR(C)25**, **80EJM341**, 82MI 839-03
(148)	XVI	*N*2, *N*4, *N*5, *N*8, *N*9, *N*11	2404.803	Pyrazino[2,1-*f*:3,4-*f*′]bis[1,2,4]triazine	**90TL7665**, **92ZOR589**
(149)	XVI	*N*2, *N*5, *N*6, *N*7, *N*8, *N*11	2404.469	Dipyrazino[1,2-*d*:2′,1′-*f*]1,2,3,4]tetrazine	**78HCA1622**
B.4 *Seven ring nitrogen atoms*					
(150)	XVII	*N*1, *N*2, *N*5, *N*6, *N*8, *N*9, *N*12	2404.813	2*H*,6*H*-Bis[1,2,4]triazino[4,3-*b*:4′,3′-*d*][1,2,4]triazine	**91FES379**
C *Four ring junction atoms*					
C.1 *Six ring heteroatoms*					
(151)			2404.3	Bis[1,2]azaborino[1,2-*a*:1′,2′-*c*][1,3,5]triazatriborine	71CCC1248

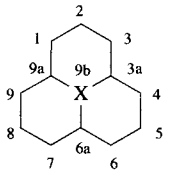
Table 3 Fused heterocyclic systems (6 : 6 : 6) with *Chemical Abstracts* ring identifier (1784) for the tricyclic skeleton. (References in bold refer to synthesis.)



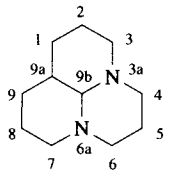
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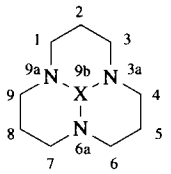
Type XX



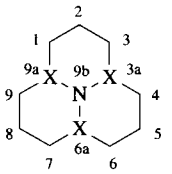
Type XXI



Type XXII



Type XXIII



Type XXIV

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
A One ring junction heteroatom					
A.1 One ring heteroatom					
(152)	XX	*N9b*	1784.137	Pyrido[2,1,6-*de*]quinolizine	*General chemistry*: **68YZ900**, **69CC24**, 69JCS(A)1754, 72BSB649, 72CC626, 72T3613, 72T3635, 72T3657, **72TL1767**, 73JA6702, 73MI 839-02, **74AJC2025**, 74TL409, **75CC565**, **75T1541**, **76CJC473**, **76CJC1494**, 76CJC1807, **76CPB2270**, **76JCS(P1)341**, **76TL2925**, 77IJC(A)238, 77JA1692, **77JOC3210**, 77JST(42)85, **77YGK739**, 78AHC(22)321, 78JST(49)415, **79JA7032**, **79TL1991**, 80JA6068, **80TL1027**, **80TL1093**, **80TL1097**, **81DIS(B)4524**, 82H(18)37, 84CCA991, **84JOC2217**, 84JPC1376, 85JA3884, **85JOC4028**, **86DIS(B)1919**, 86JA17, 86MI 839-06, 87ZC28, **88DIS(B)1662**, **89CPB1226**, 89JA7371, 89PAC2117, **91CC1261**, 92HAC19, **92SC3115**, 92TL1281, **93EJM869**, 94JHC929, **94T3139** *Applications*: 71C307, 71E1380, 72C74, 73MI 839-03, 74MI 839-02, 75E145, 78MI 839-01, 81KPS764, 86EUP172427, 91EUP451055, 91MI 839-07, 92MI 839-04, 92MI 839-05, 93MI 839-03
(153)	XXI	$S^{+}9b$	1784.152	9*b*-Thioniaphenalene	**72IZV2817**, **73ZOR636**, **74MI 839-03**
(154)	XXI	*P9b*	1784.151	9*b*-Phosphaphenalene	**69USP3435076**
(155)	XXI	*B9b*	1784.1	9*b*-Boraphenalene	

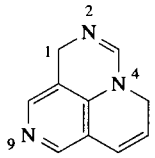
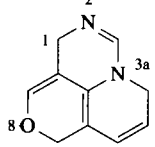
					General chemistry: 67JA5478, **68LA(717)21**, 69JA1226, 71JA7319, 73TL141, 74JOC861, 74LA54, 75CC565, **75DIS(B)1232**, 76GEP(O)2608584, **76TL2925**, 78CC805, 78JA3343, **78JOM(156)111**, **78USP4082810**, 79JMC401, **79JOC5004**, **80JOM(188)1**, **81T2359**, **83OS(61)103**, **84JOC2217**, 85JOC520, 88ZOR742, 89CC1639, 93T8311 *Applications*: 81USP4251422
A.2 Two ring heteroatoms					
(156)	XX	*N*1, *N*9*b*	1784.160	Pyrimido[2,1,6-*de*]quinolizine	**74CPB1424**, **74CPB1939**, **74YZ50**, **75CPB2759**, **75YZ1431**, **76CPB2270**, 78JST(49)415, 85JOC4028, **87H(26)2757**, **88CPB4307**, **89CPB1188**, **89CPB1226**, **92JAP(K)04338762**
(157)	XIX	*N*2, *N*6*a*	1784.113	1*H*,4*H*-Pyrido[3,2,1-*ij*][1,6]naphthyridine	**68KPS371**, **73JA8427**, **86CPB2018**
(158)	XIX	*O*1, *N*6*a*	1784.333	4*H*-Pyrano[2,3,4-*ij*]quinolizine	**91MIP9116894**
(159)	XX	*O*1, *N*9*b*	1784.138	2*H*-[1,3]Oxazino[2,3,4-*de*]quinolizine	**72TL1767**, 73MI 839-04, **74AJC2025**, **76CJC473**, **76CJC1494**, **80M783**, **80TL2229**, **93JA8851**
(160)	XIX	*O*2, *N*6*a*	1784.114	1*H*,3*H*,4*H*-Pyrano[3,4,5-*ij*]quinolizine	**58CPB222**, **59CPB241**
A.3 Three ring heteroatoms					
(161)	XX	*N*1, *N*3, *N*9*b*	1784.345	[1,3,5]Triazino[2,1,6-*de*]quinolizine	**92DIS(B)6403**
(162)	XX	*N*1, *N*4, *N*9*b*	1784.167	1,4,9*b*-Triazaphenalene	**75YZ13**, **77ACS(B)235**, **78CPB680**, **84CS170**, 85CPB3034, **87H(26)2757**, **87YZ344**, **89CPB1188**
(163)	XX	*N*1, *N*6, *N*9*b*	1784.168	1,6,9*b*-Triazaphenalene	**75CPB1629**, **85JOC4028**, **87(26)H2757**
(164)	XX	*N*1, *N*8, *N*9*b*	1784.365	1,8,9*b*-Triazaphenalene	93JIC693
(165)	XX	*N*1, *N*9, *N*9*b*	1784.166	1,9,9*b*-Triazaphenalene	**74CPB2765**, **75YZ13**, **76ACS(B)466**, **77JHC671**, **78YZ623**, 87H(26)2757, **89CPB1188**
(166)			1784.224	1*H*,5*H*-Pyrimido[5,6,1-*ij*][1,6]naphthyridine	**81CPB1193**, **82KGS518**, 83MI 839-03
(167)	XX	*N*2, *N*5, *N*9*b*	1784.363	2,5,9*b*-Triazaphenalene	93JIC693, 94JHC929
(168)			1784.230	1*H*,4*H*,7*H*-8-Oxa-2,3*a*-diazaphenalene	**82KGS518**
A.4 Four ring heteroatoms					
(169)	XIX	*N*1, *N*2, N^+6*a*, *N*9	1784.280	1*H*-1,2,9-Triaza-6*a*-azoniaphenalene	**85MI 839-03**
(170)	XX	*N*1, *N*3, *N*4, *N*9*b*	1784.178	1,3,4,9*b*-Tetraazaphenalene	**77ACS(B)235**, 85JA3884, 92HAC19

Table 3 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
(171)	XX	*N*1, *N*3, *N*6, *N*9*b*	1784.139	1,3,6,9*b*-Tetraazaphenalene	**72ACS596**, **72ACS611**, **72ACS624**, **73ACS2095**, **73ACS3259**, **73ACS3264**, **74CPB1424**, 75CPB1629, **75ACS(B)867**, 76JHC1029, **77ACS(B)239**, 81MI 839-02, **82JHC357**, 84MI 839-02, 85JCS(P2)153, 85JA3884, 85JOC4028, **86JHC381**, 87CL675, **87JHC321**, **88CPB4307**, **88JHC1837**, **90JHC1591**, **91JHC987**, 92HAC19, 93JIC693, 94JHC929
(172)	XX	*N*1, *N*4, *N*7, *N*9*b*	1784.141	1,4,7,9*b*-Tetraazaphenalene	*General chemistry*: 68JCS(B)760, **69USP3444166**, **70M1037**, **79JCS(P2)143**, **81CAR(89)237**, **84CS170**, **86JA17**, 94JHC929 *Applications*: 68USP3397167, 69GEP(O)1914955, 74P2519, 74KPS752, 74USP3794609, 84EUP113582
(173)	XX	*N*2, *N*5, *N*8, *N*9*b*	1784.364	2,5,8,9*b*-Tetraazaphenalene	93JIC693, 94JHC929
(174)	XX	*O*1, *N*4, *N*7, *N*9*b*	1784.142	2*H*-1-Oxa-4,7,9*b*-triazaphenalene	**70M1037**, 74P2519
(175)	XX	*S*1, *N*4, *N*9, *N*9*b*	1784.346	2*H*-1-Thia-4,9,9*b*-triazaphenalene	**92PS(72)145**
(176)	XX	*O*1, *O*4, *O*7, *N*9*b*	1784.144	2*H*,5*H*,8*H*-1,4,7-Trioxa-9*b*-azaphenalene	**76CB650**, 77JEC193, 77MI 839-02, **89EGP265428**, **91JOC452**
A.5 Five ring heteroatoms					
(177)	XX	*N*1, *N*3, *N*4, *N*6, *N*9*b*,	1784.143	1,3,4,6,9*b*-Pentaazaphenalene	**72CC1070**, **74JHC627**, **76JHC127**, **77JHC341**, 78AX(B)1667, **81JHC75**, **82JHC357**, **83JHC1095**, 84AX(C)2108, 84JA4374, **84JHC429**, **85JA3884**, 85JCS(P2)153, **85JHC255**, 87CL675, **88JHC1837**, 89MI 839-06, 92HAC19, 93JIC693, 94JHC929
(178)	XX	*N*1, *N*3, *N*4, *N*7, *N*9*b*,	1784.157	1,3,4,7,9*b*-Pentaazaphenalene	**73ACS2421**, 93JIC693, 94JHC929
(179)	XX	*N*1, *N*3, *N*5, *N*7, *N*9*b*,	1784.181	1,3,5,7,9*b*-Pentaazaphenalene	**77JHC679**, 93JIC693, 94JHC929
(180)	XX	*N*1, *N*3, *N*6, *N*7, *N*9*b*	1784.140	1,3,6,7,9*b*-Pentaazaphenalene	**72ACS635**, 73ACS359, 93JIC693, 94JHC929
A.6 Six ring heteroatoms					
(181)	XX	*N*1, *N*3, *N*4, *N*6, *N*7, *N*9*b*	1784.163	1,3,4,6,7,9*b*-Hexaazaphenalene	**74JHC627**, 75MI 839-04, **81JOC1457**, **85JA3884**, 92HAC19, 93JIC693, 94JHC929
(182)	XX	*N*1, *N*3, *N*4, *N*6, *N*8, *N*9*b*	1784.182	1,3,4,6,8,9*b*-Hexaazaphenalene	**77JHC679**, 92HAC19
A.7 Seven ring heteroatoms					
(183)	XX	*N*1, *N*3, *N*4, *N*6, *N*7, *N*9, *N*9*b*	1784.145	1,3,4,6,7,9,9*b*-Heptaazaphenalene	*General chemistry*: **71ZOR972**, 72ZOB419, 76JC63, **76ZOB1423**, **76ZOB1653**, **77CR(C)913**, **77ZOB1763**, 79ZAK385, 80MI 839-04, 80MI 839-05, **80URP707917**, **80USP4205167**, **81MI 839-03**, **81MI 839-04**, **81MI 839-05**, **81ZOB2377**, **82JA5497**, **82NKK662**, 83MI 839-04, **83MI 839-05**, **84DIS(B)197**, **84JA2805**, **84JAP(K)59031861**, 84JAP(K)59033353, 84JPC4324, 84MI 839-05, 84PJC3, 84PJC13, 85EUP137652, **85JA3884**, 86MI 839-02, **86MI 839-03**, 86MI 839-04, **86MI 839-05**, **86URP1237668**, **87URP1294806**,

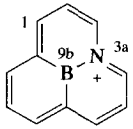
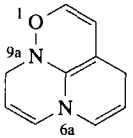
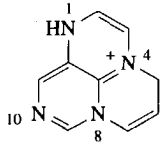
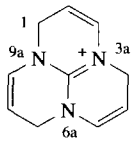
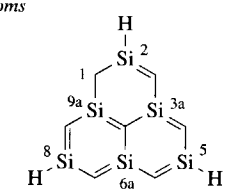
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(184)	XXI	*Sb*1, *Sb*3, *Sb*4, *Sb*6, *Sb*7, *Sb*9, *Sb*9*b*	1784.283	1,3,4,6,7,9,9*b*-Heptastilbaphenalene	87IC3797
(185)	XXI	*Si*1, *Si*3, *Si*4, *Si*6, *Si*7, *Si*9, *Si*9*b*	1784.154	1,3,4,6,7,9,9*b*-Heptasilaphenalene	**58AG701**, **59ZAAC(299)232**, 59ZAAC(299)316, **59ZAAC(302)60**
B *Two ring junction atoms*					
B.1 *Two ring heteroatoms*					
(186)			1784.2	3*a*-Azonia-9*b*-boraphenalene	**68TL2707**, 71CCC1248
B.2 *Three ring heteroatoms*					
(187)	XXII	*N*2, N^+3*a*, *N*6*a*	1784.233	1*H*,4*H*-2,6*a*-Diaza-3*a*-azoniaphenalene	**82BEP892120**, **82TL2891**, **83H(20)579**, **83H(20)1891**, **85H(23)1093**, **85H(23)1167**, **85H(23)2549**, **88MI 839-05**
(188)			1784.366	4*H*,9*H*-1-Oxa-6*a*,9*a*-diazaphenalene	**94JAP(K)06148845**
B.3 *Four ring heteroatoms*					
(189)	XXII	*N*1, *N*3*a*, *N*6*a*, *N*9	1784.133	1*H*,4*H*,7*H*-1,3*a*,6*a*,9-Tetraazaphenalene	**81TL1711**, **81TL2217**, **91T1013**
(190)			1784.222	1*H*,5*H*-Pyrimido[1,2,3-*ij*]pteridin-4-ium	**81H(15)437**

Table 3 (continued)

Tricyclic system	*Type*	*Positions of ring heteroatoms*	*Ring identifier (Chem. Abstr.)*	*Parent system*	*References*
C Three ring junction atoms					
C.1 Three ring nitrogen atoms					
(191)			1784.193	1*H*,4*H*,7*H*-6*a*,9*a*-Diaza-3*a*-azoniaphenalene	**78USP4085106**, **80JA6363**, **80JA6364**, **80JA6365**, **80TL3635**, **81TL4365**, 87AG1216, **87CC886**, 87MI 839-09, **87T1903**, 88MI 839-06, 89HCA1125, 89POL2333, **90DIS(B)1260**, 91TL7755, **92CC507**, 93AG640
C.2 Six ring silicon atoms					
(192)			1784.134	1*H*-2,3-*a*,5,6*a*,8,9*a*-Hexasilaphenalene	**72ZAAC(390)157**, **88JOM(341)109**
D Four ring junction atoms					
D.1 Four ring heteroatoms					
(193)	XXIII	*N3a*, *N6a*, *N9a*, *P9b*	1784.175	1*H*,4*H*,7*H*-3*a*,6*a*,9*a*-Triaza-9*b*-phosphaphenalene	76USP3996276, **77USP4038312**, **78TL4331**, 81JA2054
(194)	XXIII	*N3a*, *N6a*, *N9a*, *B9b*	1784.210	1*H*,4*H*,7*H*-3*a*,6*a*,9*a*-Triaza-9*b*-boraphenalene	**80JA5790**, 81JCS(D)511, **81JA6133**, **89JCS(P1)2079**, **91IC4524**
D.2 Seven ring heteroatoms					
(195)	XXIII	*P1*, *N2*, *P3*, *N3a*, *N6a*, *N9a*, *B9b*	1784.165	1*H*,4*H*,7*H*-2,3*a*,6*a*,9*a*-Tetraaza-1,3-diphospha-9*b*-boraphenalene	**74CB3806**
(196)	XXIII	*Si1*, *N2*, *Si3*, *N3a*, *N6a*, *N9a*, *B9b*	1784.5	1*H*,4*H*,7*H*-2,3*a*,6*a*,9*a*-Tetraaza-1,3-disila-9*b*-boraphenalene	**70CB2234**, **75CB3109**
(197)	XXIII	*B1*, *N2*, *B3*, *N3a*, *N6a*, *N9a*, *B9b*	1784.4	1*H*,4*H*,7*H*-2,3*a*,6*a*,9*a*-Tetraaza-1,3,9*b*-triboraphenalene	**651C886**
D.3 Thirteen ring heteroatoms					
(198)	XXIV	*N1*, *P2*, *N3*, *P3a*, *N4*, *P5*, *N6*, *P6a*, *N7*, *P8*, *N9*, *P9a*, *N9b*	1784.149	3*aH*,6*aH*,9*aH*-1,3,4,6,7,9,9*b*-Heptaaza-2,3*a*,5,6*a*,8,9*a*-hexaphosphaphenalene	71JCS(D)357, 72JCS(D)623, **73CJC520**
(199)	XXIV	*N1*, *B2*, *N3*, *B3a*, *N4*, *B5*, *N6*, *B6a*, *N7*, *B8*, *N9*, *B9a*, *N9b*	1784.136	1*H*,4*H*,7*H*-1,3,4,6,7,9,9*b*-Heptaaza-2,3*a*,5,6*a*,8,9*a*-hexaboraphenalene	67CJC2059, **84AG301**
(200)	XXIII	*Si1*, *N2*, *Si3*, *N3a*, *Si4*, *N5*, *Si6*, *N6a*, *Si7*, *N8*, *Si9*, *N9a*, *Sb9b*	1784.153	1*H*,4*H*,7*H*-2,3*a*,5,6*a*,8,9*a*-Hexaaza-9*b*-stiba-1,3,4,6,7,9-hexasilaphenalene	**72MI 839-04**
(201)	XXIII	*Si1*, *N2*, *Si3*, *N3a*, *Si4*, *N5*, *Si6*, *N6a*, *Si7*, *N8*, *Si9*, *N9a*, *Si9b*	1784.155	Tricyclo[7.3.1.$0^{5,13}$]heptasilazane	71MI 839-02, **79JAP(K)54093100**, 84MI 839-06
(202)	XXIII	*B1*, *N2*, *B3*, *N3a*, *B4*, *N5*, *B6*, *N6a*, *B7*, *N8*, *B9*, *N9a*, *B9b*	1784.3	1*H*,4*H*,7*H*-2,3*a*,5,6*a*,8,9*a*-Hexaaza-1,3,4,6,7,9,9*b*-heptaboraphenalene	67CJC2059

8.39.6.2.2 Formation of the terminal ring

This approach involves the construction of a third ring on a suitably substituted fused bicyclic substrate: **(2)**–**(4)**, **(7)** ⟨71JOC2192, 92JHC25⟩, **(11)** ⟨90ZC98⟩, **(16)** ⟨92MI 839-01⟩, **(18)**, **(22)**, **(23)** ⟨89CB1935, 90CB1415⟩, **(29)**, **(33)** ⟨78CB971⟩, **(37)**, **(41)**, **(42)**, **(47)**, **(50)**, **(59)**, **(60)**, and **(61)**.

8.39.6.2.3 Formation of two rings

Intramolecular and intermolecular tandem cyclizations of a suitably substituted six-membered heterocycle, which result in a simultaneous formation of two rings fused to the substrate ring, have been reported for **(5)** ⟨89MIP8905809⟩, **(10)**, **(13)**, **(14)**, **(19)**, **(21)**, **(31)** ⟨73CPB770⟩, **(33)** ⟨93HCA431⟩, **(44)**, and **(51)** ⟨85JMC1228⟩.

8.39.6.2.4 Formation of three rings

Derivatives of systems **(64)**, **(72)**, and **(76)** have been synthesized by one-pot cyclization of acyclic substrates.

8.39.6.2.5 Ring transformation

The synthesis of derivatives of **(23)** ⟨90CB1415⟩, **(36)**, **(48)**, and **(57)** involves a one-step ring transformation of a heterocyclic substrate.

8.39.6.3 Hetero Analogues of Phenanthrene (Table 2)

8.39.6.3.1 Formation of the central ring

The vast majority of systems in this class has been constructed by cyclization of an unfused heterobiaryl or a substrate composed of two six-membered heterocycles and linked by a two-atom bridge: **(78)**–**(82)**, **(84)**–**(87)**, **(90)**–**(92)**, **(97)**, **(102)**, **(108)**, **(109)**, **(111)**, **(112)**, **(116)**, **(118)**, **(120)**, **(126)**, **(128)**, **(140)**, **(141)**, and **(143)**. An intermolecular condensation of two appropriately functionalized six-membered heterocyclic substrates provides a facile synthetic entry to **(88)** ⟨83M1197, 86H(24)3075⟩, **(100)**, **(101)** ⟨92MI 839-02⟩, **(110)**, **(114)** ⟨91TL4473, 93JOC6976⟩, **(115)**, **(117)**, **(121)**, **(124)**, **(139)** ⟨85JOC2910⟩, **(145)**, **(146)**, **(148)**, and **(149)**.

8.39.6.3.2 Formation of the terminal ring

The cyclization of a substituted fused bicyclic substrate has been used in the preparation of derivatives of **(77)**, **(83)**, **(88)** ⟨86JHC509⟩, **(93)**–**(95)**, **(104)**–**(107)**, **(114)** ⟨90MI 839-01⟩, **(122)**, **(123)**, **(125)**, **(127)**, **(129)**–**(131)**, **(134)**, **(135)**, **(137)**, and **(138)**.

8.39.6.3.3 Formation of two rings

This approach involves mainly cyclization of substituents at a six-membered heterocycle which becomes the central ring in the product. Derivatives of the following systems have been prepared: **(89)**, **(96)**, **(99)**, **(119)**, **(132)**, **(133)**, **(136)**, **(144)**, **(147)**, and **(150)**.

8.39.6.3.4 Formation of three rings

One-pot cyclization of acyclic substrates provides a facile synthetic entry to substituted derivatives of **(103)** and **(113)**.

8.39.6.3.5 Ring transformation

Substituted derivatives of (**98**) and (**101**) ⟨87T3955, 91JA1756, 91MI 839-02⟩ have been obtained by ring transformations of heterocyclic substrates.

8.39.6.4 Hetero Analogues of Phenalene (Table 3)

8.39.6.4.1 Formation of one ring

Intramolecular cyclizations of *peri*-substituted fused bicyclic substrates (6 : 6) and intermolecular cyclizations that involve the *peri* positions of unsubstituted systems (6 : 6) have been applied to the synthesis of the following parent compounds or derivatives: (**152**) ⟨69CC24, 91CC1261⟩, (**156**)–(**158**), (**160**)–(**162**), (**165**) ⟨74CPB2765⟩, (**166**), (**168**), (**170**), (**183**) ⟨82JA5497, 84JA2805⟩, (**186**), (**187**), (**190**), (**191**) ⟨92CC507⟩, and (**195**)–(**197**).

8.39.6.4.2 Formation of two rings

A double cyclization of a substituted six-membered heterocyclic substrate provides a synthetic entry to derivatives of (**152**) ⟨94T3139⟩, (**153**), (**159**), (**165**) ⟨76ACS(B)466, 77JHC671⟩, (**169**), (**171**), (**175**), (**177**)–(**182**), and (**192**).

8.39.6.4.3 Formation of three rings

One-pot cyclization of acyclic substrates provides a facile synthetic entry to derivatives of (**152**) ⟨75CC565, 92SC3115⟩, (**172**), (**174**), (**176**), (**183**) ⟨86MI 839-05⟩, (**185**), (**189**), and (**198**)–(**201**).

8.39.6.4.4 Ring transformation

The synthesis of derivatives of parent compounds (**152**) ⟨80TL1093⟩ and (**163**) involves a one-step ring transformation of a heterocyclic substrate. Derivatives of (**153**)–(**155**), (**191**) ⟨80JA6365, 80TL3635, 81TL4365⟩, (**193**), and (**194**) have been obtained by reactions of macrocyclic compounds.

8.39.7 APPLICATIONS

Diverse applications have been found and many potential uses have been suggested for the parent compounds or derivatives of the three classes of fused heterocyclic systems (6 : 6 : 6). A detailed list of reports that deal with these topics can be found in Tables 1–3. When a particular system contains many references the publications describing mostly applications or potential applications are collected separately from the general chemistry references. The applications are also mentioned in the vast majority of the general references. The parent compounds or derivatives listed in Tables 1–3 are antitumor agents, (**37**), (**51**), (**53**), and (**144**); antibacterial and antiparasitic agents, (**22**), (**61**), and (**148**); antiallergy, antiinflammatory, and analgesic agents, (**6**), (**8**), (**17**), (**25**), (**27**), (**30**), (**32**), and (**36**); diuretics, (**109**); antihypertensives, (**111**) and (**116**); disinfectants and antiseptics, (**117**); inhibitors of phosphodiesterase, (**30**), (**34**), and (**36**); α-1-adrenergic and α-2-adrenergic receptor antagonists, (**77**); folate enzyme inhibitors, (**129**) and (**130**); fluorescent labels for DNA, (**25**) and (**101**); herbicides, (**139**); stabilizers for dyes and polymers, (**53**) and (**62**); and fireproofing agents for cotton fibers, (**193**). Compound (**155**) and its derivatives have been used in the synthesis of natural products which are derivatives of (**152**) ⟨75CC565, 76TL2925⟩.

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8.40
Systems with a Spirocyclic Heteroatom

GURNOS JONES
Keele University, UK

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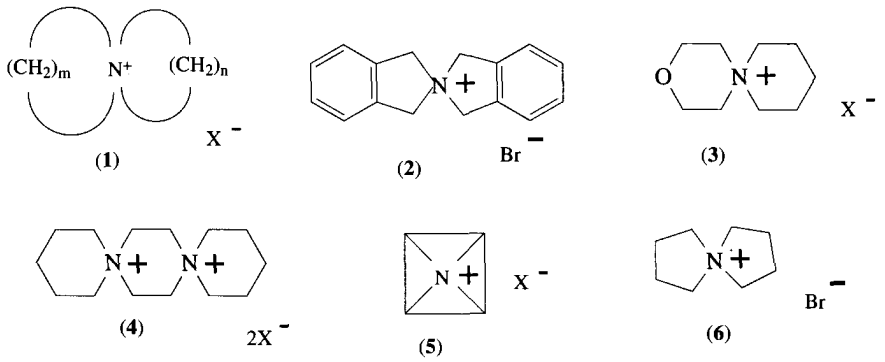
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8.40.1 INTRODUCTION

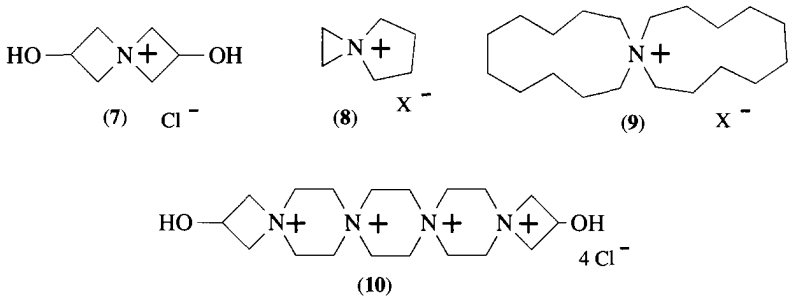
The compounds reviewed in this section are *spiro* fused, with a nitrogen atom at the point of fusion. The nitrogen is, of necessity, quaternary, and all the compounds described are salts or mesoionic. The main emphasis is on compounds where the rings attached to the nitrogen contain only carbon, but there is some coverage of rings with additional heteroatoms, and of diazonia and polyazonia systems with extra nitrogen *spiro* atoms. The range of compounds covered is illustrated by Structures (**1**)–(**5**), with the generalized azoniaspiro[*m*,*n*]alkane (**1**), the dibenzo derivative (**2**),

the 6-azonia-3-oxaspiro[5,5]undecane salts (**3**), the 6,9-diazonia-dispiro[5,2,5,2]hexadecane salts (**4**), and from a theoretical point of view only, the fenestrane (**5**).



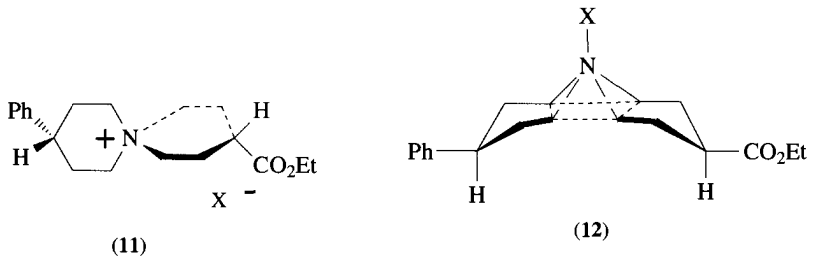
There are relatively few unsaturated compounds and, by definition, none are fully conjugated. There has been only one review published ⟨B-52MI 840-01⟩. The current nomenclature is illustrated above for compounds (**3**) and (**4**); the early literature can be confusing, describing compound (**6**) as a 1,1-spirobipyrrolidinium or *N*,*N*-tetramethylenepyrrolidinium salt.

Simple bicyclic systems (**1**) are known: from azoniaspiroheptanes (**7**) (a natural product, ⟨87JOC694⟩) and (**8**), to the heneicosane (**9**) ⟨73GEP(O)2236439⟩. There is in principle no limit to the number of fused *spiro* rings; 4,7,10,13-tetraazoniatetraspiro(3,2,2,2,3,2,2,2)docosane (**10**) has been reported as an intermediate ⟨84KFZ912⟩.



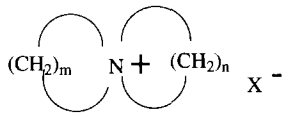
The range of compounds is shown in Tables 1–4 and Figures 1 and 2. No attempt has been made to tabulate all the *spiro* compounds which have been prepared; where there is no report of the parent system, a simple derivative is shown.

Historically, the azoniaspiroalkanes have been used to settle two controversial points of stereochemistry. There was much discussion of the valency of nitrogen in quaternary ammonium salts, the two views favouring a tetravalent tetrahedral or a pentavalent pyramidal structure. The dispute was settled by the synthesis of compound (**11**) by Mills and Warren ⟨25JCS2507⟩ which should be resolvable into enantiomers if the nitrogen has tetrahedral valencies, but not with the pyramidal formula (**12**) which has a plane of symmetry. The compound was resolved as its (*d*)-α-bromocamphorsulfonate.



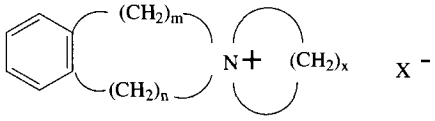
The second important result was the synthesis of a compound which was superimposable on its mirror image, although it has no plane or centre of symmetry, because it contains an alternating

Table 1 Bicyclic azoniaspiroalkanes.



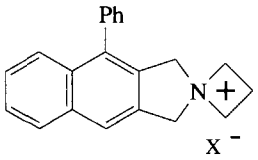
m	n	*Name*	*Ref.*
2	4	3-Azoniaspiro[2,4]heptane	68MI 840-01
2	5	3-Azoniaspiro[2,5]octane	65JOC821
3	3	4-Azoniaspiro[3,3]heptan-2,6-diol	87JOC694
3	4	4-Azoniaspiro[3,4]octan-2-ol	56GEP1111638
3	5	4-Azoniaspiro[3,5]nonane	1896CB2381, 68JOC1322
3	6	4-Azoniaspiro[3,6]decan-2-ol	56GEP1111638
4	4	5-Azoniaspiro[4,4]nonane	61MI 840-01
4	5	5-Azoniaspiro[4.5]decane	09CB545, 61MI 840-01
4	6	5-Azoniaspiro[4.6]undecane	54JA5099
4	7	5-Azoniaspiro[4,7]dodecane	54JA5099
4	8	5-Azoniaspiro[4,8]tridecane	54JA5099
5	5	6-Azoniaspiro[5,5]undecane	06CB4347, 61MI 840-01
5	6	6-Azoniaspiro[5,6]dodecane	54JA5099
5	7	6-Azoniaspiro[5,7]tridecane	54JA5099
5	8	6-Azoniaspiro[5,8]tetradecane	54JA5099
6	6	7-Azoniaspiro[6,6]tridecane	75JPC1527
6	7	7-Azoniaspiro[6,7]tetradecane	54JA5099
10	10	11 Azoniaspiro[10,10]heneicosane	73GEP(O)2236439

Table 2 Benzologues.

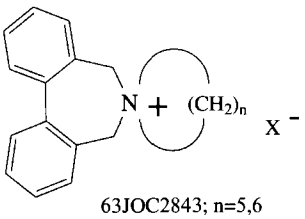


m	n	x	*Ref.*
1	1	4	63JOC2843
1	1	5	1898CB414, 10CB2304, 63JOC2843
1	1	6	54JA5099
1	1	7	54JA5099
1	1	8	54JA5099
1	2	4	12JCS1748, 16CB2629
1	2	5	16CB2629

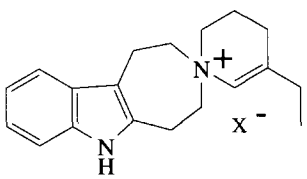
Miscellaneous



76MI 840-01



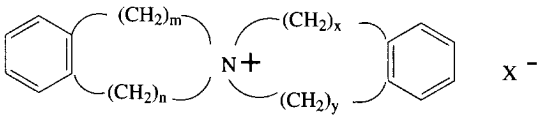
63JOC2843; n=5,6



78JOC3705
Reported intermediate

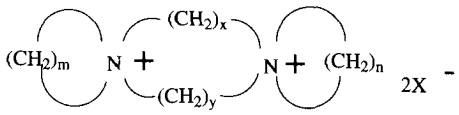
axis of symmetry (inversion axis). McCasland and Proskow showed, by synthesis of all the possible isomers of compound (**13**), that the isomer shown as (**14**) had zero rotation, whether synthesized as shown in Equation (1) from the two (*l*-) starting materials or from the isomeric (*d*-) pair ⟨55JA4688, 56JA5646⟩.

Table 3 Dibenzologues.

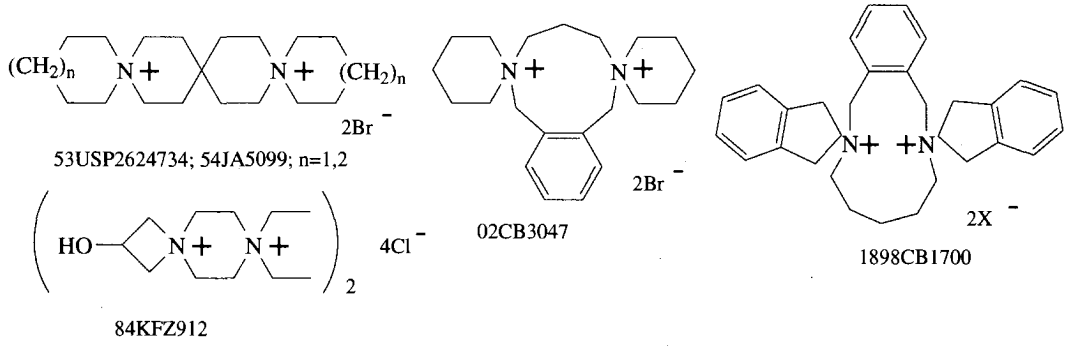


m	n	x	y	*Ref.*
1	1	2	0	14CB2162
1	1	3	0	10CB2304, 14CB2162
1	1	1	2	16CB2629

Table 4 Diazoniadispiroalkanes.



m	n	x	y	*Ref.*
2	2	2	2	25LA(445)247, 73USP3723621
4	4	2	2	54JA5099
4	4	2	3	54JA2427
4	5	2	2	54JA2427
4	5	2	3	54JA2427
5	5	2	2	54JA2427, 84AX(C)1478
5	5	2	3	54JA2427, 86AX(C)496, 87MI 840-01
5	5	3	3	02CB3047, 06CB1429
5	6	2	2	54JA2427
5	6	2	3	54JA2427
5	7	2	2	54JA2427
6	6	2	2	54JA2317, 54JA2427
6	6	2	3	54JA2427
6	7	2	3	56USP2743269
6	8	2	2	54JA2427, 56USP2743269
6	8	2	3	54JA2427
8	8	2	2	56USP2743269



53USP2624734; 54JA5099; n=1,2

02CB3047

1898CB1700

84KFZ912

Figure 1 Miscellaneous di- and polyazoniaspiroalkanes.

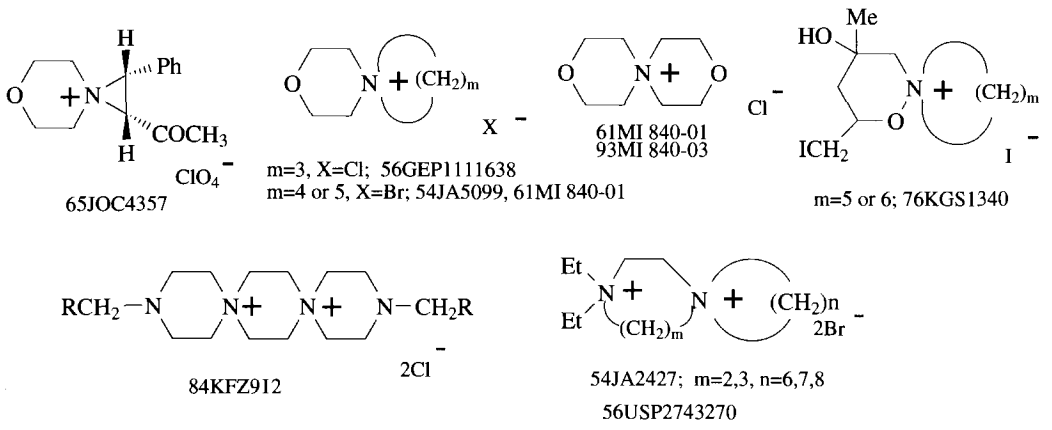
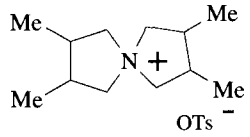
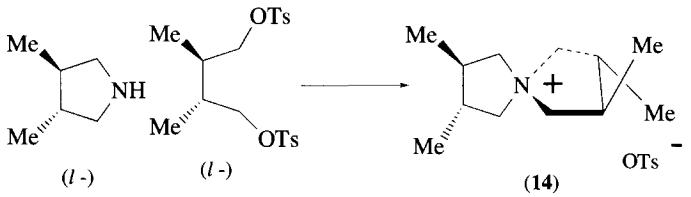


Figure 2 Azoniaspiroalkanes with additional heteroatoms.



(13)

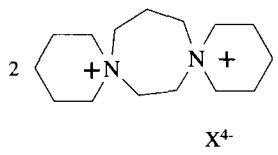


(1)

(*l*-) (*l*-) (14)

8.40.2 THEORETICAL METHODS

Little of significance has been done in the theoretical field with these, largely saturated, molecules. Molecular mechanics MM2 calculations of the dihedral angles of diazonia compound (**15**) were said to be well in agreement with those determined by x-ray diffraction ⟨86AX(C)1512⟩. The binding of some azoniaspiroundecanes to enzymic anionic sites is said to be dependent on $\delta C+$ on the carbon atoms adjacent to the quaternary nitrogen, and these values have been calculated ⟨61MI 840-02⟩. The most interesting calculations relate to the azoniafenestrane (**16**). Calculations using MINDO/3 and the *ab initio* STO-3G predict that the system will be stable in the pyramidal form shown in Figure 3, and "in principle experimentally detectable" ⟨82ZOR2009, 83MI 840-01, 84MI 840-01⟩.

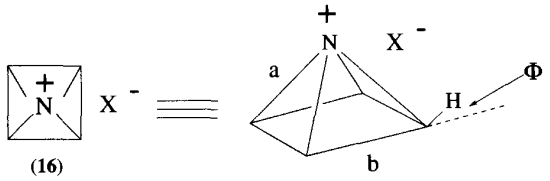


(15)

8.40.3 EXPERIMENTAL STRUCTURAL METHODS

8.40.3.1 X-ray Diffraction Studies

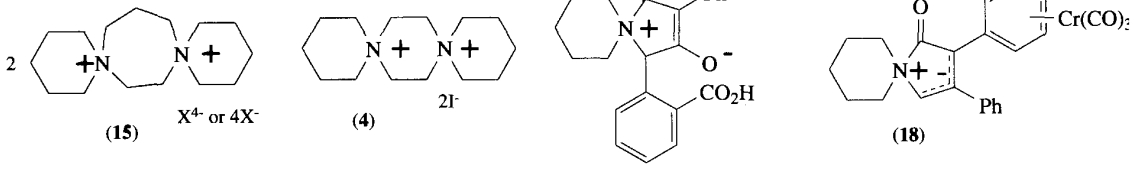
X-ray diffraction studies have been published on the diazoniadispiro derivatives (**15**; X = 4I) ⟨86AX(C)496⟩, (**15**; X = Ag_2I_8) ⟨86AX(C)1512⟩ and (**4**; X = I) ⟨84AX(C)1478⟩, in which the piperidine



(16)

Figure 3 Calculated bond lengths and angles for compound (**16**): a = 1.5772 Å, b = 1.478 Å, Φ = 5.2° (MINDO/3); a = 1.632 Å, b = 1.425 Å, Φ = 7.8° (STO-3G).

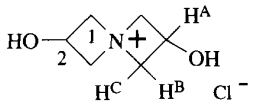
rings are shown to be in the chair form, with the central rings as distorted chairs. Structure (**4**; X = I) is centrosymmetric, with the N1 and N2 +0.65 Å with respect to the plane formed by C1, C2, C1′, C2′. The dihedral angles of compound (**15**; X = Ag_2I_8) agree well with those calculated by the molecular mechanics program MM2. X-ray diffraction has been used to determine the structures of the unusual unsaturated *spiro* derivatives (**17**) ⟨76JOC390⟩ and (**18**) ⟨91CC1075, 92JA8088⟩. All the structures firmly establish the tetrahedral bonding in the quaternary nitrogen.



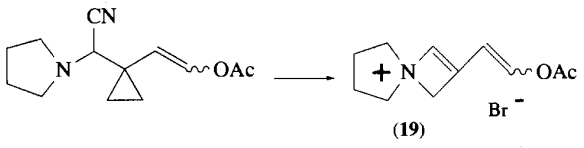
(15) (4) (17) (18)

8.40.3.2 NMR Spectroscopy

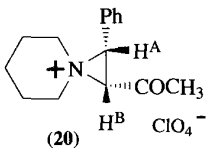
There are no systematic studies of NMR spectra. Individual reported spectra have been used for structure determination, as for the azoniaspiroheptane (**7a**) from the alga *Chara globularis* ⟨87JOC694⟩, and the azoniaspirononane (**19**) obtained by rearrangement as shown in Equation (2) ⟨85JA2191⟩. The ^1H and ^{13}C NMR spectra have been particularly useful for establishing the structures of azoniaspirooctanes such as (**20**) ($J_{A,B}$ = 9.7 Hz, therefore *cis*) ⟨65JOC4357⟩, where syntheses sometimes give diazoniadispiro[5,2,5,2]-hexadecanes ⟨92BMC1551⟩. NMR signals have been used to indicate the structure (**10**) for the intermediate obtained during the hydrolysis of Prospidine (Equation (3)) ⟨84KFZ912⟩. Line broadening in the ^1H signals of methyl groups has been used to study binding of quaternary ammonium salts which inhibit acetylcholinesterase, but the application of the method to salt (**21**) proved impractical because the signals were multiplets ⟨81MI 840-01⟩.



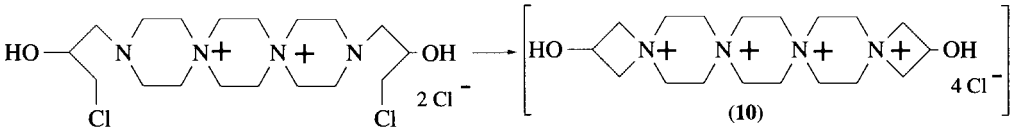
(**7a**) δ C1=64.5, δ C2=74.1ppm
$J_{A,B}$=4.0, $J_{A,C}$=6.2, $J_{A,B}$=12Hz



(19) (2)

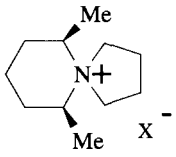


(20)



(10)

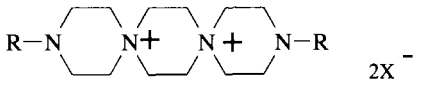
(3)



(21)

8.40.3.3 Mass Spectroscopy

There is no systematic study of mass spectra of azoniaspiroalkanes. Mass spectra of Prospidine and related compounds (**22**), using secondary emission spectroscopy, have been reported ⟨90OMS(25)432, 91KFZ78⟩. A minor adduct from prospidine and deoxyguanosine-5′-phosphate has been studied by soft-ionization mass spectrometry (Cf^{252} particle desorption mass spectrometry—PDMS) ⟨94RCM195, 94MI 840-01⟩.



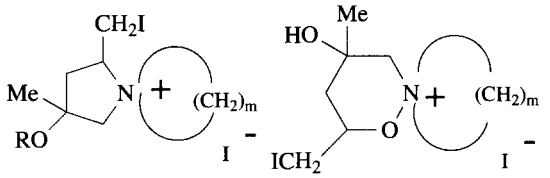
(**22**) R=$COCH_2CH_2Br$, X=Cl
R=$COCH_2CH_2Cl$, X=Br
R=$CH_2CH(OH)CH_2Cl$

8.40.3.4 Ultraviolet and Visible Spectroscopy

Most of the systems described have no absorption in the ultraviolet or visible region.

8.40.3.5 Infrared Spectroscopy

There are virtually no useful infrared absorptions reported for azoniaspiroalkanes. For the compounds (**23**) absorptions in the region 2400–3000 cm^{-1} are attributed to N^+ and in the related series (**24**) with heterocyclic oxygen, NOC stretch is reported at 1025–1030 cm^{-1} and CNO stretch at 1048–1060 cm^{-1} ⟨76KGS1340⟩. There is a report of the effect of azoniaspiroalkanes on the differential absorption spectra of H_2O/D_2O (1450 cm^{-1}) from 2 °C to 55 °C ⟨77MI 840-01⟩.

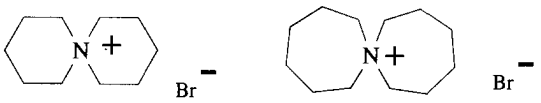


(**23**)

(**24**)

8.40.4 THERMODYNAMIC ASPECTS

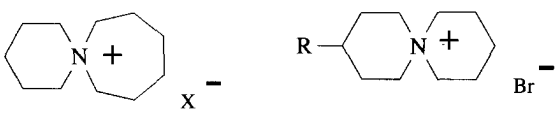
Quaternary ammonium salts have been widely used in studies of solution properties, and azoniaspiroalkanes have provided useful contrasts with the simple tetraalkylammonium salts where the N^+—C bonds have free rotation. In general terms a *spiro* derivative is less hydrophobic than the simple salt with the same number of carbon atoms. Almost all thermodynamic studies have been made on three azoniaspiroalkanes: (**6**), (**25**), and (**26**).



(**25**) (**26**)

Determination of densities and heat capacities of aqueous solutions of the salts (**25**) and (**26**) ⟨76JPC466⟩ and of the corresponding chlorides and iodides ⟨79MI 840-01⟩ at 25 °C, using a flow microcalorimeter and a flow densimeter, allowed the calculation of limiting apparent molal volumes and apparent molal heat capacities, which were compared with those of the equivalent tetraalkylammonium salts. The *spiro* compounds are smaller than the equivalent tetra-*n*-alkylammonium salts, and the heat capacity of water surrounding the ions is substantially reduced. Enthalpies of solution of salts (**6**), (**25**), and (**26**) were determined calorimetrically in water and in D_2O at 25 °C ⟨75JPC1527⟩, giving apparent molal heat contents and enthalpies of transfer. Enthalpies of solution of the three salts (**6**), (**25**), and (**26**) in binary solvent mixtures of H_2O and DMF ⟨79MI 840-02, 81JCS(F1)1191⟩ and in DMF/NMF(*N*-methylformamide) and DMF/H_2O at infinite dilution ⟨93PAC983⟩ again showed smaller hydrophobic contributions than for the tetraalkylammonium salts. Osmotic coefficients and enthalpies of dilution for salts (**6**), (**25**), and (**26**) were determined at 25 °C by an isopiestic method, and by flow microcalorimetry; activity coefficients, relative molal enthalpies, and excess apparent molal entropies were reported ⟨77JPC1813⟩. Solute–solute hydrophobic interaction of salts (**6**) and (**26**) and 1,2-dipalmitoyl-L-3-glycerylphosphatidylacetylcholine in aqueous dispersions with alcohols were studied by highly sensitive differential scanning microcalorimetry ⟨81JPC603⟩. A lowering of the transition phase temperature and a change in ΔH and ΔS was observed, paralleling the capacity for hydrophobic hydration and hydrophobic interaction with protein. The iodides corresponding to (**6**) and (**25**) were included in a study of molecular connectivity in which δ values were related to Van der Waal's radii; the predicted volumes were in good agreement with experimental data ⟨81EJM399⟩. Viscosity B_η and D_η coefficients for salts (**6**), (**25**), and (**26**) were determined using the Jones–Dole equation and were significantly lower than those of the equivalent tetra-*n*-alkylammonium salts ⟨79MI 840-03⟩.

The equivalent conductance of tetraalkylammonium perchlorates, determined in HMPA, included a value for salt (**27**) of 22.7 $cm^2\Omega^{-1}$ mol^{-1}, allowing the calculation of the effective radius from Stokes' Law ⟨77NKK135⟩. Determination of total conductivity of the double salt (**15**; X = Ag_2I_8) at 25 °C gave a value of 0.0083 Ω^{-1} cm^{-1}; a modification of Owens' Rule for the relationship between conductivity of solid electrolytes and cation volume of organic iodides was found necessary when more than one quaternary centre was present ⟨87MI 840-01⟩. Dielectric constants for salts (**6**), (**25**), and (**26**) were measured in the range 3–40 GHz at 25 °C by the interferometric transmission method; the dielectric relaxation times of the *spiro* derivatives were appreciably shorter than those for R_4N^+ X^- ⟨77JPC177⟩. Surface tensions of 10^{-2} M solutions of salts of type (**28**) were measured, and plotted against concentration ⟨63JPP167⟩. No break in the curve was observed, indicating that no micelles were formed.



(**27**) (**28**) R = various alkyl groups

In polarographic reduction of metal ions Na^+ and K^+ ⟨81MI 840-02⟩ and Zn^{2+}, Co^{2+}, and Ba^{2+} ⟨80MI2⟩, maximum waves in HMPA with *n*-Bu_4N^+ ClO_4^- as supporting electrolyte were effectively suppressed by addition of salt (**27**; X = ClO_4).

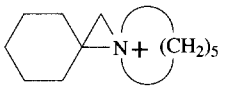
8.40.5 REACTIVITY OF FULLY CONJUGATED RINGS

There are no reported examples of fully conjugated rings.

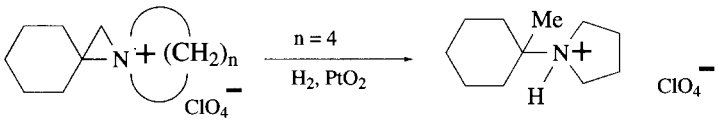
8.40.6 REACTIVITY OF NONCONJUGATED RINGS

8.40.6.1 Reduction

Polarographic reduction of the tricyclic azoniaspiroalkane (**29**) was compared with that of other aziridinium salts, proceeding via cleavage of the three-membered ring ⟨81JHC991⟩. The closely related salt (**30**) was cleaved regiospecifically by hydrogenation with a platinum oxide catalyst (Equation (4)) ⟨62JA4806⟩. There is one example of the reduction of a double bond within one of the spirocyclic rings of the diene (**31**) (Equation (5)) ⟨60JOC2230⟩.



(**29**)



(4)

(**30**)

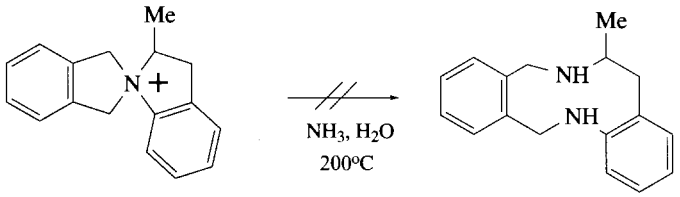


(5)

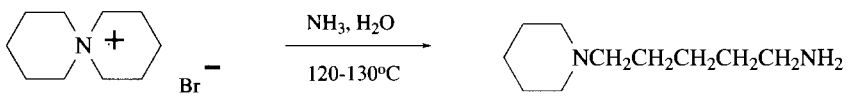
(**31**) 79%

8.40.6.2 Reaction with Ammonia and Amines

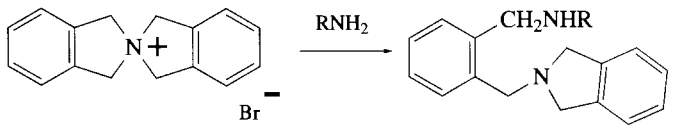
The reaction between ammonia or amines and azoniaspiroalkanes at high temperatures was for many years thought to give medium ring amines, as shown in Equation (6) ⟨1898CB414⟩, but von Braun and his co-workers showed that the products were *N*-(ω-aminoalkyl)pyrrolidines or -piperidines as illustrated by Equations (7), (8) and (9) ⟨25LA(445)247, 26CB2337⟩. In the case of the azoniaspiro[4,5]decane (**32**) the pyrrolidine ring was preferentially cleaved, giving *N*-(4-aminobutyl)piperidine (Scheme 1). Morpholinium salts (**33**) react similarly (Equation (10)) ⟨93MI 840-01⟩.



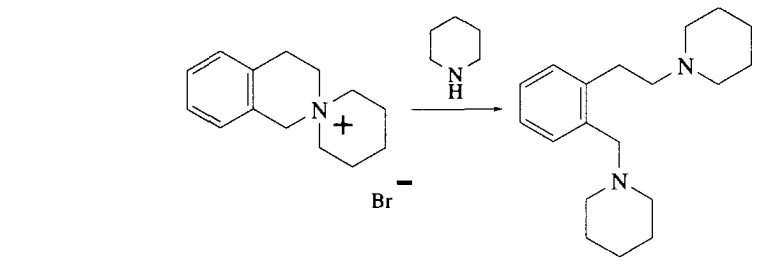
(6)



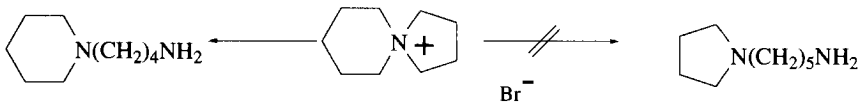
(7)



(8)

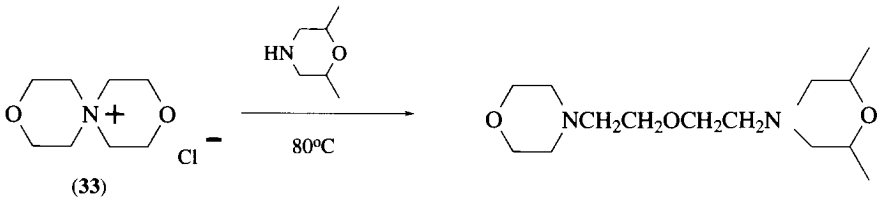


(9)



(32)

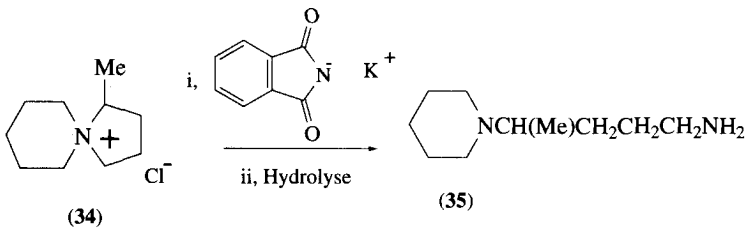
Scheme 1



(33)

(10)

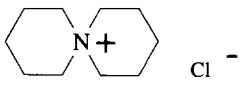
It has been reported that the azoniaspirodecane (**34**) reacts with potassium phthalimide to give, after hydrolysis, the *N*-alkylpiperidine (**35**) (Equation (11)), while the isomeric azoniaspiroundecane (**36**) fails to react ⟨44JOC359⟩. When one of the rings contains reactive groups, reaction with amines results in more profound changes, as in the formation of pyrroles (**39**) and (**40**) by treatment of the azoniaspiroalkenones (**37**) and (**38**) with benzylamine at 150–160 °C (Equation (12)) ⟨73ZOR2572, 74IZV2381⟩.



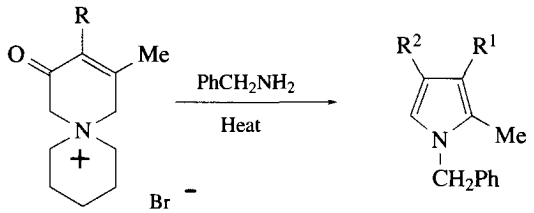
(34)

(35)

(11)



(36)



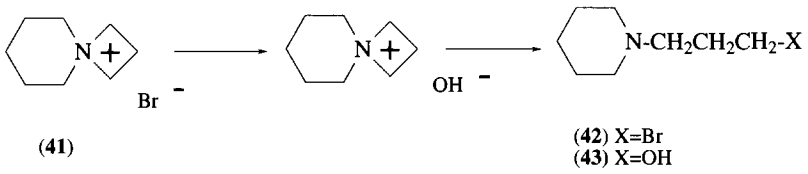
(37) R = H
(38) R = Et

(39) R^1 = H, R^2 = Me
(40) R^1 = Me, R^2 = Et

(12)

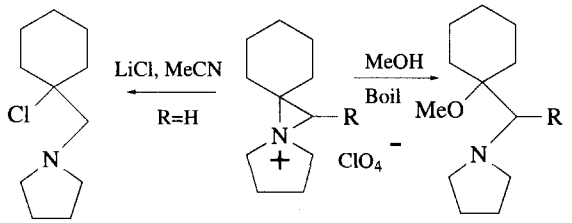
8.40.6.3 Hofmann Degradation and Related Reactions

The earliest degradation of azoniaspiroalkanes by heating the hydroxide was performed by Gabriel and Stelzner, in an attempt to prove the structure of their azoniaspirononane (**41**) (Scheme 2) ⟨1896CB2381⟩. Silver oxide treatment of the bromide, followed by steam distillation and treatment with hydrobromic acid gave the alkyl bromide (**42**). The intermediate alcohol (**43**) was subsequently isolated ⟨12JCS2000⟩. The most easily opened *spiro* compounds are those containing aziridinium rings. Boiling methanol opens the aziridinium ring in compound (**44**; R = H) by an S_N1 process to give the ether (**45**; R = H) (Scheme 3) ⟨62JA4806⟩. The ring opening is much slower when the central ring has an alkyl substituent as in (**44**; R = Me or Et). Equally striking is the ring opening of (**44**; R = H) by lithium chloride in acetonitrile, which gives a quantitative yield of the pyrrolidine (**46**) ⟨65JOC821⟩. Other examples are reported ⟨68JCED593, 67JOC3273⟩. At higher temperatures, chloride ion is reported to open the four-membered ring in salt (**47**) to give the piperidine (**48**) (Equation (13)) ⟨37CB210⟩.



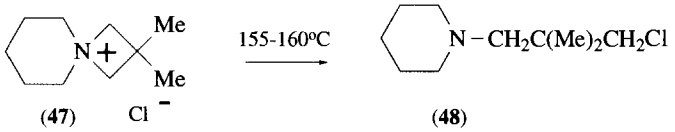
(**41**) (**42**) X=Br (**43**) X=OH

Scheme 2



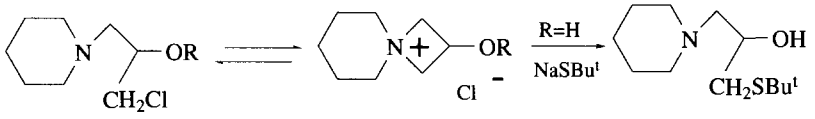
(**46**) (**44**) (**45**)

Scheme 3



(**47**) (**48**) (13)

A study of the formation from and ring-opening to compound (**50**) of the 4-azoniaspiro[3,5]nonanes (**49**) showed the equilibrium to be considerably changed by the substituent at position 2 ⟨68JOC523⟩. Thus, the free hydroxy derivative was 89.25% in the cyclic form, while the acetate was only 11.86% in the cyclic form; enthalpy and entropy values were calculated. The salt (**49**; R = H) gave the *t*-butylthioether (**51**) when treated with sodium *t*-butylthiolate (Scheme 4).

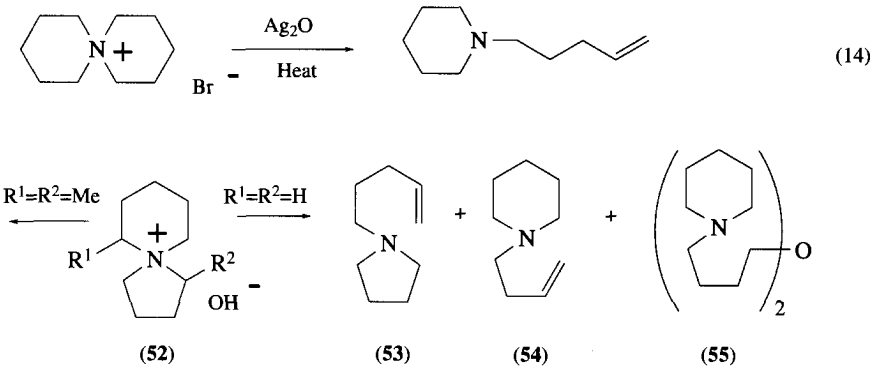


(**50**) (**49**) R=H or Ac (**51**)

Scheme 4

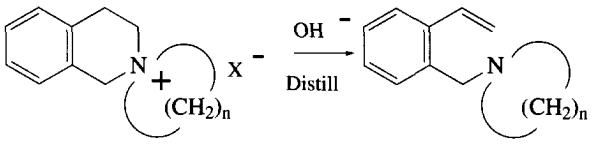
When both rings of the azoniaspiroalkane have five atoms or more, normal Hofmann elimination reactions occur, as in the early sequence shown in Equation (14) ⟨06CB4347⟩. Where the choice is available, elimination can occur with opening of either ring. Jewers and McKenna ⟨58JCS2209⟩ have examined the degradation of 5-azoniaspiro[4,5]decanes (**52**) in some detail. For the parent system (**52**; $R^1 = R^2 = H$) a 1 : 1 mixture of alkenes (**53**) and (**54**) was obtained; a substantial amount

of ether (**55**) was also formed; formation of ether was also observed in the degradation of 4-azoniaspiro[3,5]nonane ⟨07CB424⟩. In the system (**52**; $R^1 = R^2 = Me$) elimination gave only the pentenylpiperidine (**56**). These reactions are shown in Scheme 5.



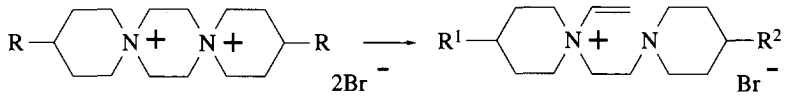
Scheme 5

In the benzologues (**57**) and (**58**), elimination gave the styrenes (**59**) and (**60**), the double bond forming in conjugation with the benzene ring (Equation (15)) ⟨16CB2629⟩. The tricyclic diazonia-dispiro compounds (**61**) related to prospidin undergo opening of the central ring under basic conditions; the side chains also undergo base-catalyzed reactions (Equation (16)) ⟨89KFZ794⟩. Other cases where direction of elimination is determined by potential conjugation are provided by salts (**62**) and (**63**) (Equation (17)) ⟨92ZOR343⟩. A case where α,β retroaldol bond cleavage followed by rearrangement is preferred is shown by the carbinol (**64**) (Equation (18)) ⟨82AG(E)198⟩.

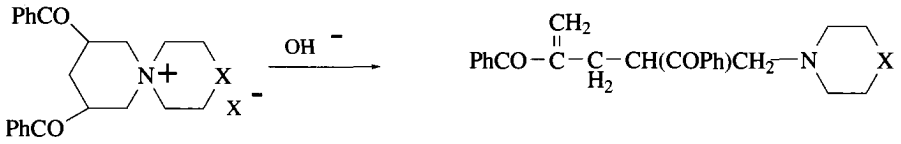


(**57**) n = 4
(**58**) n = 5

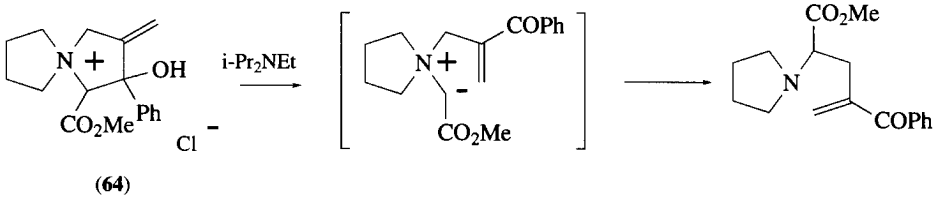
(**59**) n = 4
(**60**) n = 5



(**61**) R = $COCH_2CH_2Br$



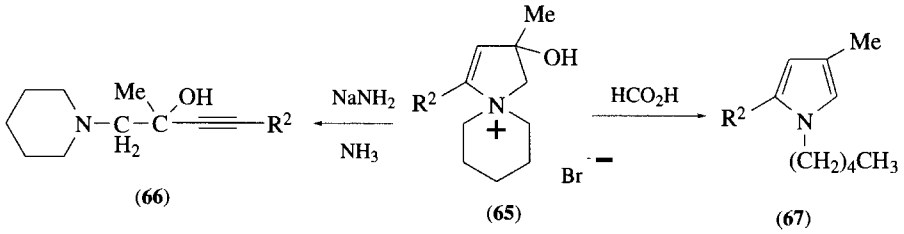
(**62**) X = CH_2
(**63**) X = O



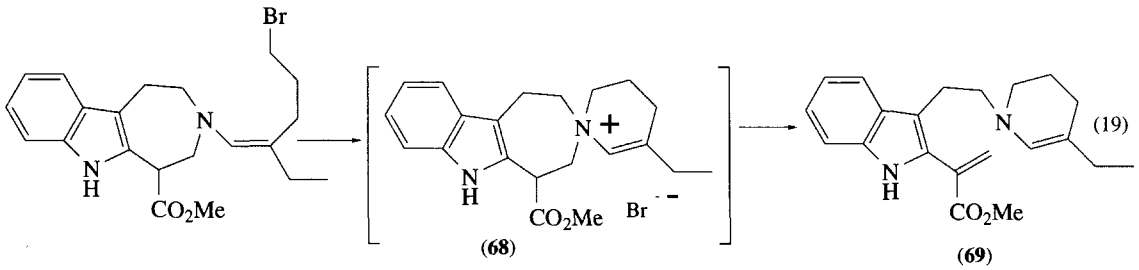
(**64**)

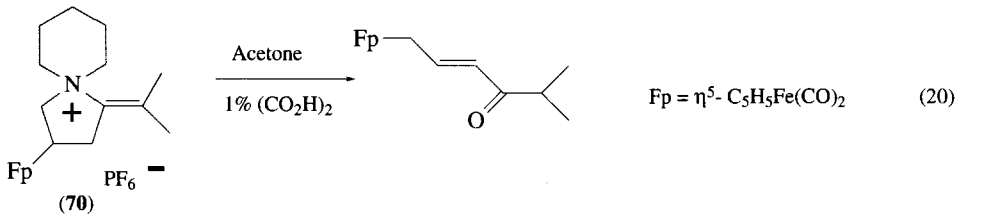
8.40.6.4 Miscellaneous Ring-opening Reactions

The azoniaspiroalkene (**65**) reacts with sodamide in liquid ammonia, with opening of the pyrrolenine ring, to give the alkyne (**66**), but with formic acid it gives the pyrrole (**67**) (Scheme 6) ⟨75BSF1777⟩. The instability of an azoniaspirododecene (**68**) has been used to produce an intermediate (**69**) for the synthesis of an indole alkaloid (Equation (19)) ⟨78JOC3705⟩. Dilute acid treatment of the azoniaspirodecane (**70**) gives an enone with the loss of the piperidine ring (Equation (20)) ⟨76JA3495⟩. The mesoionic *spiro* compounds (**71**) react with water, with methanol, or with dimethyloxirane to give products (**72**), (**73**), and (**74**) ⟨92JA8088⟩; thermolysis in boiling toluene gives compounds (**75**) (Scheme 7).



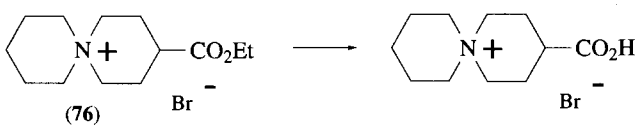
Scheme 6





8.40.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The ester (**76**) was hydrolyzed by boiling hydrobromic acid (Equation (21)) ⟨25JCS2502⟩.

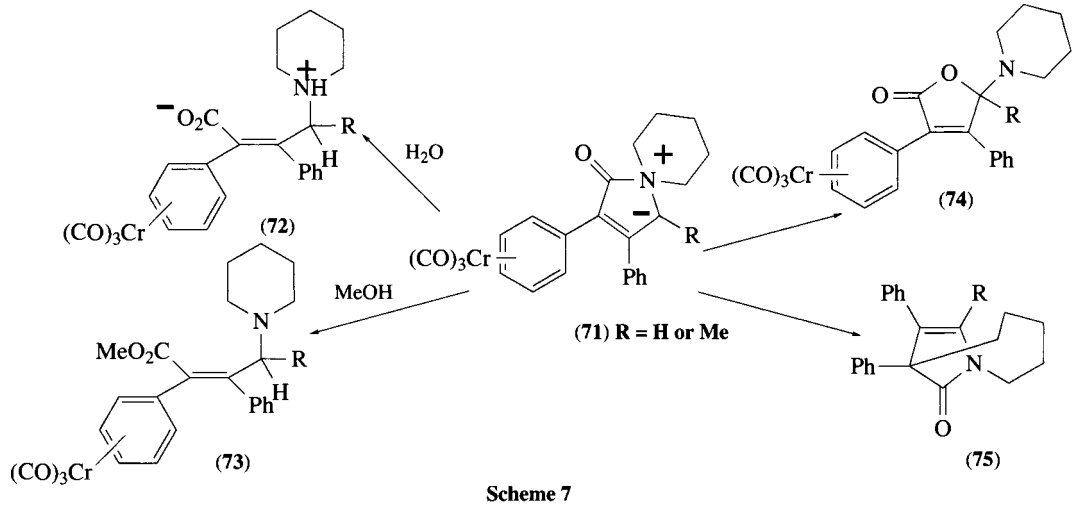


8.40.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

There are no examples of this type of reactivity.

8.40.9 RING SYNTHESES

The normal classification of syntheses adopted in these volumes is not suitable for the azoniaspiroalkanes. The syntheses are classified as follows: 8.40.9.1, Syntheses from acyclic components;

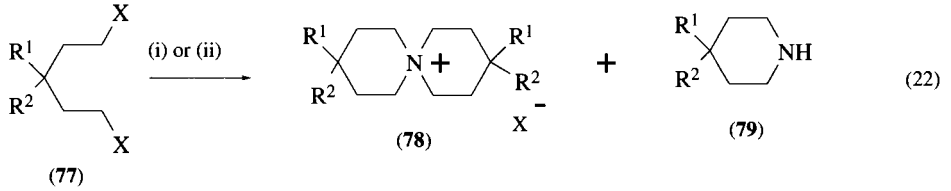


Scheme 7

8.40.9.2, Syntheses from a single monocyclic component; 8.40.9.3, Syntheses from a monocyclic amine and an acyclic component; 8.40.9.4, Syntheses from a diamine and one or more acyclic components; 8.40.9.5, Syntheses by ring transformation.

8.40.9.1 Syntheses from Acyclic Components

The most obvious route to azoniaspiroalkanes is from ammonia and an α,ω-dihalogenoalkane. The yields are never high, because of competing oligomerization, and usually mixtures of monocyclic amine and spirocompounds are obtained. Examples are provided by the synthesis from compounds (**77**) of 6-azoniaspiro[5,5]undecanes (**78**) mixed with amines (**79**) (Equation (22)) ⟨39JPR257, 52JA2885⟩. The second reference provides a comparison of the efficiency of this method compared with that described in Section 8.40.9.2; the dichloride (**77**; $R^1 = R^2 = Me$, X = Cl) reacts with piperidine to give an 80% yield of 3,3-dimethyl-6-azoniaspiro[5,5]undecane, which can be compared with average yields of around 30% shown in Table 5. The use of liquid ammonia to give a better yield of the (*d,l*) *cis,cis* compound (**80**) has been described (Equation (23)) ⟨55JA1862⟩.

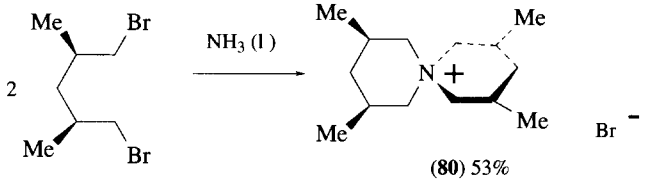


(22)

(i) MeOH / NH_3, 130-140°C
(ii) Aq. NH_3, 210°C

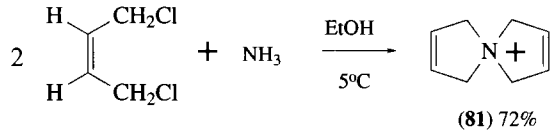
Table 5 Methods, substituents, and yields for Equation (22).

Method	R^1	R^2	*X*	% (*78*)	% (*79*)
(i)	Pr^i	H	Br	23	26
(i)	$(Et)_2CH$	H	Br	32	29
(i)	Ph_2CH	H	Br	38	36
(ii)	Me	Me	Cl	27	49

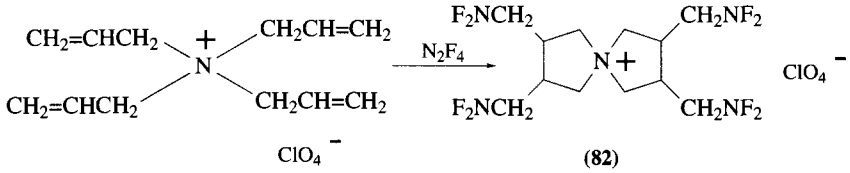


(80) 53% (23)

Dihalides of fixed *cis* geometry are obviously better suited to the synthesis; 5-azoniaspiro[4,4]nona-2,7-diene chloride (**81**) is obtained in 72% yield from the (*Z*) dichloride (Equation (24)) ⟨60JOC2230⟩. There is one example of the cyclization of a tetraalkylammonium perchlorate to the *spiro* compound (**82**) by dinitrogen tetrafluoride (Equation (25)) ⟨67USP3346589⟩.



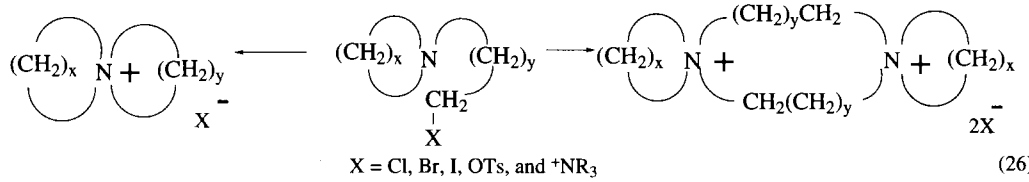
(**81**) 72% (24)



(**82**) (25)

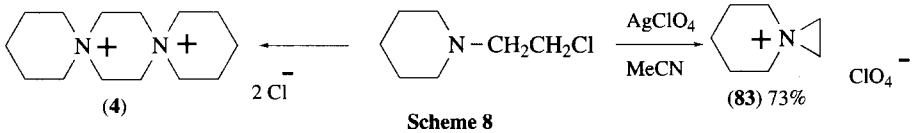
8.40.9.2 Syntheses from a Single Monocyclic Component

This route provides the most common method for the production of azoniaspiroalkanes and of diazoniadispiroalkanes, from *N*-ω-halogenoalkyl derivatives of cyclic amines. The generalized route is shown in Equation (26); the formation of diazonia species increases as *y* decreases.



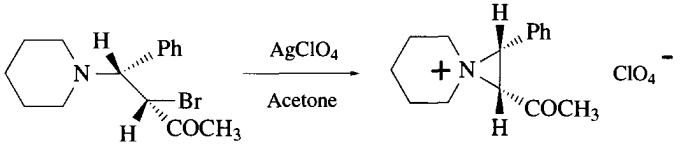
X = Cl, Br, I, OTs, and $^+NR_3$ (26)

Examples will be given in increasing ring size, with a variety of leaving groups, halogen being the most common. The intramolecular cyclization of *N*-(2-chloroethyl)piperidine in aqueous solution was reported by Marckwald and Frobenius in 1901 ⟨01CB3544⟩ to give 3-azoniaspiro[2,5]octane (**83**), but it is clear from the work of Leonard and his co-workers that under such conditions the product is the diazonia derivative (**4**) (Scheme 8). Leonard's conditions (nonaqueous solvent and silver perchlorate) ⟨65JOC821⟩ have been widely used to produce azoniaspirooctanes. Retention of configuration of substituents has been demonstrated by formation of compound (**20**) (Equation (27)) ⟨65JOC4357⟩, and by the chiral compound (**84**) from (*S*) propylene oxide (Equation (28)) ⟨92BMC1551⟩. The yield of compound (**20**) (61%) indicates a degree of toleration of steric hindrance in the cyclization. Cyclization of chloride or bromide (**85**), measured by first-order release of halide ion, is almost instantaneous in aqueous acetone buffered to pH 7.4 at 25°C or 37°C (Equation (29)) ⟨92MI 840-01, 93MI 840-02⟩, although the *spiro* compound was not isolated, being estimated by thiosulfate titration (see 8.40.10.2).



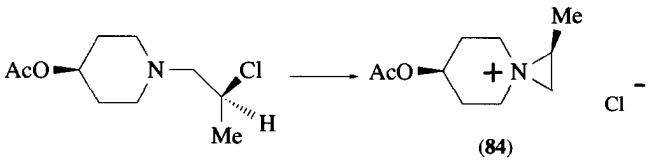
(**4**) (**83**) 73%

Scheme 8



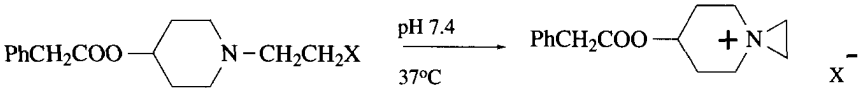
(20) 61%

(27)



(84)

(28)



(85) X = Cl, Br

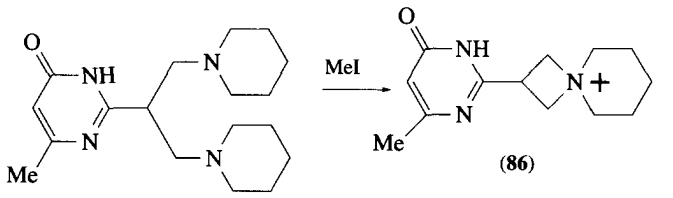
(29)

The formation of four-membered rings was also in dispute, although in this case the preparation of a 4-azoniaspiro[3,5]nonane (**41**) (Equation (30)) by Gabriel and Stelzner ⟨1896CB2381⟩ was repeated by Dunlop ⟨12JCS2000⟩ and finally confirmed by an NMR study on the perchlorate by Leonard and Durand ⟨68JOC1322⟩. Chloride, bromide, or iodide can be used as leaving group under aqueous or nonaqueous conditions. There is one case of a tertiary amine as leaving group under very mild conditions, to give the pyrimidinyl salt (**86**) (Equation (31)) ⟨54JA118⟩. Substituents on the four-membered ring affect the equilibrium between cyclized and uncyclized components (see Section 8.40.6.3) as does the size of the larger ring, piperidine being the least inhibiting to cyclization ⟨68JOC523⟩.



(41) X = Cl, Br, ClO_4

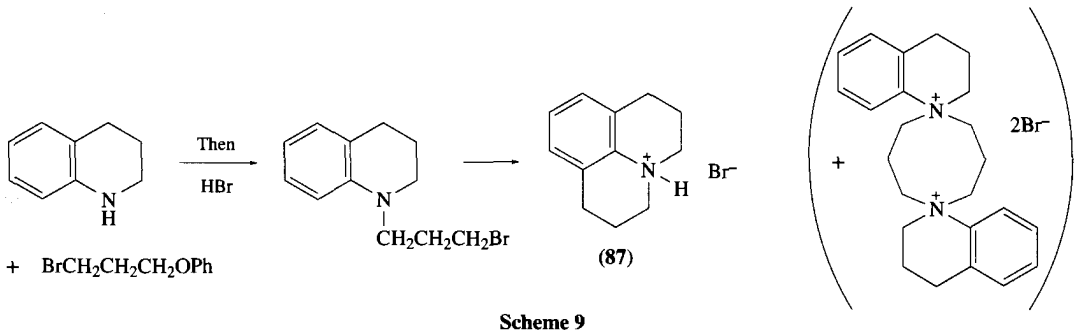
(30)



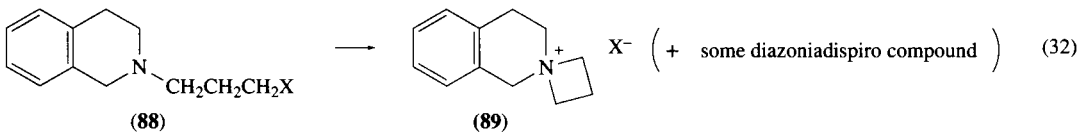
(86)

(31)

A curious reaction which has not been re-examined, is that of *N*-(3-bromopropyl)1,2,3,4-tetrahydropyridine, prepared as shown in Scheme 9, heated with base, and reported to give the julolidine salt (**87**) ⟨12JCS1748⟩. The corresponding *N*-alkyltetrahydroisoquinoline (**88**) gave the expected azoniaspiroalkane bromide (or iodide) (**89**) (Equation (32)). In both cases some diazonia-dispiroalkane, for example, (**90**), was obtained.

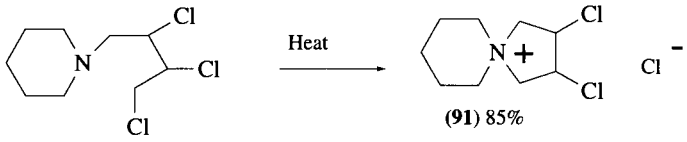


Scheme 9

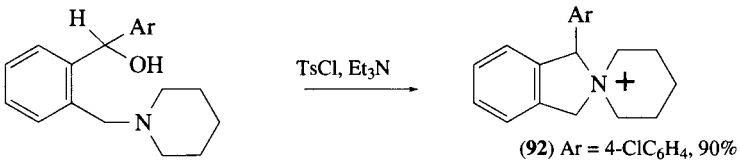


(88) (89) (32)

Five-membered rings are easily prepared by this route, with little interference from intermolecular alkylation. Examples have been chosen which show the preference for five-membered ring formation over competing three- or four-ring formation in compound (**91**) (Equation (33)) ⟨67JOC3273⟩, the high yield of the benzologue (**92**) achieved with tosylate as the leaving group (Equation (34)) ⟨62JOC4412⟩ (the stereochemistry is particularly favorable here), and the degree of hindrance which can be tolerated in the alkylating group in the synthesis of compound (**93**) (Equation (35)) ⟨06CB4347⟩.



(**91**) 85% (33)

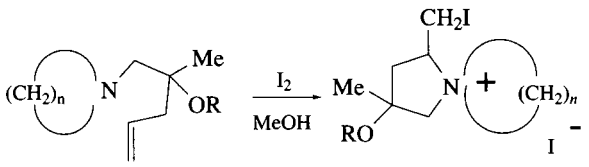


(**92**) Ar = 4-ClC_6H_4, 90% (34)

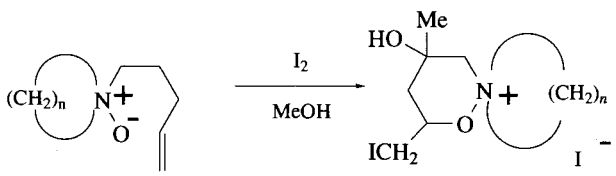


(**93**) 94% (35)

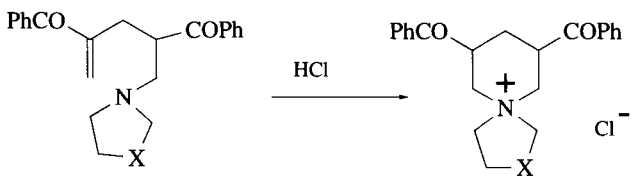
A variant used to form five- or six-membered rings relies on electrophilic attack by iodine upon a remote double bond followed by cyclization. Compounds of type (**23**) and (**24**) have thus been prepared (Equations (36) and (37)) ⟨76KGS1340⟩. A similar reaction initiated by hydrogen chloride has been reported to give compound (**94**) (Equation (38)) ⟨92ZOR343⟩.



(**23**) *n* = 2,5,6, R = H, Ac (36)

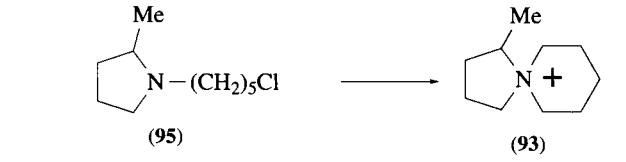


(**24**) *n* = 5,6 (37)

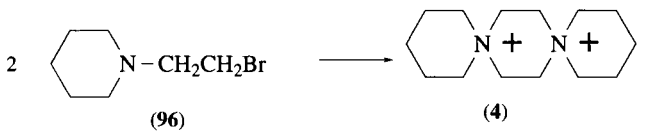


(**94**) X = CH_2 (82%) or OCH_2 (72%) (38)

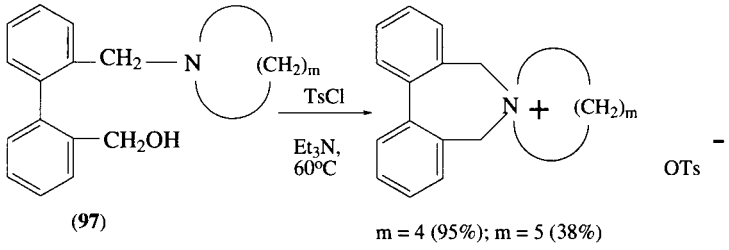
A simple example of the formation of a six-membered ring by unimolecular cyclization is provided by an alternative synthesis of the chloride of compound (**93**) from the pyrrolidine (**95**) (Equation (39)) ⟨44JOC359⟩, while bimolecular reaction of piperidine (**96**) gives the diazoniadispiro derivative (**4**) (Equation (40)) ⟨65JOC821⟩. A seven-membered ring can be formed if the stereochemistry of the starting material is suitable, as in compound (**97**) (Equation (41)) ⟨63JOC2843⟩; there is no obvious reason for the difference in yield between pyrrolidine and piperidine derivatives.



(39)

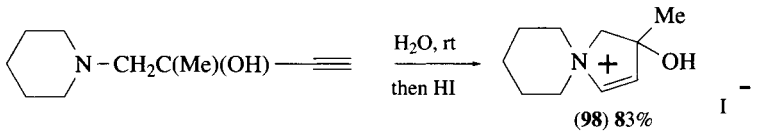


(40)

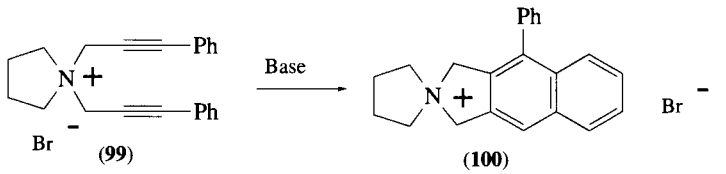


(41)

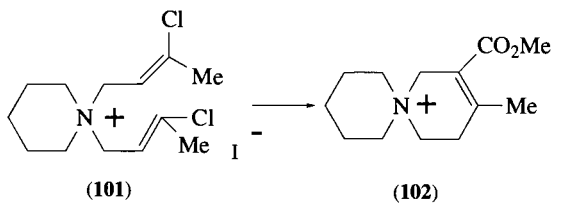
One synthesis makes use of nucleophilic addition of the amine to a suitably placed triple bond (5-*endodig*), producing compound (**98**) (Equation (42)) ⟨75BSF1777⟩. There are some syntheses under this heading in which the starting material is a quaternary salt, and cyclization occurs between carbon atoms. One involves the dialkyne (**99**), cyclized by base in 80–95% yield to the tetracycle (**100**) (Equation (43)) ⟨76AKZ173⟩, the second the cyclization of the diene (**101**) to give the azoniaspiroundecene (**102**) (Equation (44)) ⟨79MI 840-04⟩, and the third an aldol reaction to give compound (**64**) (Equation (45)) ⟨82AG(E)198⟩.



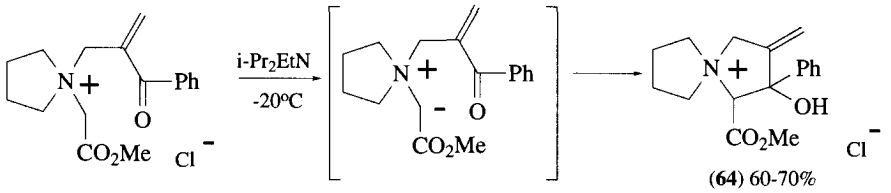
(42)



(43)



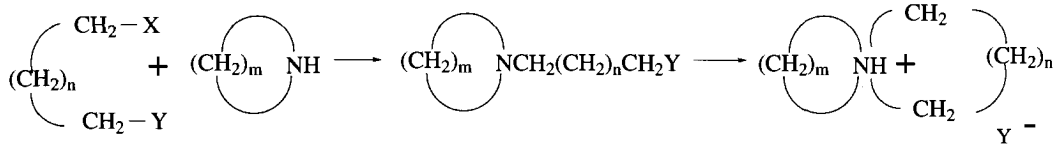
(44)



(45)

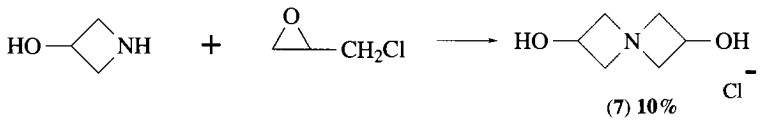
8.40.9.3 Syntheses from a Monocyclic Amine and an Acyclic Component

Some syntheses inevitably overlap with those described in Section 8.40.9.2; by far the most popular route is shown in Scheme 10, where the intermediate alkylated amine is sometimes isolated and subsequently cyclized.

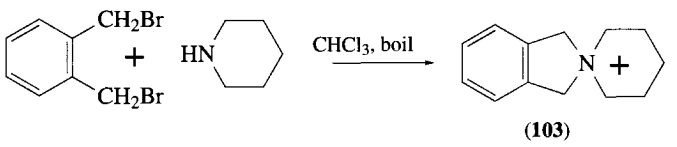


Scheme 10

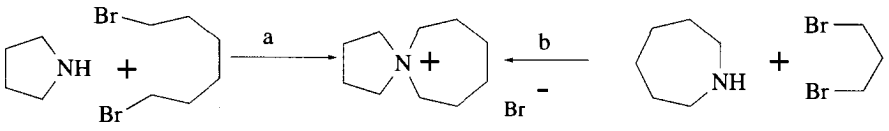
The smallest ring size obtained by this route is four membered, as shown by the synthesis, in poor yield, of 4-azoniaspiro[3,3]heptan-2,6-diol (**7**) from an azetidinol and a chloroepoxide (Equation (46)) ⟨87JOC694⟩. This method has undoubtedly been the method of choice for five- and for six-membered rings, often giving very high yields. The early cyclizations were performed in chloroform, with a subsequent treatment with base and solvent extraction to remove starting secondary amine and any intermediate tertiary amine, as illustrated by the synthesis of the benzologue (**103**) (Equation (47)) ⟨1898CB414⟩. When a choice of starting material is available, the use of α,ω-dihalobutanes or pentanes gives better yields than dihalohexanes, as shown for the synthesis of 5-azoniaspiro[4,6]undecane (**104**) (Scheme 11) ⟨54JA5099⟩. A range of syntheses is given, to illustrate the tolerance of steric hindrance in the production of compounds (**21**) from dimethylpyrrolidine ⟨69MI 840-02⟩ or from the hindered compound (**105**) ⟨57LA(608)22⟩ (Scheme 12) ⟨57LA(608)22⟩, and the incorporation of substituent groups of known stereochemical relationship, in compound (**106**) (Equation (48)) ⟨54JA3486⟩ (see also Section 8.40.1). The use of an *N*-benzoylamine is reported to give high yields of compound (**25**; X = Br) (Equation (49)) ⟨93MI 840-03⟩.



(46)

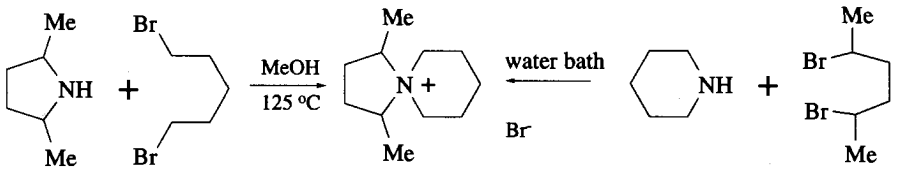


(47)



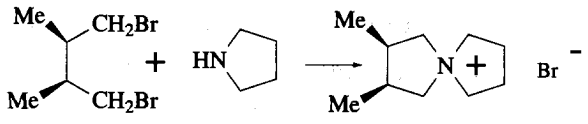
(**104**) route a (41%) route b (93%)

Scheme 11



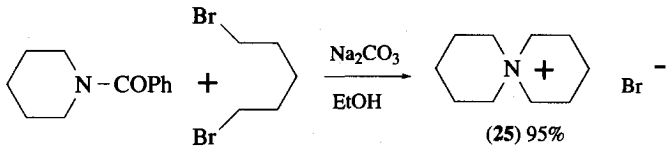
(105)

Scheme 12



(106) 60%

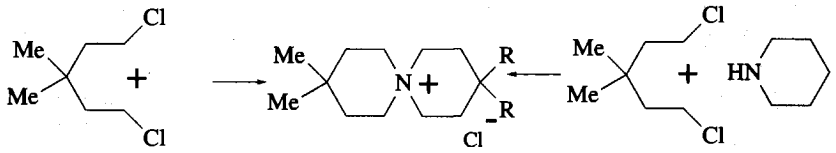
(48)



(25) 95%

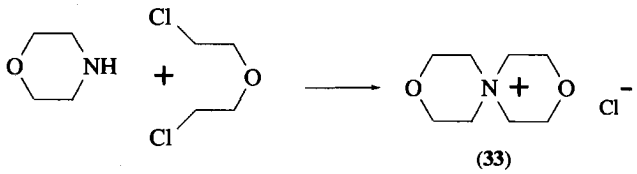
(49)

The advantages in yield to be gained over the alternative use of ammonia and excess halide can be seen in the synthesis of the substituted azoniaspiroundecane (**107**) (Scheme 13) ⟨52JA2885⟩, and the synthesis of compound (**33**) (Equation (50)) illustrates the production of azoniaspiroalkanes containing additional heteroatoms ⟨61MI 840-01⟩.



(**107**) R = Me(27%)
(**108**) R = H (80%)

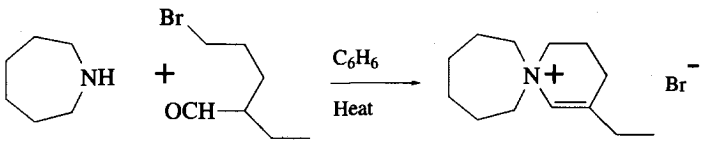
Scheme 13



(**33**)

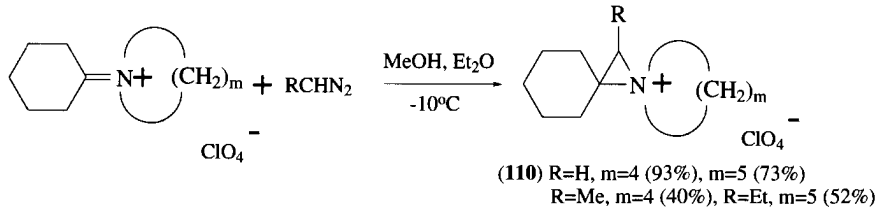
(50)

An azoniaspirodecene (**109**) has been prepared from hexahydroazepine and a 5-bromopentanal (Equation (51)) ⟨78JOC3705⟩. A number of aziridinium *spiro* compounds of type (**110**) have been made by addition of diazomethane to iminium salts (Equation (52)) ⟨60JA6418, 62JA4806⟩, and a cyclohexaazoniaspirononene (**111**) from an enamine and an acrylonitrile (Scheme 14) ⟨77BSB543⟩.

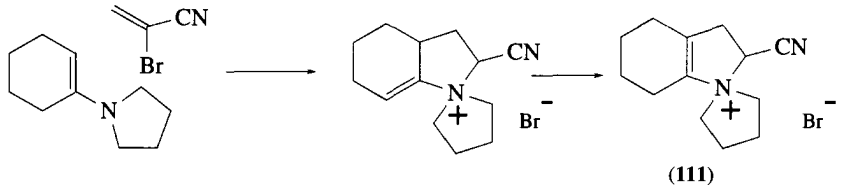


(**109**)

(51)

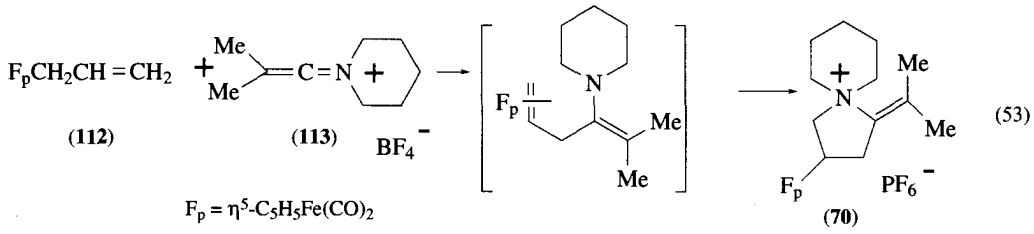


(52)

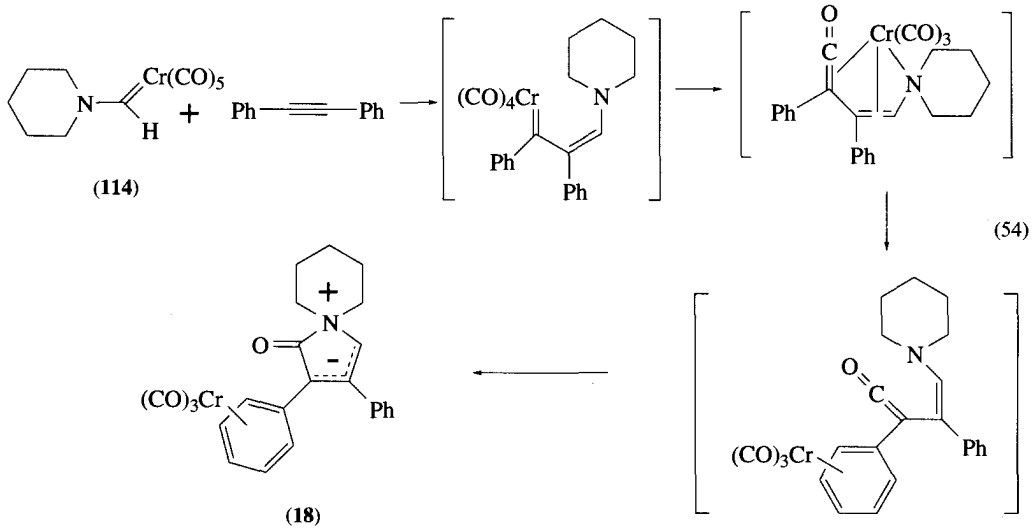


Scheme 14

Two routes involving organometallic reagents have been described. The allylcyclopentadienylirondicarbonyl (**112**) and the ketiminium salt (**113**) react at −60 °C to give an azoniaspiroundecane (**70**) (Equation (53)) ⟨76JA3495⟩, while the chromium tricarbonyl derivative (**114**) reacts with diphenylethyne to give the mesoionic derivative (**18**) (Equation (54)) ⟨91CC1075, 92JA8088⟩.



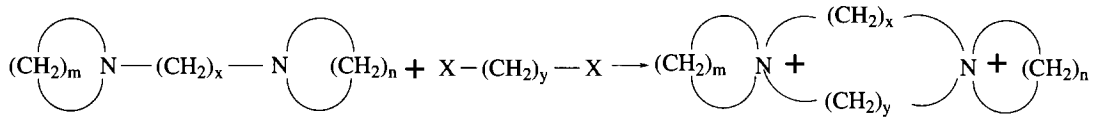
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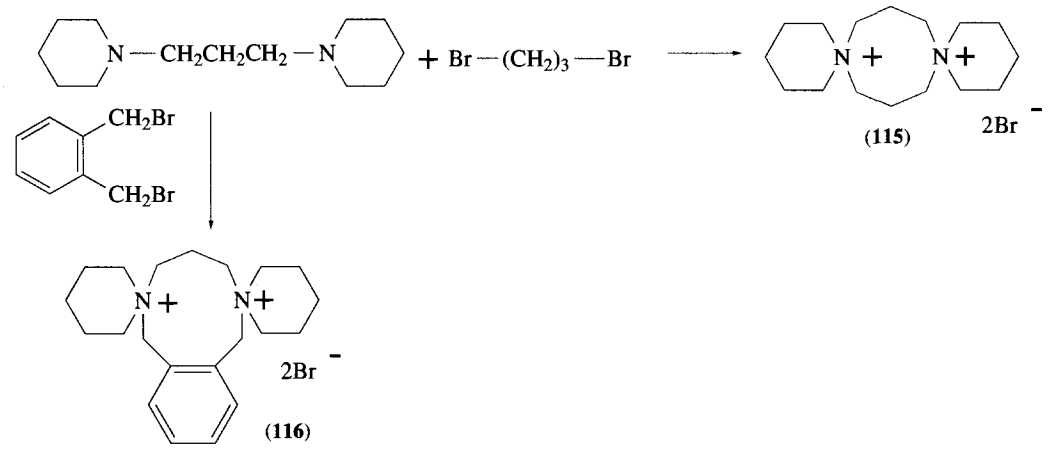
(54)

8.40.9.4 Syntheses from a Diamine and One or More Acyclic Components

A flexible route to diazoniadispiroalkanes is provided by the reaction shown in Equation (55). Using this route, Scholtz prepared compounds with central rings containing eight and nine atoms, (**115**) and (**116**) (Scheme 15) ⟨02CB3047⟩, and Blicke and Hotelling prepared bicyclic diazoniaspiroalkanes such as (**117**) and tricyclic diazoniadispiroalkanes with various rings A, B and C, up to the 7,11-diazoniadispiro[6,2,8,3]eicosane (**118**) ⟨54JA2427, 56USP2743269, 56USP2743270⟩.



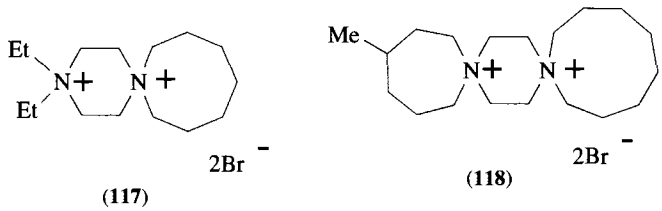
(55)



(115)

(116)

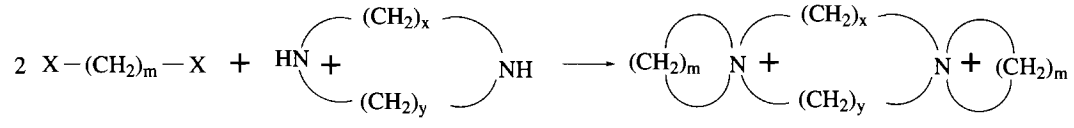
Scheme 15



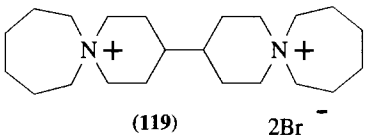
(117)

(118)

The alternative approach to these diazoniadispiroalkanes is from a diamine and two equivalents of dihaloalkane, as in Equation (56). This route is less versatile since the outer rings must be of the same size. Thus, piperazine gives compound (**4**, X = Br) ⟨25LA(445)247, 54JA5099⟩, 1,4-diazetidine gives compound (**15**; X = Br) ⟨87MI 840-01⟩, and 4,4′-bipiperidine gives compound (**119**) ⟨54JA5099⟩.



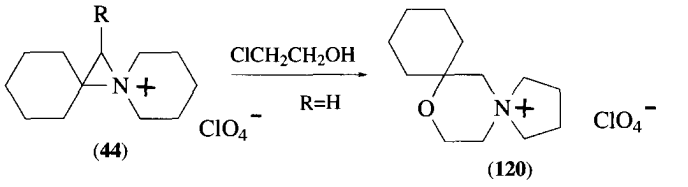
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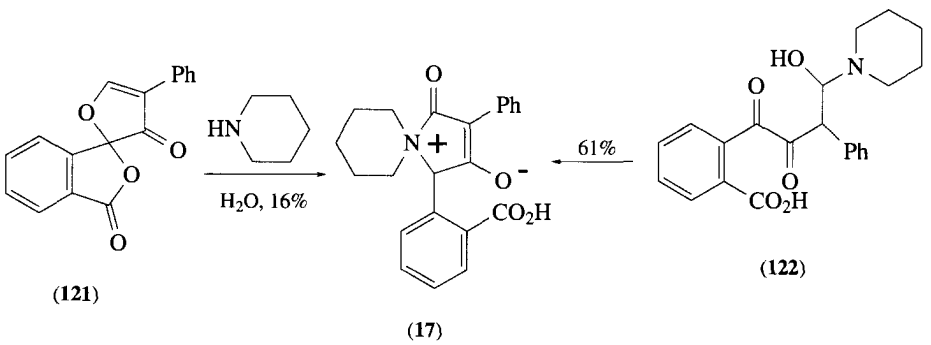
(119)

8.40.9.5 Syntheses by Ring Transformation

The aziridinium salt (**44**; R = H) reacts with 2-chloroethanol to give the 1,4-oxazinium derivative (**120**) (Equation (57)) ⟨76JOC390⟩. The dioxaspirononanedione (**121**) reacts with aqueous piperidine to give the mesoionic azoniaspirodecenone (**17**) ⟨76JOC390⟩, obtained in better yield from the benzil (**122**) (Scheme 16).



(57)

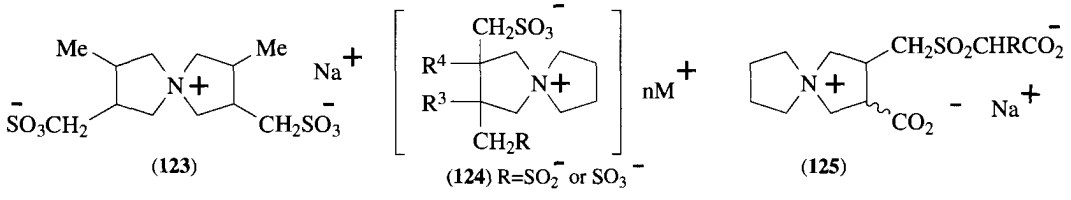


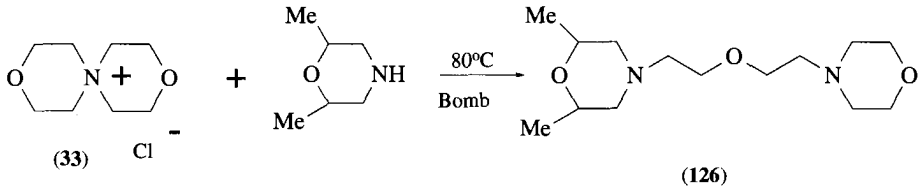
Scheme 16

8.40.10 IMPORTANT COMPOUNDS AND APPLICATIONS

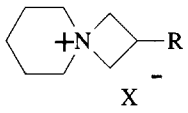
8.40.10.1 Applications which are Not Medical or Pharmaceutical

Compounds of type (**123**), (**124**) and (**125**) have been patented as surfactants or surfactant intermediates ⟨83EGP200739, 85EUP163319, 91EUP434175⟩, and azoniadioxaspiroalkane (**33**) as a starting material for the synthesis of urethane polymer catalysts such as (**126**) (Equation (58)) ⟨93MI 840-01⟩. Various azoniaspiroalkanes, including (**127**), have been reported as components of fluoroelastomer compositions ⟨87JAP(K)62104863⟩, and the similar compound (**128**) in the hydroxide form has been reacted with norbornanones to form sunscreen components ⟨80BRP2025957⟩. The azonia-spiroheneicosane (**9**) has been used as a stabilizer in the catalytic carbonylation/hydration of terminal alkenes to carboxylic acids ⟨73GEP(O)2236439⟩, and 5-azonia-spirononanes as templates in the production of zeolites SS2-19 ⟨85USP4510256⟩ and Losod, a new sodium zeolite ⟨74HCA1533⟩. Azonia-spiro[4,5]decanes and -[5,5]undecanes, with a range of complex cations, were used in nonaqueous electrolyte solutions in an electrical double-layer capacitor showing good withstand voltage ⟨92JAP(K)92196511⟩. The fluorinated salt (**82**) was an intermediate in the synthesis of rocket propellants ⟨67USP3346589⟩.





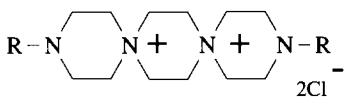
(58)



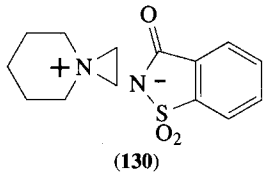
(**127**) R = H
(**128**) R = OH

8.40.10.2 Compounds of Medical or Pharmaceutical Interest

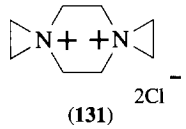
The most widely studied diazoniadispiroalkane is prospidine (**129**) which has antitumor activity. Many related compounds have been prepared and studied. The original patents and references since 1990 are listed; from these, other citations can be obtained ⟨69BRP1164857, 70MI 840-01, 71URP278028, 89KFZ794, 89KFZ959, 90MI 840-01, 91MI 840-01, 91MI 840-02, 92KFZ56, 93MI 840-04, 93MI 840-05, 94KFZ7⟩. The compound Charamin (**7**) from *Chara globularis* is reported to have antibacterial activity ⟨87JOC694⟩, the salt (**130**) is a fungicide ⟨83JAP(K)5821672⟩, and the diazoniadispiroalkane (**131**) promotes the growth of vertebrates at 25mg/kg body weight ⟨73USP3723621⟩. A range of bicyclic azoniaspiroalkanes (**132**) were synthesised as potential depressors; some of the tricyclic compounds (**133**) were pressor agents ⟨54JA5099⟩. A more general range of diazoniadispiroalkanes were screened for hypotensive activity; not much was found ⟨54JA2427⟩. Another series, including compound (**134**), were found to be antidepressants ⟨71BRP1236078⟩. A series of *spiro* compounds based on tropane, such as (**135**), were shown to be more effective than known quaternary tropines in spasmolytic properties, with reduced undesirable effects relative to atropine ⟨65GEP1194422⟩.



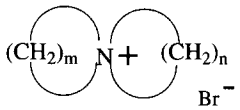
Prospidine (129)
R = $CH_2CH(OH)CH_2Cl$



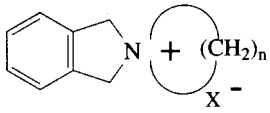
(**130**)



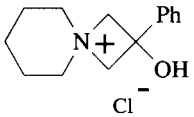
(**131**)



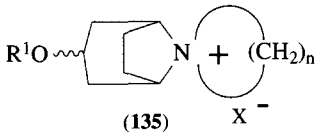
(**132**) m = 5,6; n = 6,7



(**133**) n = 6,7,8

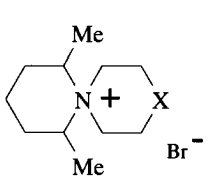


(**134**)

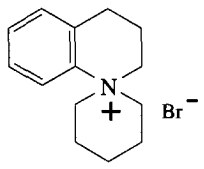


(**135**)

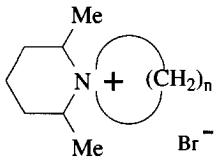
Azoniaspiroalkanes have been studied as inhibitors of acetylcholinesterase. Thomas and his coworkers used a wide range of azoniaspiroalkanes, including benzologues and compounds containing extra heteroatoms. In general, α-methyl groups, as in compound (**136**), increase activity, oxygen as additional heteroatom (as in (**137**)) decreases activity, and fused aromatic rings increase activity, especially as in (**138**) when the *spiro* nitrogen is next to the aromatic ring ⟨61JPP752, 61MI 840-01, 61MI 840-02⟩. Electrostatic binding to the enzyme anionic site using the δ^+ on α-carbon was suggested, with substituent methyl groups increasing Van der Waal's forces. A similar group of azoniaspiro derivatives was studied as possible potentiators of the hydrolysis of acetylcholine by acetylcholinesterase ⟨68JPP135⟩. A study of the effect on the rate of decarbamoylation and deacetylation by acetylcholinesterase, by addition of the closely related salts (**21**; X = Br), (**136**) and (**139**), showed that the first two were inactive, but that salt (**139**) accelerated decarbamoylation and deacetylation ⟨69MI 840-01⟩. The amides (**140**) and (**141**) had a low inhibitory activity on isolated human plasma "pseudo" cholinesterase compared with that of nonquaternary compounds of type (**142**) ⟨63JMC811⟩. Modification of acetylcholine-induced excitation on the heart of *Tapes Watlingi* was caused by 5-azoniaspiro[4,4]nonane ⟨69MI 840-02⟩.



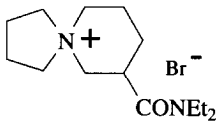
(**136**) X = CH_2
(**137**) X = O



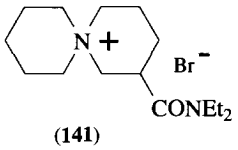
(**138**)



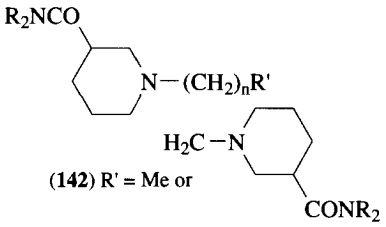
(**136**) n = 5
(**139**) n = 4



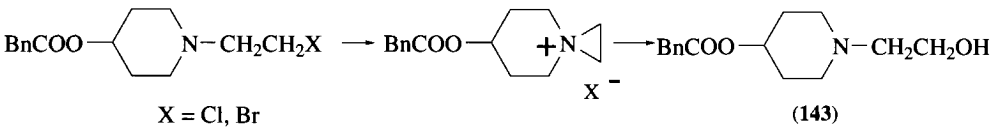
(**140**)



(**141**)



(**142**) R' = Me or



X = Cl, Br

(**143**)

Scheme 17

Binding to, and irreversible inhibition of, muscarinic receptors (selectively M_3 compared with M_2) was observed with some *N*-(chloro- or bromoethyl)piperidines, and shown by kinetic studies of their hydrolysis, to be related to the intermediate azoniaspiro[2,5]octanes (Scheme 17) ⟨92MI 840-01, 93MI 840-02⟩. The aziridinium ion is the most potent compared with the parent piperidines or with the alcohol (**143**).

Studies have been made of the effect of stereochemistry of quaternary salts on their interaction with protein, using a range of physical methods (see Section 8.40.4) ⟨78JPC2781, 81JPC603⟩. Azoniaspiroalkanes differ appreciably from acyclic isomers, being less hydrophobic. Houseflies were sterilized by aziridine derivatives, including 3-azoniaspiro[2,4]heptane salts ⟨68MI 840-01⟩.

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8.41
Compounds containing a Spiro Phosphorus Atom

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Staffordshire University, Stoke-on-Trent, UK

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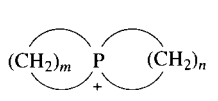
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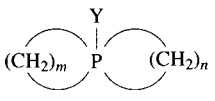
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8.41.1 INTRODUCTION

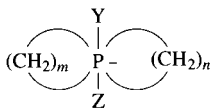
Compounds which have four coordinate phosphorus at the spiro position are analagous to the corresponding quaternary ammonium compounds in that they may be salts, for example phosphoniaspiro(m,n)alkanes (**1**), or mesoionic, for example an ylide. However, phosphorus may also be five coordinate, for example spirophosphorane (**2**), and indeed these compounds have attracted the major attention of phosphorus chemists. There are also a number of six coordinate spiro phosphorus compounds which may also be a salt, for example anion (**3**), or mesoionic. The six coordinate state permits the formation of a third ring, for example anion (**4**). In these valence expanded states, the compounds are stabilized by small rings (usually five membered rings), and by the presence of electronegative atoms or groups bound to phosphorus, either as part of a ring(s) and/or as the noncyclic group(s). There also exists an example of a tetraaza analogue of a phosphonium fenestrane (**5**) ⟨81JA1281⟩. A further consequence of the five and six coordinate states is the possibility of a new spiro situation where the spiro phosphorus atom is also a bridgehead atom, for example phosphorane (**6**).



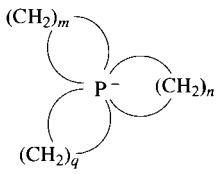
(1)



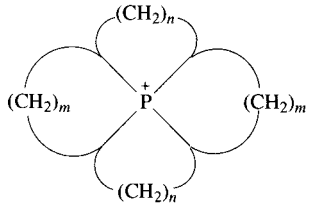
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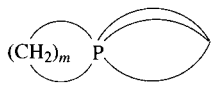
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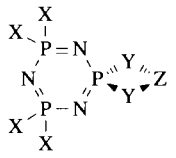


(5)



(6)

As with the nitrogen analogues there are no fully conjugated compounds, but there are many examples of spiro phosphorus atoms which are part of five- and six-membered rings possessing six p electrons, for example the cyclotriphosphazene (**7**). However in these coordination states the phosphorus atom is not able to transmit the potential conjugation and the compounds show no evidence of aromaticity. Organophosphorus chemistry is renowned for its nomenclature problems. One striking fundamental nomenclature problem relates to the six coordinate compounds R_6P^- which have been called phosphates and causing confusion with four coordinate (ortho)-phosphates. However IUPAC rules indicate that the six coordinate compounds R_6P^- should be named "perphosphoranides" the four coordinate phosphorus anions R_4P^- being named as phosphoramides as usual. There are many compounds which have a variety of heterocyclic atoms and structural features which makes the formal IUPAC system unduly complex. As a consequence in this review the more common ring systems have been abbreviated to a set of three letters to represent the atoms and groups making up the ring apart from the central phosphorus atom, for example the glycol group OCH_2CH_2O is abbreviated to Glc. A list of abbreviations is given below (see Figure 1).



(7)

The range of cyclic systems is shown in the tables below (Tables 1–16), *m* and *n* representing the sizes of the spiro rings. The four, five, and six coordinate compounds will normally be reviewed in

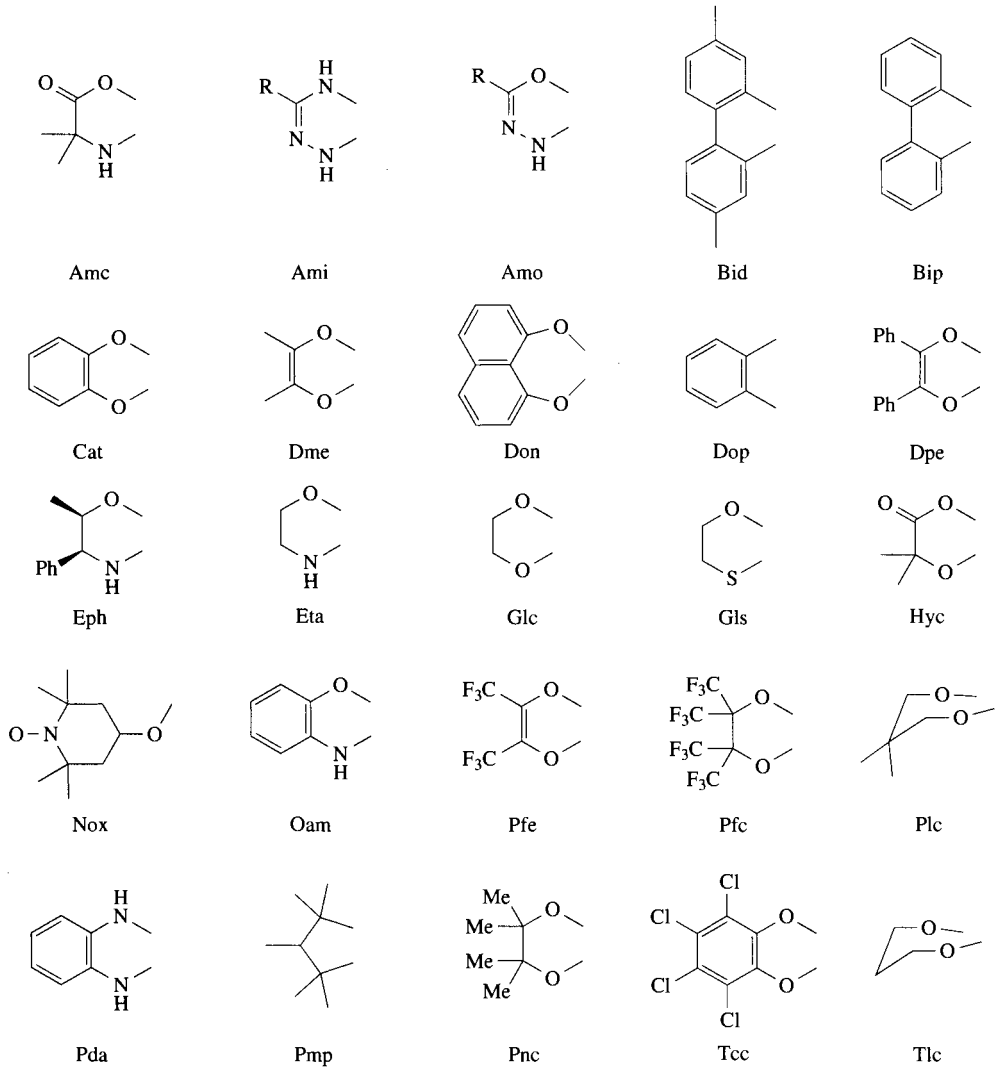


Figure 1 Structural abbreviations used in Chapter 8.41.

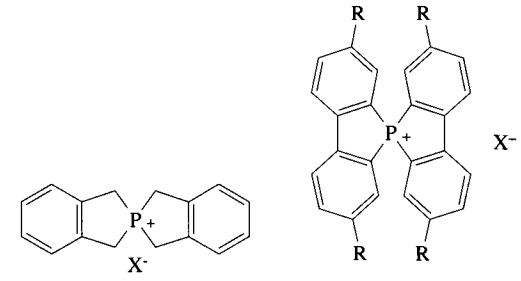
this sequence. There are very few alicyclic compounds which have phosphorus as the only hetero atom. There are more examples of benzo derivatives, but the vast majority of compounds incorporate a number of additional hetero atoms within the ring systems.

The five coordinate spirophosphoranes have played an important role with respect to understanding the stereochemistry of four coordinate phosphorus reactions which proceed via phosphorane intermediates. Variable temperature NMR studies have established the apicophilicities of a wide range of groups (i.e. relative preferences of a series of groups to occupy an apical position rather than an equatorial position of a trigonal bipyramidal (t.b.p.) conformation of a phosphorane). The spiro ring system has been used to stabilize transient reaction intermediates of acyclic compounds, for example hydrolysis intermediates such as hydroxyphosphoranes.

8.41.2 THEORETICAL METHODS

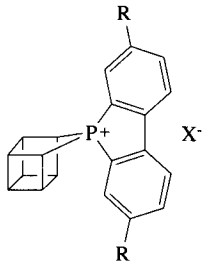
The stabilizing influence on the hypervalent state of phosphorus produced when phosphorus is incorporated into small rings is very well established and is especially effective in the spiro compounds

Table 1 Phosphoniaspiro compounds with *P*-bound atoms = C_4.

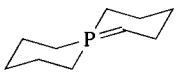


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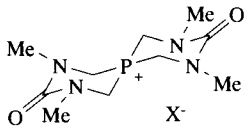
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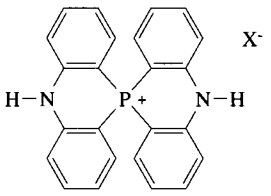
(10)



(11)



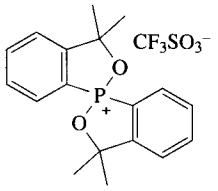
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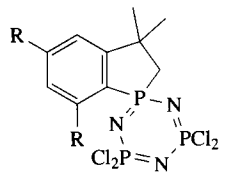
(13)

m	*n*	*Compound*	*Ref.*
4	4	5-phosphoniaspiro(4,4)nonane triiodide (**1**)	68ZOB331
4	4	5-phosphonia(b,e)dibenzospiro(4,4)nonane (**8**)	73JHC395
4	4	5-phosphonia(a,c,d,f)tetrabenzospiro(4,4)nonane (**9**; R = H)	69JOC1130
4	4	5-phosphonia(a,c,d,f)tetrabenzospiro(4,4)nonane (**9**; R = Me)	73RTC1308
4	4	(**10**)	72CC404
5	5	6-phosphoniaspiro(5,5)undecane bromide (**1**)	80ZN(B)990
5	5	6-phosphoniaspiro(5,5)undecane ylide (**11**)	81CB3161
5	5	urea (**12**)	81PS207
5	5	dibenzophosphorin (**13**)	75JOC766

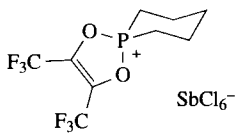
Table 2 Phosphoniaspiro compounds with *P*-bound atoms = C_2XY.



(14)



(15)

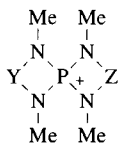


(16)

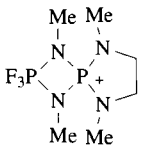
m	*n*	*XY*	*Compound*	*Ref.*
4	4	O_2	benzodioxaphospholan (**14**)	78JA7434
4	5	N_2	cyclotriphosphazene (**15**)	90JCS(D)2303
4	5	O_2	(**16**)	88ZAAC(561)49

covered here. Extended Hückel MO calculations indicated that the small rings lowered the occupation of the phosphorus 3d orbitals and favored nucleophilic attack at phosphono leading to t.b.p. phosphoranes ⟨69JA1200⟩. Possible mechanisms for the permutational isomerism of five coordinate phosphoranes have been explored ⟨74CC15⟩. The Berry pseudorotation mechanism ⟨75CPL(30)276⟩ involving t.b.p. intermediates, which deform via square pyramidal (s.p.) geometries where the two

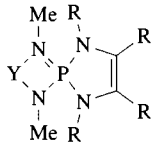
Table 3 Phosphoniaspiro compounds with four *P*-bound nitrogen atoms.



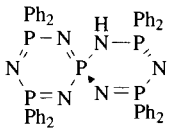
(17)



(18)



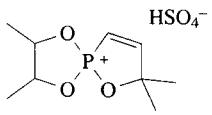
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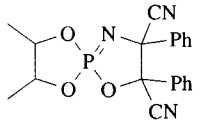
(20)

m	*n*	*P-bound*	*Compound*	*Ref.*
3	3	N_4	(**17**; Y = Z = CO)	87JGU2143
3	3	N_4	(**17**; Y = Me_2Si, Z = P(NR)NHR)	87CB1183
3	4	N_4	(**18**)	74JCS(D)2153
3	5	N_4	(**17**; Y = NH, Z = Me_2Si)	77MI 841-03
4	4	N_4	(**19**; Y = N = CMe)	86TL2971
4	4	N_4	(**19**; Y = C_6H_4)	91TL501
4	5	N_4	(**7**; Y = NMe, Z = $[CH_2]_2$)	77CB3231
4	5	N_4	(**7**; Y = NMe, Z = C_6H_4)	72JGU1490
5	5	N_4	(7; Y = NMe, Z = $PCl_2NMePCl_2$)	77CB3231
5	5	N_4	cyclotriphosphazene (**20**)	75CB1454

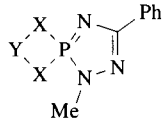
Table 4 Phosphoniaspiro compounds with *P*-bound oxygen or sulfur atoms.



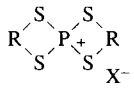
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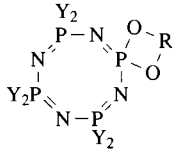
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(23)



(24)

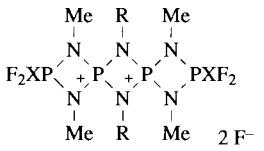


(25)

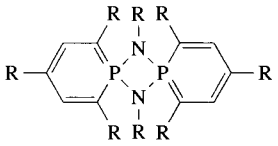
m	*n*	*P-bound*	*Compound*	*Ref.*
4	4	CO_3	(**21**)	84PS(21)249
4	4	NO_3	phosphazene (**22**)	82JGU189
4	4	N_2O_2	(**23**; X = O, Y = CMe = CMe)	84TL5521
4	4	S_4	(**24**; R = $[CH_2]_2$)	83ZN(B)1046
4	5	N_2O_2	(**7**; Y = O, Z = $[CH_2]_2$)	76ZAAC(426)275
4	5	N_2O_2	(**7**; Y = O, Z = $[C_6H_4]$)	76JA5120
4	5	N_2O_2	(**23**; X = O, Y = $[CH_2]_3$)	76T2039
5	5	N_2O_2	(**7**; Y = O, Z = 1,8-dinaphthyl)	71IC1643
5	5	S_4	(**24**; R = $[CH_2]_3$)	83ZN(B)1046
5	5	S_4	(**24**; R = C_6H_4)	73CC144
5	6	N_2O_2	(**7**; Y = O, Z = Bid)	76JA5120
5	7	N_2O_2	(**25**; R = $CH_2CMe_2CH_2$, Y = Cl)	91PS(55)59

apical bonds join two of the equatorial bonds—the remaining equatorial bond (the pivot) being transformed into the apical bond of the s.p. structure, remains the most favored mechanism ⟨77JA3318⟩, although a turnstile mechanism ⟨74T371⟩ based on NMR studies of (**83**) has been explored.

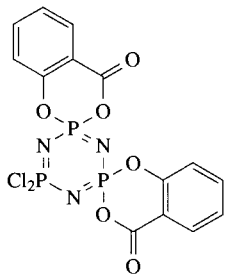
Table 5 Four coordinate compounds with two or more phosphoniaspiro centers.



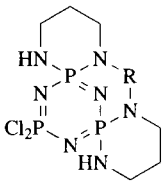
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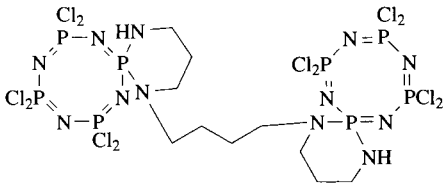
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(28)



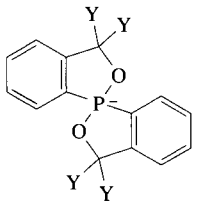
(29)



(30)

m	*n*	*P-bound*	*Compound*	*Ref.*
3	3	N_4	(**26**)	86MI 841-01
3	5	C_2N_2	diphosphorin (**27**)	93TL3107
5	5	N_2O_2	(**28**)	75ICA(14)L40
5	5	N_4	(**29**; R = $(CH_2)_3$)	89JST(196)221
5	7	N_2O_2	(**25**); R = Bip, Y_2 = Cat)	76JA5120
6	7	N_4	(**30**)	91PS(57)111
6	7	N_2O_2	(**25**); R = Bip, $Y_2 = OC_6H_4C_6H_4O$)	71IC1643

Table 6 Four coordinate spirophosphoranides R_4P^-.

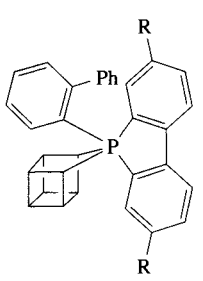


(31)

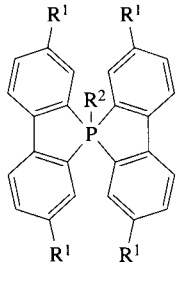
m	*n*	*P-bound*	*Compound*	*Ref.*
4	4	C_2O_2	(**31**; Y = Me)	78JA7434
4	4	N_4	Tme_2P^-	94CCR53

Molecular mechanics calculations have been extended from four coordinate phosphoryl compounds to five coordinate phosphoranes by adding a term which measures the effects of electron pair repulsions, modified by the ligand electronegativity, and taking into account the t.b.p. and s.p. conformational possibilities ⟨77JA5461⟩. These studies were extended to calculations of the relative energies of t.b.p. and s.p. conformations ⟨75JA5379⟩. It was concluded that the s.p. conformation is stabilized relative to the t.b.p. conformation when the phosphorus atom was part of an unsaturated

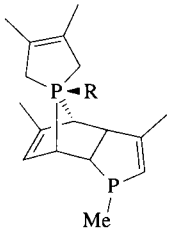
Table 7 Five coordinate spirophosphoranes with *P*-bound atoms = C_5.



(32)



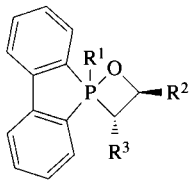
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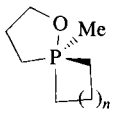
(34)

m	*n*	*P-bound*	*Compound*	*Ref.*
4	4	C_5	(**2**; Y = Me)	72AG(E)722
4	4	C_5	(**32**)	72CC404
4	4	C_5	(**33**; R^1 = H, R^2 = CH=CMe_2, 2-furyl, 2-thienyl)	70JCS(C)1425
4	4	C_5	(**33**; R^1 = H, R^2 = Bu^n, C≡CBu^n)	70LA(742)163
4	4	C_5	(**33**; R^1 = Me, R^2 = Ph, 2-Pr)	74JA5398
4	4	C_5	(**34**; proposed intermediate)	83TL5831

Table 8 Five coordinate spirophosphoranes with *P*-bound atoms = C_4X.



(35)

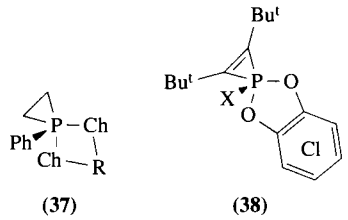


(36) *n* = 2, 3

m	*n*	*X*	*Compound*	*Ref.*
3	4	O	Wittig intermediate (**35**)	90JA3905
4	4	H	(**33**; R^1 = R^2 = H)	69CB528
4	4	O	(**36**; n = 2)	79CB501
4	5	O	(**36**; n = 3)	79CB501

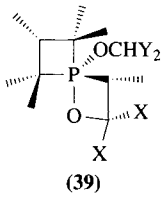
ring and when the phosphorus was bound to highly electronegative atoms; that the t.b.p. conformation was destabilized by additional ring strain (3–4 kcal mol^{-1} for the dioxaphospholenes) produced by the need for the different bond length requirements of the t.b.p. conformation and that the s.p. conformation also accommodated four membered rings better than the t.b.p. conformation. A method for the calculation of the barriers to pseudorotation for the interconversion of the above conformations ⟨78JA433⟩ also took into account the apicophilicities of the P-bound atoms. This was achieved using an element effect based on electronegativity preferences for the t.b.p. axial, equatorial, and s.p. apical and basal orientated atoms, which were then optimized to obtain the best fit with recorded barrier energies. In 1989 a set of force field parameters which include 1–3 interactions have been developed for molecular mechanics calculations of phosphoranes including those for hydridospirophosphorane (**61**; X = O, Y = Z = NH) ⟨89CC1103⟩.

Table 9 Five coordinate spirophosphoranes with *P*-bound atoms = C_3X_2.

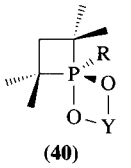


(37)

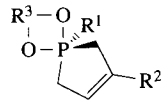
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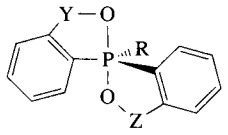
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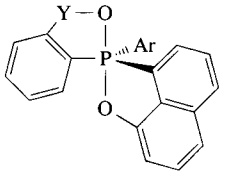
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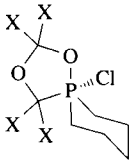
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(42)



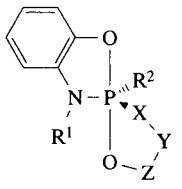
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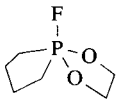
(44)

m	*n*	X_2	*Compound*	*Ref.*
2	4	O_2	(**37**; Ch = O, R = CMe_2CMe_2)	78CC854
2	4	S_2	(**37**; Ch = S, R = CCF_3=CCF_3)	74JA317
2	4	O_2	(**38**; X = CN)	90TL3429
3	3	O_2	(**39**)	73JCS(P1)1300
3	4	O_2	(**40**; Y = CH_2CH_2, R = Ph)	78IC3265
3	4	O_2	(**40**; Y = $C[CF_3]_2C[CF_3]_2$, R = 4-Br-Ph)	74JA4143
3	5	O_2	(**40**; Y = 1,3-cyclopentyl, R = Ph)	83JOC2621
3	6	O_2	(**40**; Y = $[CH_2]_4$, R = Ph)	77PS(3)51
4	4	O_2	(**41**; R^1 = Me, Et, R^3 = CH_2CH_2)	71JGU471
4	4	O_2	(**41**; R^1 = Et, R^2 = H, R_3 = C_6H_4)	75JGU686
4	4	O_2	(**41**; R^1 = Ph, R^2 = Me, R^3 = C_6H_4)	77JA3332
4	4	O_2	(**42**; Y = Z = CO, R = Me, Ph)	75CC399
4	4	O_2	(**42**; Y = CMe_2, Z = CO, R = Me)	79JA3687
4	4	O_2	(**43**; Y = CMe_2)	76ZN(B)948
4	5	ClO	(**44**; X = CF_3)	88ZAAC(561)49

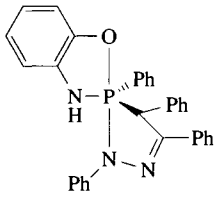
Table 10 Five coordinate spirophosphoranes with *P*-bound atoms = C_2X_3.



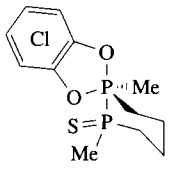
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(46)



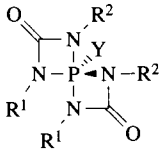
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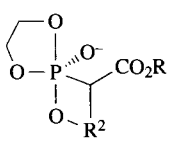
(48)

m	*n*	X_3	*Compound*	*Ref.*
2	4	O_2X	(**38**; X = Br, Cl, F, N_3)	90TL3429
4	4	O_3	(**42**; Y = Z = CO, R = OH)	79JA3687
4	4	O_3	Hydroxyphosphorane (**42**; R = OH, Y = Z = CMe_2)	79JA4618
4	4	O_3	(**42**; R = OH, Y = Z = $C(CF_3)_2$)	81JA1049
4	4	NO_2	(**45**; R = H, X = CH_2, Y = CHR, Z = CO)	78IZV2185
4	4	FO_2	(**46**)	70CC476
4	4	N_2O	(**47**)	89PS(45)255
4	5	O_2P	(**48**)	88CB391

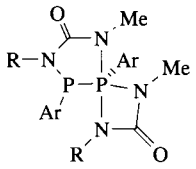
Table 11 Five coordinate spirophosphoranes with *P*-bound atoms = CX_4.



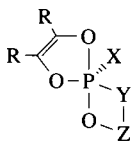
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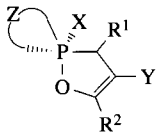
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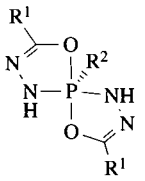
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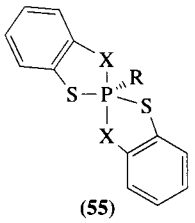
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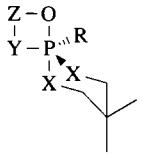
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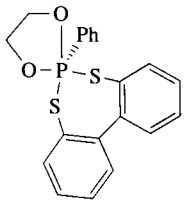
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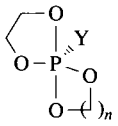
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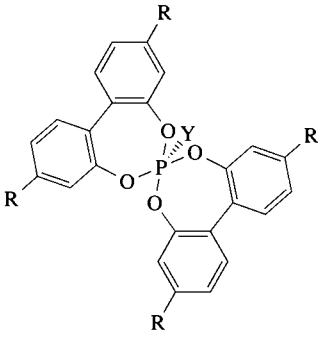
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(57)



(58)



(59)

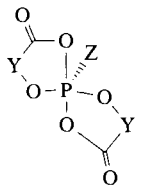
m	*n*	X_4	*Compound*	*Ref.*
3	3	N_4	(**49**; R^1, R^2 = Me, Y = Me)	95ZAAC(621)2001
3	4	O_4	Horner Intermediate (**50**)	79TL2203
3	4	N_3P	(**51**; R = Me, Ar = Ph)	81CB2132
3	4	N_2O_2	(**52**; R = Me, X = NHR, Y = NR, Z = PR)	85JGU2327
4	4	O_4	(**53**; R^1 = Ph, R^2 = Me, X = OMe, Y = Ac, Z = Pnc)	72CR(C)288
4	4	NO_3	(**52**; R = Me, Ph, X = Ph, Y = NMe, Z = CHMeCHPh)	92JOC5195
4	4	NO_3	(**45**; R^1 = Ph, R^2 = Ar, X = O, Y, Z = CHMeCHPh)	75JCS(P1)2376
4	4	N_2O_2	(**54**)	77CB1124
4	4	O_2S_2	(**55**; X = O, R = Ph)	78JOM(156)253
4	4	S_4	(**55**; X = S; R = Ph)	78JOM(156)253
4	5	O_4	(**56**; X, Y = O, R = Ph, Z = CPh = CPh)	91IC1052
4	5	O_4	(**56**; R = OMe, X = O, Y = CH_2, Z = CH=CH)	77IZV2000
4	6	O_2S_2	(**57**)	83JOC3815
4	7	O_4	(**58**; n = 5)	79CC191
5	5	O_4	(**56**; R = Ph, X = O, Z = $CH_2CMe_2CH_2$)	77JCS(P1)80
6	6	O_4	(**59**; Y = Ph)	92IC5494

8.41.3 EXPERIMENTAL STRUCTURAL METHODS

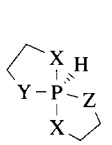
8.41.3.1 X-ray diffraction

X-ray diffraction studies of four coordinate phosphonium compounds include the cyclotriphosphazenes (**21**) ⟨79ZN(B)911⟩ and (7; X = NMe_2, Y = NH, Z = CH_2 CH_2) ⟨78ZN(B)588⟩, and the bis spirophosphazene (**84**) ⟨82IC3916⟩.

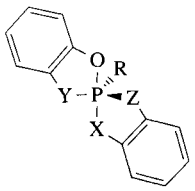
Table 12 Five coordinate spirophosphoranes with *P*-bound atoms = HX_4.



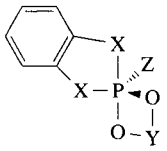
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(61)



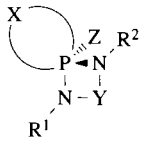
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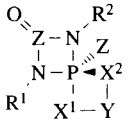
(63)

m	*n*	X_4	*Compound*	*Ref.*
4	4	O_4	(**60**; Y = CMe_2, Z = H)	79TL4205
4	4	X_2YZ	(**61**; X, Y, Z = O, S, NH)	75BSF407
4	4	N_2O_2	(**62**; R = H, X = O, Y = Z = NH)	75JGU252
4	4	N_2O_2	(**63**; X = NH, Y = CMe_2, Z = H)	75CR(C)809
4	5	O_4	(**63**; X = O, Y = $(CH_2)_3$, Z = H)	86PS(27)321

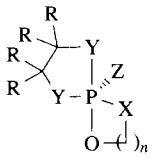
Table 13 Five coordinate spirophosphoranes with *P*-bound atoms = X_5.



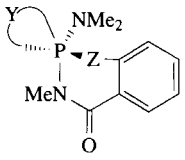
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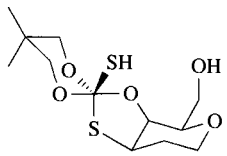
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(66)



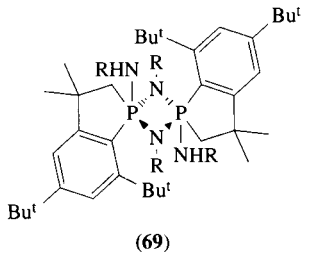
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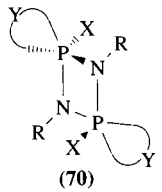
(68)

m	*n*	X_5	*Compound*	*Ref.*
3	3	N_5	(**49**; R^1, R^2 = Me, Y = N_3)	84JA7065
3	4	FN_2O_2	(**64**; R^1, R^2 = Me, X = O, Y = PF_3, Z = F)	76JCS(D)306
3	4	IN_4	(**65**; R^1, R^2 = Me, X^1 = NMe, X^2 = N^+Me_2, Y = (CH_2CH_2), Z = I	90PS(54)227
4	4	N_2O_3	(**52**; R = Ph, X = NMe_2, Y = NMe, Z = CHMeCHPh)	75PS(5)285
4	4	NO_4	(**66**; n = 2, R = H, X = O, Y = O, Z = NMe_2)	75TL2529
4	5	NO_4	(**66**; n = 3, R = CF_3, X = NMeY = O, Z = OAr)	76CC1031
4	5	N_3O_3	(**67**; Y = C_6H_4)	93PS(78)271
4	5	O_3S_2	intermediate (**68**)	91JA7945
4	10	O_4X	crown ethers (**63**; X = O, Y = $(CH_2CH_2O)_2CH_2CH_2$	84JGU1754
6	6	FO_4	(**59**; Y = F)	77PS(3)35

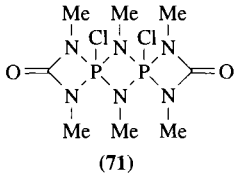
Table 14 Five coordinate bis spirophosphoranes.



(69)



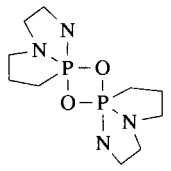
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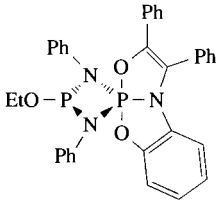
(71)

m	*n*	X_5	*Compound*	*Ref.*
3	4	C_2N_3	(**69**; R = CO_2Me)	86TL2863
3	4	N_3O_2	(**70**; R = Ph, X = N_3, Y = Glc)	83JGU247
4	4	ClN_4	(**71**)	70ZAAC(372)285

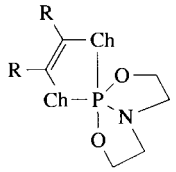
Table 15 Five coordinate spirophosphoranes incorporating a bridgehead phosphorus.



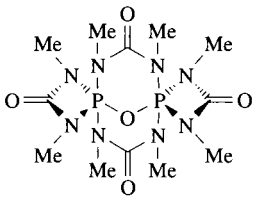
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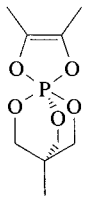
(73)



(74)



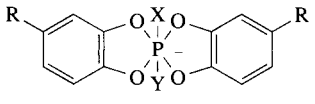
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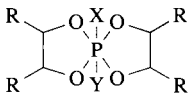
(76)

m	*n*	*o*	X_5	*Compound*	*Ref.*
3	4	4	CN_2O_2	(**72**)	87CC1131
3	4	4	N_3O_2	(**73**)	78CB2086
3	3	3	NO_4	(**74**; Ch = O, R = CF_3)	80JA5073
3	5	5	N_4O	(**75**)	86PS(26)193
5	5	5	O_5	(**76**)	70CR(C)418

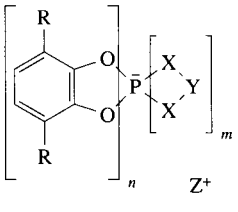
Table 16 Six coordinate mono and bis spiroperphosphoranides F_6P^-.



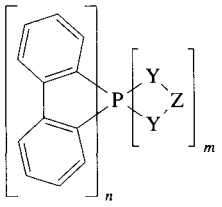
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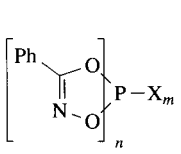
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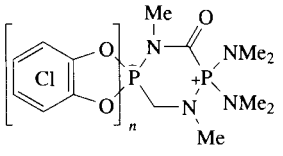
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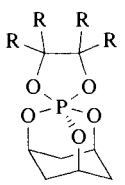


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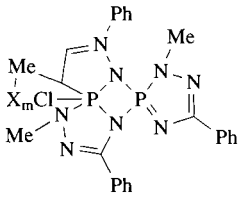


(82)

m	*n*	*o*	X_6	*Compound*	*Ref.*
4	4		HNO_4	(**77**; R = Me, X = $C_5H_5N^+$, Y = H)	74CR(C)1353
4	4		HO_5	(**78**; R = CO_2Me, X = OCHRCHROH, Y = H)	79PS(6)435
4	4		N_2O_4	(**77**; R = H, X = Y = $C_5H_5N^+$)	78ZN(B)583
3	4	4	N_2O_4	(**79**; m = 1, n = 2, R = H, X = NPh, Y = $(PhNH)_2P^+$)	90JGU1491
4	4	4	C_6	(**80**; m = 0, n = 3)	70JCS(B)640
4	4	4	O_6	(**79**; m = 0, n = 3, R = Pr^i, Z = Et_3N^+H)	76JA6755
4	4	4	O_6	(**81**; m = 0, n = 3)	77ZAAC(437)53
4	4	4	O_6	(**79**; m = 0, n = 3, R = H, Z = Et_3N^+H)	73JA3154
4	4	5	CNO_4	(**82**)	93PS(75)233
4	4	5	O_6	(**79**; m = 1, n = 2, X = O, Y = CMe=CHC$^+$Me)	79PS(7)305
5	5	5	O_6	(**79**; X = O, Y = Bip, Z = brucineH)	79TL795

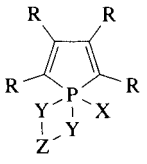


(**83**) R = CF_3



(**84**)

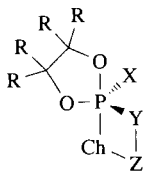
Many five coordinate phosphorane compounds have been examined, the keen interest arising primarily from the variation of structures which have relevance with respect to their stereochemical importance as reactive intermediates in the reaction pathways of four coordinate compounds ⟨74JA4143⟩. The stereochemistry of phosphoranes vary on a structural coordinate between trigonal bipyramidal (t.b.p.) and square pyramidal (s.p.). Phosphoranes which have been found to have conformations closer to the t.b.p stereochemistry include thienyl phosphorane (**33**; R^1 = H, R^2 = 2-thienyl) ⟨83ZN(B)466⟩, spiro(4,4)phosphoranes (**41**) ⟨77JA3332⟩, (**47**) ⟨89PS(45)255⟩, (**42**; R = Ph, Y = C(O)O) ⟨79JA3687⟩, (**85**; R = CO_2Me, X = OMe, Y = O, Z = CMe_2CMe_2) ⟨81TL3533, 82AX(B)3024⟩, (**49**; R^1 = Me, R^2 = $C_6H_4CF_3$, Y = C_6F_5) ⟨80CB1847⟩, hydroxyphosphorane (**60**; Y = CPh_2, Z = OH) ⟨82JCR(S)180⟩, (**55**; X = S, R = Ph) ⟨78JOM(156)253⟩, (**55**; X = S, R = Me) ⟨73CC144⟩, (**86**; X = O, R = Ph, Cl) ⟨77IC2294, 77JA3326⟩, (**86**; n = 2, X = O, S; R = adamantyl) ⟨78IC3265⟩, (**86**; X = O, S; R = OPh) ⟨76JOC473, 79JA3790⟩, (**66**; X = Y = S, Z = Ph, R = CF_3) ⟨74PS(4)203⟩, (**87**; R = H, X = OMe, Ch = Se, Y = $C(CF_3)_2$, Z = N = $CNMe_2$) ⟨78AG(E)774⟩, (**88**; X = NMe, Y = CHMe, Z = CHPh) ⟨81PS(11)87⟩ (**64**; R^1 = H, R^2 = Me, X = O, Y = CH_2CH_2, Z = NPr_2) ⟨84MI 841-01⟩, (**81**; n = 2, X = Cl) ⟨78PS(5)217⟩, the phenolic derivative (**89**; R = Bu^t Y = Ar) ⟨84JSK568⟩, as well as some spiro(4,5)phosphoranes such as (**90**; n = 3, Y = OAr) ⟨91IC1052⟩, (**66**; n = 3, R = CF_3, X = NMe, Y = O, Z = OAr) ⟨76CC1031⟩, (**56**; R = OAr, X = O, Y = NH, Z = *o*-$C_6H_3R^2$) ⟨91IC3928⟩, (**67**; Y = Pfp, Z = NMe) ⟨93PS(78)271, 95CB627⟩, and (**91**) ⟨85CC1764⟩ and some spiro(6,6)phosphoranes (**59**) ⟨92IC5494⟩. Whereas there are a number of phosphoranes whose structure tend towards a r.p. geometry such as phosphetans (**92**; X = CF_3, Y = Ar) ⟨74ZN(B)32⟩ and (**92**; X = H, Y = Ar) ⟨78IC3265⟩, (**51**; R, Ar = Ph) ⟨79CB1365⟩, (**49**; R^1, R^2 = Me, Y = Ph_2P) ⟨83ZN(B)702⟩, and phospholanes (**93**; X = S, Y = Ph, Z = Ar) ⟨75CC773⟩, (**94**; R = Me, X = S, Y = O, Z = Ph) ⟨83IC1771⟩, (**86**; R = Me, X = O) ⟨74AX(B)935⟩, the tetrachloro and octachloro derivatives of (**86**; X = O, R = Ph) ⟨79IC1668⟩, (**66**; n = 2, R = CF_3 X = Y = O; Z = Ph, Bu^t) ⟨78IC3276⟩, (**64**; R^1, R^2 = Me, X = Tcc, Y = CS, Z = NR_2) ⟨92PS(73)195⟩. These trends have been reviewed ⟨74JA4143⟩ and the factors contributing to their conformational preferences studied (see Section 8.41.2) ⟨75JA5379⟩. Whilst four and five membered rings almost without exception bridge apical–equatorial positions, six membered rings commonly follow this trend also and in the case of spirophosphorane (**90**; n = 3) this occurs despite the fact that this requires a sulfur atom to occupy an apical position in preference to an electronegative aryloxy group ⟨90JA6092⟩. Intermolecular hydrogen bonding was found in the crystal spirophosphorane (**86**; R = CH_2Cl, X = NH) ⟨91JGU1344⟩. Structural studies include several hydridospirophosphoranes, for example (**86**; R = H, X = NH) ⟨78IC3270⟩, (**95**; R^1 = H, R^2 = R^3 = Me) ⟨71MI 841-01⟩. Whilst some NMR studies have found hydrogen to have a suprisingly high apicophilicity, in the crystal it usually occupies an equatorial orientation.



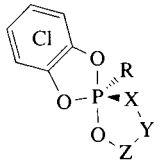
(**85**)



(**86**)



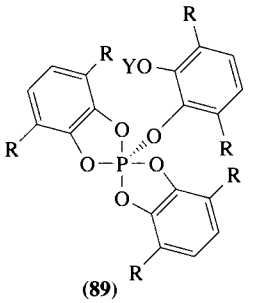
(**87**)



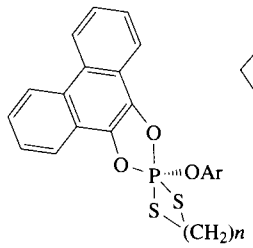
(**88**)

There have been x-ray diffraction studies of spirophosphoranes which also incoporate a bridgehead phosphorus atom of the type (**96**) ⟨76CC449, 79ZN(B)906, 80CB1406, 90JA7451, 96PS(109)629⟩, as well as some bis spirophosphoranes such as (**70**; Y = Glc) ⟨77CB1887, 77MI 841-01, 78TL2857, 81CC810⟩.

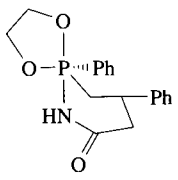
There have been x-ray diffraction studies of several six coordinate perphosphoranides, for example (**77**) ⟨78ZN(B)583⟩, (**79**; R = H) ⟨73JA3154⟩, the potassium salt of (**79**; R = Bu^t) ⟨88MI 841-01⟩, (**97**; R = CF_3, X = OPh) ⟨79PS(5)323⟩.



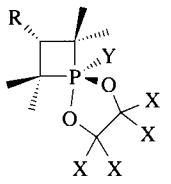
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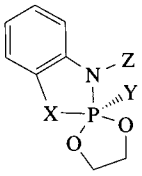
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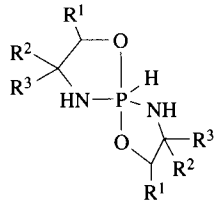
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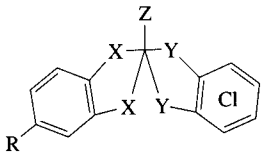
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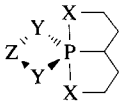
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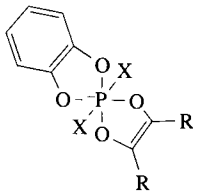
(94)



(95)



(96)



(97)

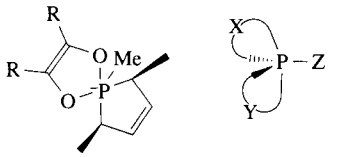
8.41.3.2 Magnetic Resonance

8.41.3.2.1 NMR Spectroscopy

The power of NMR spectroscopy for the study of phosphorus compounds is greatly enhanced not only by the structural dependence of ^{31}P NMR chemical shifts but also through the couplings it produces in ^{1}H and ^{13}C spectra ⟨B-91MI 841-01⟩. Like all chemical shifts ^{31}P NMR chemical shifts are dependent on the coordination state, the directly bound atoms as well as stereochemistry. Of particular relevance to spiro compounds is the fact that the incorporation of five valent phosphorus into a small ring such as a 5 or 4 membered one, generally causes the signal to move downfield, whereas incorporation into a six membered ring usually causes the signal to move upfield. Following this trend the rare tetrathiophosphonium salts (**24**; R = $(CH_2)_2$) and (**24**; R = $(CH_2)_3$) have δ_P 147 and 110 ppm ⟨83ZN(B)1046⟩. The four coordinate group includes the spirophosphoranides such as (**31**; Y = Me) whose δ_P −34 ppm ⟨78JA5229⟩ is well upfield of related phosphonium salts at δ_P 50 ppm despite any small ring effect ⟨79JA4623, 91MI 841-01⟩. Since large atoms such as bromine and iodine bound to phosphorus usually cause the phosphorus signal to move upfield in phosphonia compounds, this effect balances small ring trends and an intermediate shift δ_P −109 ppm is observed, for spiro(3,3)phosphorane (**65**; R = Me, X^1 = NMe, $X^2 = N^+Me_2$, Y = CH_2CH_2, Z = I) ⟨90PS(54)227⟩, and δ_P −132.6 ppm for silyl derivative (**86**; X = O, R = TMS) ⟨86PS(27)297⟩. However contradicting the large atom effect bromophosphorane (**86**; X = O, R = Br) is reported as having δ_P −28 ppm ⟨82PS(13)157⟩.

The pentaaryl spiro(4,4)phosphoranes have chemical shifts δ_P −88 to −98 ppm which move downfield as oxygen replaces P-bound carbon c.f. tetraoxaspirophosphoranes ⟨81PS(10)395, 91MI 841-01⟩. Indeed the presence of two five membered rings in spirodoxaphosphoranes (**98**) can cause the ^{31}P NMR signal to move as far downfield as 27 ppm ⟨72JA9264⟩. Dioxaphosphirane (**37**; Ch = O, R = CMe_2CMe_2) has δ_P −87 ppm which is well upfield of related 4,5 and 5,4 spirophosphoranes indicating that the small ring effect for three membered phosphiranes is in the opposite direction to those of 4 and 5 membered rings ⟨78CC854⟩. On the other hand the presence of sulfur atoms bound

to phosphorus, for example (**90**; n = 2, Y = Me) ⟨88PS(35)133⟩, (**99**; X = Y = Pfp, Z = SH) δ_P 14.2 ppm ⟨85ZN(B)1589⟩, and (**60**; Y = CMe_2, Z = S^-) δ_P −4.3 ppm ⟨84CC225⟩ exerts the usual deshielding effect.



(**98**) (**99**)

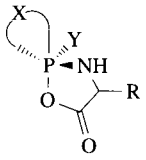
Variable temperature ^{1}H NMR studies of phosphoranes (**33**; R^1 = Me, R^2 = Ph) ⟨69TL3423, 79CB218⟩ and (**66**; R = Me, Y = O, Z = H) ⟨69CC443⟩ were among the first to investigate the pseudorotation process ⟨74JA5398⟩ and also highlighted the possibility of isolating chiral compounds. The spiro structure has been used to stabilise Wittig intermediates (**35**) sufficiently to establish their stereochemistry by NMR and follow their conversion to alkenes ⟨87TL3445, 90JA3905⟩.

Variable temperature NMR studies of the pseudorotation process i.e. ligand positional exchange, have been carried out on a wide range of spiro structures, for example (**53**; R^1 = Me, Ph, R^2 = H, X = Y = Ph, OEt, NEt_2, Z = Glc, Tlc) ⟨76TL749, 78JGU650⟩, (**52**) ⟨75PS(5)73, 92JOC5195⟩, (**45**) ⟨75JCS(P1)2376⟩, and hydridophosphoranes such as (**99**; X = Glc, Y = Amc, Z = H) ⟨78BSF(2)65⟩. The pseudorotation barriers of spirophosphoranes such as (**92**) and (**99**: X = Y = Dnp, Z = R) ⟨71PS(1)91, 77JCSP(1)437⟩ and for hydridophosphoranes (**66**; R = CF_3, X = Y = O, Z = H) ⟨86PS(27)321, 86ZOB1193⟩ are dependent on ring size. Comparisons have also been made between spiro(4,5) and spiro(5,6) pentaoxophosphoranes, for example (**99**; X = Bio, Y = Bid, Z = OAc) ⟨90JA6095⟩.

Pseudorotation barriers have been used to estimate the apicophilicities of P-bound atoms or groups Y in (**92**) ⟨71CC1011⟩, and (**99**; X = Cat, Y = Pfp) acknowledging the limitations and assessing the accuracies ⟨74JCS(P1)2125⟩. In general the more electronegative atoms or groups dominate the apical position of a t.b.p. However together two small rings tend to dominate both apical and two equatorial positions thus tending to push the noncyclic group into an equatorial position. In the case of spiro(3,3)phosphorane, for example (**64**; X = O, Z = F) ⟨76JCS(D)306⟩, a fluorine atom was thought to be forced into an equatorial position of a t.b.p. However for the spiro(4,4)phosphorane (**86**; X = O, R = F) it is possible for the molecule to adopt the square pyramidal geometry shown ⟨74ZN(B)32⟩. This may also be the case for the fluorophosphorane (**46**) ⟨70CC476⟩. A further increase in ring size, as in spiro(6,6) phosphorane (**59**; Y = F) ⟨77PS(3)35⟩ allows the fluorine to re-occupy the apical position of a t.b.p. On the other hand bulky groups favor the more spacious equatorial (radial) positions whereas small groups, for example hydrogen, have a strong tendency to occupy the apical position ⟨74JCS(P1)2125⟩. This latter result threw doubt on many previous assumptions that hydrogen would prefer an equatorial position, for example ⟨69CC443⟩. In a study of (**53**; R^1 = Ph, R^2 = Me, X = OAr, Y = Ac, Z = 2-SC_6H_4O) ⟨81JCS(P1)3074⟩ sulfur showed no tendency to occupy the apical position, whereas the noncyclic group Y in (**99**; X = Cat, Y = Pfp) (**99**; X = Glc, Y = Pfp) and (**53**; R^1 = Ph, R^2 = Me, Y = Ac, Z = Pnc), ethoxy and thioethoxy groups exhibited the same apicophilicity ⟨77JCS(P1)273⟩. Spirophosphorane (**99**; X = Pnc, Y = Tcc, Z = CN, Cl, NCO, NCS, N_3, OPh) has also been used to study apicophilicities of group Z ⟨79PS(7)167⟩. The configuration of spirophosphoranes (**53**; R^1, R^2, Y = H, X = OMe, Z = $O(CH_2)_2CHMe$) was studied by ^{1}H NMR spectroscopy ⟨72DOK(205)1370, 72PAS717⟩.

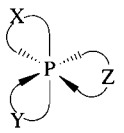
Vicinal spin–spin coupling constants through saturated carbon in spirophosphoranes may be quite large, for example 28.8 Hz for (**99**; X, Y = Oam, Z = CH_2Cl) ⟨72JGU1895⟩ and has been shown to be 22 and 45.9 Hz for the *cis* and *trans* isomers of tetraoxaphosphorane (**99**; X = Y = Glc, Z = CE = CHE) ⟨76CR(C)849⟩. PCH geminal couplings are 11 Hz for (**33**; R^1 = H, R^2 = Me), 24.3 for (**33**; R^1 = H, R^2 = CH = CMe_2) a case being made for these couplings to be positive in comparison with the negative phosphonium salt geminal couplings ⟨70JCS(C)1425⟩. The couplings $^1J_{PH}$ ca 770 of hydridospirophosphoranes of the type (**99**; X = Y = Eta, Z = H) tend to be at the lower end of the phosphorane series ⟨70CR(C)865⟩ and $^2J_{PNH}$ 21 Hz was recorded for hydridophosphorane (**100**; R = Me, X = Glc, Y = H) ⟨72CR(C)1413⟩. Coupling constant $^1J_{PP}$ was 270 and 156 Hz for phosphines (**49**; Y = Ph_2P) ⟨83ZN(B)702⟩ and (**51**), and larger, as expected, (709 Hz) for the phosphonate (**49**; R^1, R^2 = Me, Y = $(EtO)_2P(O)$ ⟨82IC844⟩.

Six coordinate spiroperphosphoranides have ^{31}P chemical shifts in the range −57 to −181 ppm upfield of the corresponding five coordinate phosphoranes but towards the low field region of the range (δ_P −57 to −440) for all six coordinate compounds ⟨B-91MI 841-01⟩, for example (**80**; m = 0,



(100)

n = 3) δ_P −181 ppm ⟨65CB576⟩, (**101**; X = Y = Bip, Z = Cat), and (**101**; X = Y = Bip, Z = Don) δ_P −147 and −168 ppm respectively ⟨76CB1056⟩, (**101**; X = Y = Z = Glc) δ_P −89 ppm ⟨71CC1070⟩, (**101**; X = Y = Bip) δ_P −82 ppm ⟨65CB576, 77ZOB1432⟩. The methyl groups of the 2-propyl derivative of perphosphoranide (**79**; m = 0, n = 3, R = Pr^i) have been shown to be diastereotopic ⟨76PS(6)91⟩.



(101)

8.41.3.2.2 Electron spin resonance spectrometry

The variable temperature ESR spectra of the spirophosphorus radical ($Pnc_2P^•$) indicated that pseudo rotation is slow even at 120°C, ΔG* being 54 kJmol^{-1} ⟨72JOM(42)C47⟩. Spin labeled spirophosphoranes (**99**; X = Glc, Y = Dme, Z = Nox) ⟨78ZN(B)305⟩, and (**87**; Y = odd electron ●) have been reported ⟨78BAU1064⟩. A deep violet color develops when hydridobisphenylene-phosphorane (**33**; R = H) dissolved in benzene is kept in the dark. Although this was attributed to the bisphenylene phosphoryl radical an ESR spectrum was not reported ⟨69CB528⟩.

8.41.3.3 Mass Spectrometry

The mass spectra of spirobiphenylenephosphoranes (**33**) show abundant M-1 and M-R^2 fragments and there was a tendency to form doubly charged ions ⟨73PS(2)167⟩. The mass spectra of cyclophosphazenes such as (**7**) ⟨76ZAAC(426)275⟩ have been used to identify substitution patterns around the rings. Migration of groups to and from phosphorus is common and therefore mass spectral results must be interpreted with care.

8.41.3.4 Electronic Spectroscopy, Circular Polarization, and Polarimetry

Phosphorus, whilst having an auxochromic effect, does not transmit conjugation effects from one chromophore to another. Thus the UV spectra of spirobiphenylene-phosphoranes were dominated by the biphenyl ring system. Comparisons of the spectra with the precursor dibiphenylene phosphonium salt and pentaphenylphosphoranes showed the spirophosphoranes to have more bands than the salt. This was attributed to different auxochromic effects of phosphorus through apical and equatorial bonds. ⟨70JCS(C)1425⟩.

The kinetics of isomerization of ephidrene based hydridospiro(4,4)-phosphoranes ⟨74TL3971⟩ and related L-alanine based phosphoranes ⟨80PS(8)153⟩ can be followed by polarimetry. The molecular rotation of optically active spiro(4,4)hydridodioxa-phosphoranes (**61**; X = O, Y, Z = NR), and ephidrene derived (**99**; X = Glc, Y = Eph, Z = H), permitted the separation of rotational contributions from the ligands and the helix structures. This allowed the assignment of the absolute configuration of a large number of phosphoranes ⟨81PS(10)53⟩. The polarimetric temperature jump method has been used to obtain more accurate kinetic and thermodynamic parameters for the isomerization of hydridophosphoranes (**99**; X = Eta, Y = Eph, Z = H) ⟨77JCS(D)570⟩.

Six coordinate perphosphoranide (**101**; X = Y = Cat, Z = $OCHPhCO_2$) was isolated in one form

by second order asymetric induction. Its equilibration was studied by polarimetry ⟨76JCS(P2)955⟩. Circular dichroism of trisbiphenyleneperphophoranide showed that the (−)-stereoisomer has a left handed screw stereochemistry ⟨70JCS(B)640⟩.

8.41.3.5 Vibrational Spectroscopy

Whilst infrared spectroscopy is used extensively as additional evidence for structural assignments there have been relatively few studies which focus on this area. One such study involved hydridospirophosphorane (**94**; $R^1 = R^2 = Me$, $R^3 = H$) where the ν_{NH} solvent dependence resembled pyrrole and ν_{PH} correlated with $^1J_{PH}$ ⟨69SA(A)1201, 72CR(C)1156⟩. Ring-chain isomerism and hydrogen bonding of hydridophosphorane (**99**; X = Pnc, Y = Pda, Z = H) was studied by IR spectroscopy ⟨75CR(C)809⟩.

8.41.4 THERMODYNAMIC ASPECTS

The barriers to intramolecular ligand exchange (permutational isomerism) via a pseudo rotation process have been measured for a large number of five coordinate phosphoranes using the variable temperature NMR signal coalescence approach (see 8.41.3.2.1). Care has to be taken to check that a dissociation–association mechanism is not operating, thus low ΔS^* and lack of deuterium exchange was used as evidence for the absence of a dissociation mechanism ⟨74JCS(P2)1668⟩. For the spirophosphoranes the largest barriers are observed when isomerism requires the formation of a conformer with a small ring bridging two equatorial (radial) orientations. The barrier to interconversion of isomeric phosphinates via spiro(3,4)hydroxyphosphoranes was shown to be $\Delta G^* = 17$ kcal mol^{-1} by variable temperature NMR spectroscopy ⟨76TL4381, 79JCS(P1)879⟩ c.f. $\Delta G^* = 24$ kcal mol^{-1} for the pseudorotation barriers of dimethylaminospirophosphorane derived from cis cyclohexane diol ⟨75JGU2088⟩.

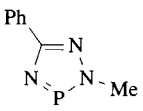
8.41.5 REACTIVITY OF FULLY CONJUGATED RINGS

There are no fully conjugated spirophosphorus compounds.

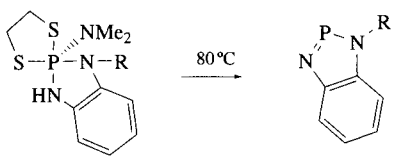
8.41.6 REACTIVITY OF NONCONJUGATED RINGS

8.41.6.1 Spirophosphonium Salts and Ylides

The extrusion of disulfide from spirophosphazene (**24**; X = S, Y = $(CH_2)_3$) provides a useful route to two coordinate triazaphosphole (**102**) ⟨76T2039⟩. The related extrusion reaction of (**103**) includes the loss of dimethylamine (Equation (1)) ⟨80TL1307⟩. In some cases there is an equilibrium between the phosphorane, for example (**57**) and the phospholan plus disulfide ⟨83JOC3815⟩. Spirophosphonium ylide (**11**) can be converted to its lithium diylide which forms a nickel complex ⟨81CB3161⟩. Spirophosphoranide (**31**; Y = CF_3) has also been converted to a series of metal complexes ⟨93PS(76)87⟩.



(**102**)

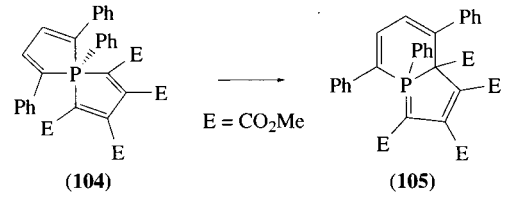


(1)

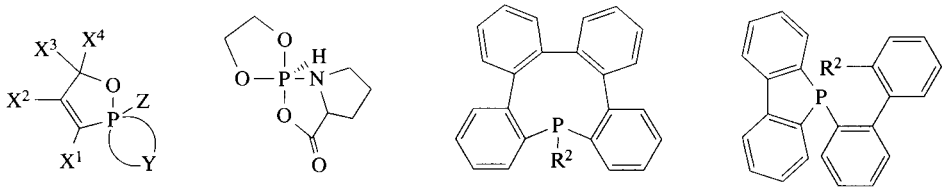
(**103**)

8.41.6.2 Spirophosphoranes

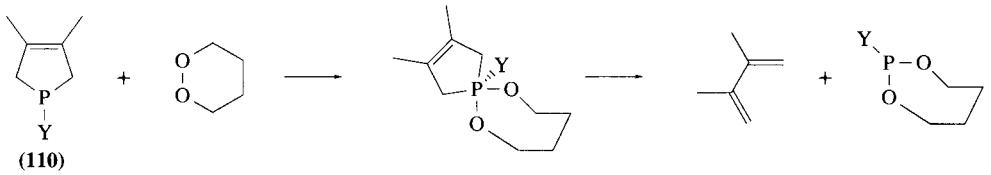
The stabilities of spirophosphoranes vary widely. Whilst small rings induce stability, they are not always sufficient to ensure a stable phosphorane. Thus triphenylphosphole reacts with two equivalents of ethyne dicarboxylate to give a transient spirophosphorane (**104**) but this rearranges spontaneously to give the ylide (**105**) (Equation (2)) ⟨68T3437⟩. The saturated analogues, for example phosphorane (**2**; m = n = 3, Y = Me) can be isolated but this is probably due to the lack of a rearrangement or degradation pathway rather than having thermodynamic stability. Two electronegative atoms are usually desirable. Some spirophosphoranes, for example (**106**; X^1 = H, $X^2 = X^3 = X^4$ = Me, Y = Glc, Z = OAc) are stable under quite vigorous reaction conditions ⟨71JGU228⟩ whereas others (**107**) can slowly ring open to give the carboxylic acid isomer ⟨79JCR(S)172⟩ or exist in equilibrium with the open chain form ⟨74BSF2193⟩. Monocyclic phosphoranes undergo 1,2-aryl migration from phosphorus to carbon under thermal conditions and in some cases spontaneously ⟨61JCS2126, 71PS(1)139⟩. The thermally induced rearrangement of spirobiphenylenephosphoranes (**33**; R^1 = H) to phosphines (**108**) and (**109**) are further examples, the former predominating when R^2 is Me or Ph, the latter predominating if R is larger, for example anthryl ⟨76CB1497⟩. The reaction of phospholene (**110**; Y = Ph) with a peroxide gave P-phenyldioxaphosphepan which was rationalised as involving an unstable spiro(4,6)phosphorane shown in Scheme 1 ⟨74PS(4)265⟩. Similarly spirophosphorane (**34**) formed in cycloaddition reactions underwent retrocycloaddition ⟨83TL5831⟩. Spirophosphiranes (**37**) undergo related reactions ⟨78CC854, 74JA317⟩. On the other hand heating the urea derived spiro(3,4)phosphorane (**65**; X^1 = NMe, X^2 = PPh, Y = CONMe) gave phosphole (**111**) as if by hydrolysis ⟨81CB2132⟩. The bis spirophosphorane (**70**; R = Ph, X = OEt, Y = Dpe, Pfp) fragmented in a similar manner ⟨76BCJ1924⟩.



(104) (105) (2)

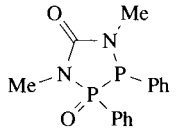


(106) (107) (108) (109)



(110)

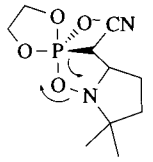
Scheme 1



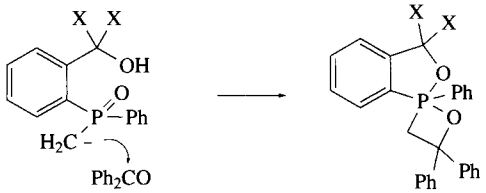
(111)

Whilst spirophosphetanes (**35**) have been generated for reactivity studies via the Wittig reaction, they have also been generated as oxyanions (**35**; $R^1 = O^-$, $R^2 = R^3$ = Ph) from β-hydroxyalkylphosphine oxides and found to fragment stereospecifically to *cis* stilbene ⟨85JCS(P1)1953⟩. Another exam-

ple is the detection of a related glycolyl oxyanion in a Horner reaction ⟨79TL2203⟩. A related spiro oxyanion (**112**) fragments with the formation of an aziridine ⟨79E851⟩. The formation and isolation of a spiro oxaphosphetan was achieved via a Horner reaction of a ketone with an oxyanion followed by cyclization as shown in Equation (3) ⟨92JA4008⟩.

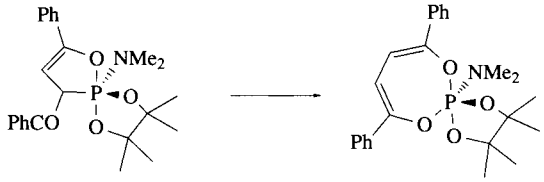


(**112**)



(3)

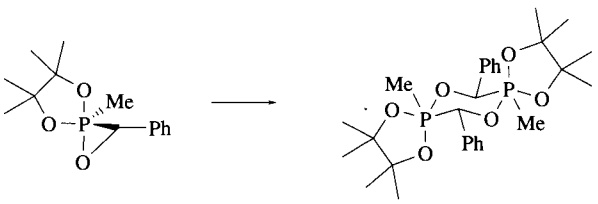
There have been a number of studies of the hydrolysis of spirophosphoranes. These include a range of spirotetraoxyphosphoranes (**66**) ⟨79PS(6)435⟩, (**106**; $X^1 = CONH_2$, $X^2 = H$, $X^3 = X^4 = OMe$, Y = Pnc) ⟨90PS(47)443⟩, (**99**; X = Y = Plc, Z = Ph) ⟨85JA5198⟩, and of dioxyphosphoranes (**41**) the products of which were characterized by acylation ⟨72JGU782⟩. The hydrolysis of hydroxyphosphoranes (**42**; R = OH, $Y = CMe_2$) have also been studied ⟨86JA2416⟩. Cycloaddition reactions of an aminodioxaphosphole with chalcone gave a spiro(4,4)phosphorane ⟨82PS(13)85⟩ which undergoes ring expansion to give a spiro(4,6)phosphorane as shown in in Equation (4) ⟨85PS(25)319⟩.



(4)

Spiro(2,4)phosphorane (**113**) was a postulated intermediate in the formation of bis spirophosphorane (**114**) from a dioxaphospholan and benzaldehyde (Equation (5)) ⟨88CC615⟩. Thermal cleavage of phosphazenes to a phosphole as shown in Scheme 2 is rationalized as involving a spiro(4,5)phosphorane ⟨74JCS(P1)1694⟩.

Hydridospirophosphorane (**60**; $Y = CH_2$, Z = H) in the presence of a tertiary amine has been used to convert ketocarboxylic acids such as pyruvates into the corresponding α-hydroxycarboxylates ⟨92PS(70)263⟩. However in aqueous alcohol hydridophosphoranes such as (**99**; X = Glc, Y = Amc, Z = H) are converted to phosph(III)olanes ⟨80PS(9)183⟩.

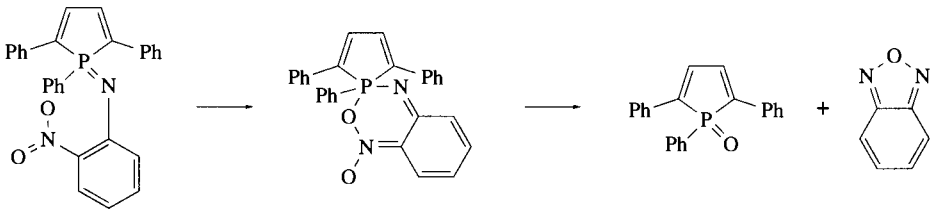


(**113**) (**114**)

(5)

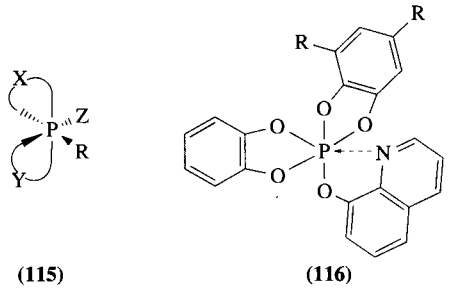
8.41.6.3 Spiroperphosphoranides

The interconversion and *cis*:*trans* isomerization of six coordinate spiroperphosphoranides (**115**; X = Gls, Y = Pfe, $Z = OC_6H_4F$, R = F) have been studied ⟨81JCR(S)218⟩. Five and six coordinate

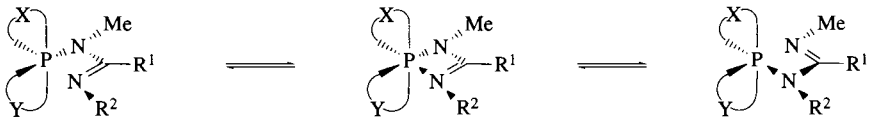


Scheme 2

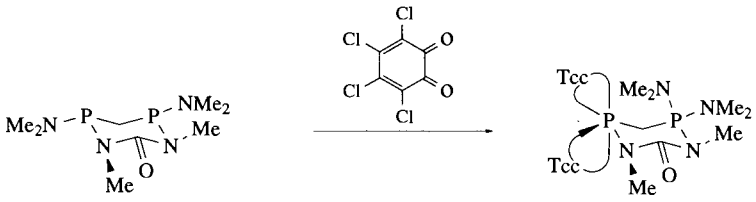
structures are often in equilibrium, the latter usually being favored over the five coordinate structure in compounds such as (**116**) ⟨79T1825⟩. The equilibrium shown in Scheme 3 (R^1 = Ph, CF_3, CCl_3; R^2 = Me, 2-Pr, X = Y = Cat) was found to depend on solvent and temperature ⟨85ZOB1982⟩. A quite remarkable reaction shown in Equation (6) involves a 1,3 migration of a dimethylamino group (Y) from one phosphorus atom to the other at some stage during the reaction ⟨93PS(75)233⟩.



(**115**) (**116**)



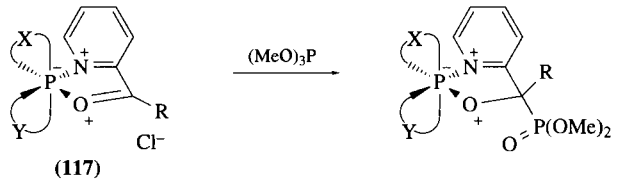
Scheme 3



(6)

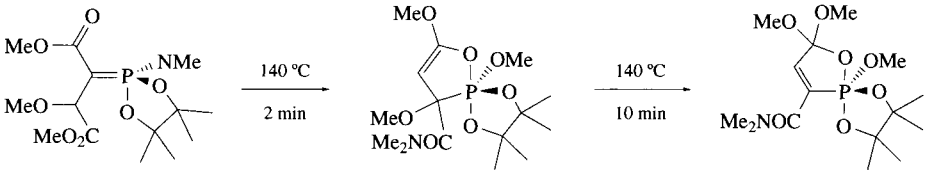
8.41.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON

The tendency for reactivity to focus at phosphorus leads to relatively few reports on the reactivity of carbon substituents. The 1,3-allylic migration of a methoxy group across a spirooxyphospholene ring was induced by heating at 140°C for 10 minutes (Scheme 4) ⟨85PS(24)235⟩. Secondary amines and phosphorous esters add to the activated double bond of spirophosphorane (**99**; X = Y = Glc, Z = CE=CHE) ⟨79CR(C)165⟩. Spiroperphosphoranide (**117**) reacts with trimethyl phosphite as shown in Equation (7) ⟨79PS(7)305⟩.



(**117**)

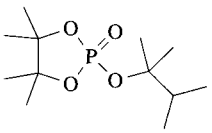
(7)



Scheme 4

8.41.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS INCLUDING SPIRO PHOSPHORUS

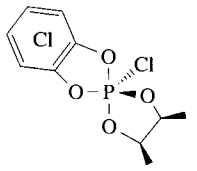
The physical and chemical properties of the hydrido P—H group in spirophosphoranes have been studied. The pK_a's of hydridophosphoranes (**62**; X = O, NH) were found to be 5.89 and 11.96 ⟨77IZV434⟩. Hydridophosphorane (**60**; Y = CMe_2, CPh_2, Z = H) was oxidized to the corresponding hydroxyphosphorane by N_2O_4 in DMSO which was then in equilibrium with the open chain carboxylic acid ⟨80T2467⟩. The PH bond of hydridophosphoranes undergoes many addition reactions to unsaturated compounds ⟨79PS(7)81⟩, thus (**61**; X = Y = Z = O) adds to chloral or benzaldehyde, ⟨68CR(C)270⟩, (**61**; X = Y = O, Z = O/NH) adds to acrylic ester in the presence of alkoxide to give Michael adduct (**99**; X = Glc, Y = Glc/Gln, Z = CH_2CH_2E, Z = O/NH) ⟨70BAU2637⟩, and in a similar manner hydridophosphoranes adds to imines ⟨74CR(C)1301⟩. Addition reactions of hydridophosphoranes to unsaturated compounds such as vinylethyl ether and alkynic carboxylic esters can be achieved using an AIBN catalyst, thus compounds such as (**99**; X = Y = Glc, Z = CH_2CH_2OEt/CE=CHE) have been made this way ⟨76T2253, 79CR(C)165, 81PS(9)285⟩. However di-t-butylperoxide converts (**66**; X = Y = Pnc, Z = H) into the phosphate (**118**) ⟨85JGU1810⟩ and dimethyldisulfide under photolysis conditions converts (**99**; X = Glc, Y = Pfp, Z = H) into (**99**; X = Glc, Y = Pfp, Z = MeS) ⟨86PS(27)313⟩. Interestingly, methanol and an enamine (which is hydrogenated) converts the PH group of hydridospirophosphoranes (**61**; X = Y = Z = O) directly to the corresponding methoxyspirophosphorane ⟨76T2253⟩, whereas the P-H group of (**60**; Y = CPh_2, Z = H) is oxidized to its hydroxyphosphorane by DMSO in DMF ⟨78CC219⟩ and is converted by sodamide or butyllithium into phosphoranides which can be acylated or alkylated to give spirophosphoranes (**60**; Z = R or PhCO) ⟨75JCS(P1)1220, 75JOM(93)331, 79TL4205⟩. However, in some cases the intermediate perphosphoranide is in equilibrium with the ring opened isomer ⟨78JA7434⟩. The P—H bond has also been converted to P—Hal ⟨83ZAAC(507)93⟩, P—S^-, P—Se^-, P—NTs^-, P—PS_2Ar^-, ⟨87PS(32)1⟩, and P—BH_3 ⟨88PS(35)309⟩. Photolysis of the azide (**99**; X = Y = Cat, Z = N_3) gave a nitrene which abstracted hydrogen from the solvent (benzene) to give the amino derivative (**99**; X = Y = Cat, Z = NH_2) ⟨84JA7065⟩, and a related azide of spiro(3,3)phosphorane (**49**; R^1, R^2 = Me, Y = N_3) was reacted with Ph_3P ⟨86PS(26)193⟩ to give the corresponding phosphazene.



(**118**)

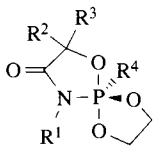
The chlorine atom of (**86**; X = O, R = Cl) was reacted with Y-TMS; Y = Ph_2P, CN, Br, I, MgTMS, N=CHPh, to produce the derivatives (**49**; R^1, R^2 = Me, Y = Ph_2P, CN, Br, I, TMS, N=CHPh) ⟨83ZAAC(507)702, 85JGU2333, 86PS(27)297, 91PS(62)139⟩, and with $(EtO)_2P(O)Na$ to give (**49**; Y = $(EtO)_2P(O)$) ⟨82IC844⟩. *P*-Halo perfluoropinacol-spirophosphoranes (**99**; X = Y = Pfc, Z = Hal) react with aq. KOH to give an isolable potassium salt (**99**; X = Y = Pfc, Z = O^-) and with alcohols to give stable alkoxy derivatives (**99**; X = Y = Pfc, Z = OR) which can be sublimed from sulfuric acid ⟨82AG(E)208⟩. In the case of an ambident nucleophile $(EtO)_2NHAr$, a P—P bond was formed initially upon reaction with (**86**; X = O, Y = Cl) and this was followed by rearrangement to the PNP isomer ⟨86JGU2218⟩. In the case of chlorophosphorane (**119**), dimethylamine replaced chlorine (at −78 °C in THF) with inversion whereas reaction with PhONa was nonstereospecific ⟨79TL193⟩. Bromophosphorane (**86**; X = O, Y = Br) reacted with chloral to give (**86**; X = O, Y = $POCHBrCCl_3$) ⟨89JGU2583⟩. Exocyclic P—N bonds are also readily substituted and provide ready routes to alkoxy and carboxy derivatives (**99**; X = Pnc, Y = Dpe, Z = OR/OCOPh) ⟨73TL3455⟩. When one of the rings has a carboxy group (**99**; X = Glc, Y = Hyc) compounds with exocyclic groups Z = PhO or

X_3CCH_2O are readily converted to alkoxy groups by the action of alcohol ⟨80CL1599⟩. Also an exocyclic vinyl ether group can be replaced by Br by the action of bromine which in turn may be converted to methoxy by methanol ⟨84JGU486⟩. The chlorine in (**86**; R = Cl, X = O) has also been replaced by $Mn(CO)_5$ ⟨83ICAL139⟩.

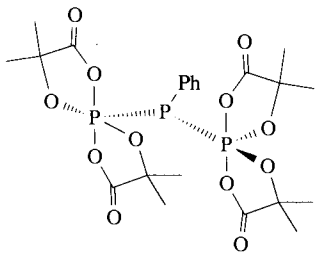


(**119**)

Methylation of hydroxyphosphorane (**42**; R = OH, Y = CO) by diazomethane gives the methoxy derivative (**42**; R = OMe, Y = CO), whereas methylmagnesium iodide gives trimethylated phosphorane (**42**; R = Me, Y = CO, Z = CMe_2) ⟨79JA3687⟩. Whilst the NH group of spirophosphorane (**120**; $R^1 = R^2 = H$, $R^3 = R^4 = Ph$) was methylated by KH and MeI to give (**120**; $R^1 = Me$, $R^2 = H$, $R^3 = R^4 = Ph$) ⟨90PS(49)385⟩, when the phosphorane also had a PH group as in (**120**; $R^1 = H$, $R^2 = R^3 = Me$; $R^4 = H$) NaH and MeI methylated at phosphorus to give (**120**; $R^1 = H$; $R^2 = R^3 = R^4 = Me$) ⟨84CJC2179⟩. The bis spirophosphorane (**121**) was made by the reaction of hydridophosphorane (**60**; Y = CMe_2, Z = H) with phenyldichlorophosphine ⟨90T3527⟩.



(**120**)



(**121**)

The six coordinate hydridospiroperphosphoranide (**115**; R = H, X = Y = Cat, Z = Et) on standing for several days with 2-aminophenol undergoes conversion to phosphorane (**99**; X = Cat, Y = Oam, Z = Et) probably with loss of hydroquinone ⟨75JGU2292⟩.

8.41.9 RING SYNTHESES

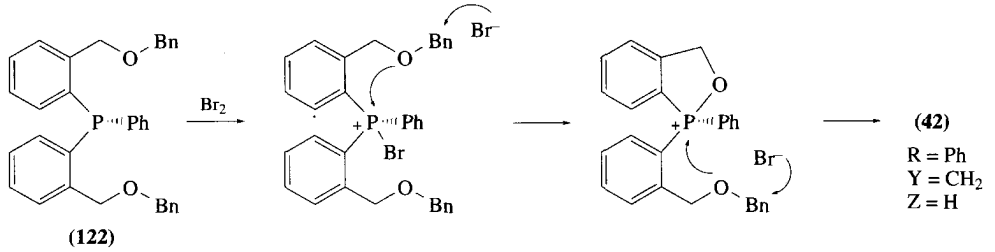
8.41.9.1 All Components Acyclic

8.41.9.1.1 Spirophosphonia compounds

Spiro(4,4)phosphonianonane triiodide (**1**; m = n = 4) was prepared (40%) by heating phosphorus and 1,4-diiodobutane at 200°C ⟨68ZOB331, 77AG(E)722⟩. The dibenzo derivative (**8**) was prepared from o-xylidene dibromide ⟨73JHC395⟩. The tetrabenzo salts (**9**) may be made from dilithium biphenyl and either trichlorophosphine ⟨72RTC836⟩ or triphenyl phosphate ⟨73RTC1308⟩ or by the original method involving bis di-iodobiphenyl and phosphorus ⟨65CB576⟩.

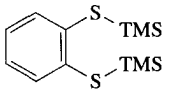
When the aryl ring is activated towards electrophilic attack as in diphenylamine, trichlorophosphine is able to substitute at the ortho position and, at 200°C, ultimately produce the spirophosphonium salt (**13**) ⟨71CC1213⟩. If the forming bond to phosphorus is from a heteroatom, a P(III) phosphorus can be made electrophilic. Such an example is the the cyclization of the dibenzyl ether (**122**) to give phosphorane (**42**; Y, Z = CH_2, R = Ph) as shown in Scheme 5 ⟨82JCS(P1)735⟩.

Spiro(5,5)phosphonia-undecane chloride (**12**) was produced in low yield by the reaction of dimethylurea with the little exploited, readily available, tetrakis(hydroxymethyl)-phosphonium salts ⟨81PS(10)147⟩. Tetrathiodibenzo quasiphosphonium salts (**24**; R = Dop; $X^- = PF_6^-$) have been produced by the reaction of silylated dithiocatechol (**123**) with PF_5 ⟨73CC144⟩. Spiro(5,5)phosphazenes (**20**) may be made directly from trichlorophosphine and diaminophosphazene, $H_2NPR_2{=}PR_2NH_2$,



Scheme 5

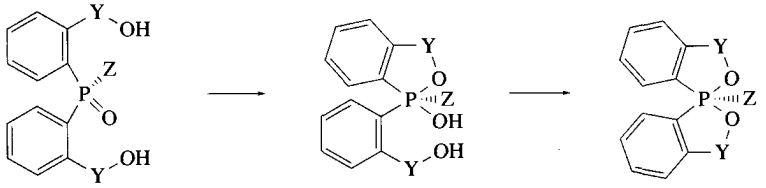
⟨75CB1454⟩. On the other hand, bis spirophosphazene (**27**) was made by the reaction of substituted phosphabenzenes with phenylazide ⟨93TL3107⟩. Rhenium carbonyls have been used to dicyclize a silylated diphosphazene to produce the salt (**17**) ⟨87CB1183⟩.



(**123**)

8.41.9.1.2 Spirophosphoranes

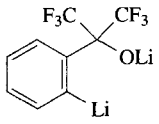
The formation of phosphoranes is greatly enhanced when the phosphorus atom is involved in a five membered ring which has apical electronegative atoms such as oxygen. Thus pentachlorophosphorane (PCl_5) reacts with acylhydrazines to give P-chloro spirophosphoranes ⟨89JGU1333⟩, and with *o*-methylaminothiophenol to give chlorophosphorane (**55**; X = NH, R = Cl) ⟨77JGU436⟩. Also intramolecular addition of a benzylic alcohol to the phosphoryl group gives an intermediate hydroxyphosphorane which undergoes intramolecular condensation to produce the spirophosphorane as shown in Scheme 6 ⟨78JA5130⟩.



Scheme 6

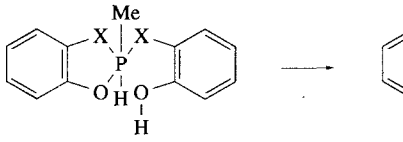
The dilithium salt (**124**) with $POCl_3$ gives, after work up and treatment with KOH, the dibenzospirophosphorane potassium salt (**42**; $Y = C(CF_3)_2$, R = OK) ⟨81JOC1049⟩. Hexachlorocyclotriphosphazene, $(NPCl_2)_3$, may be used as a source of phosphorus in place of PCl_3, thus with o-aminophenol, spirophosphorane (**86**; X = NH, R = *o*-$OC_6H_4NH_2$) may be obtained via a NH bridged bis spiro compound ⟨75IC2831⟩. Methyltetraphenoxyphosphorane, prepared from methyltriphenoxyphosphonium iodide, using $(MeO)_2CCHNMe_2$, was converted by ethane-1,2-diol to the spirophosphorane (**66**; $R = CF_3$, X = Y = O, $Z = NMe_2$) ⟨89JGU634⟩. Analagous reactions occur when pentaphenoxyphosphorane, $(PhO)_5P$, reacts with catechol ⟨68T5041⟩ and with *o*-aminophenol ⟨76IZV2624⟩, as well as for the reactions of pentaethoxyphosphoranes, $(EtO)_5P$, with diols ⟨71JA4004⟩. Silylated oxygen or sulfur functional groups react with RPF_4 to produce phosphoranes (**99**; X = Y = Cat, Z = F, Et, Pr^i, CH_2TMS) ⟨71JCS(A)1295⟩, its naphthdiol analogue (**99**; X = Y = Don), ⟨92PS(69)231⟩, (**99**; X = Y = Ami, Z = H) ⟨92CB801⟩ and (**55**; X = S) ⟨73CC144⟩.

The use of trisphosphoramidites, for example $(Me_2N)_3P$, often has advantages over trichlorophosphine with amidrazones to give hydridophosphoranes (**99**; X = Y = Ami, Z = H) ⟨72CR(C)2209⟩. They have also been used in combination with CCl_4 in which case the reaction proceeds via quaziphosphonium salts ⟨75TL2529⟩. The P—N bonds are quite labile and strong acids are not generated. Thus spirophosphorane (**54**) has been prepared by the reaction of either $RP(Ch)Cl_2$ or

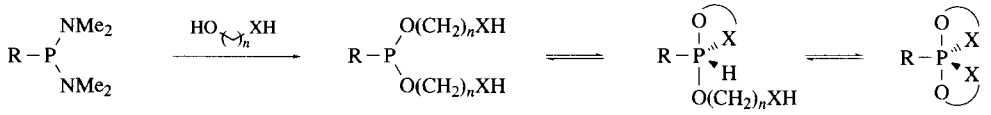


(124)

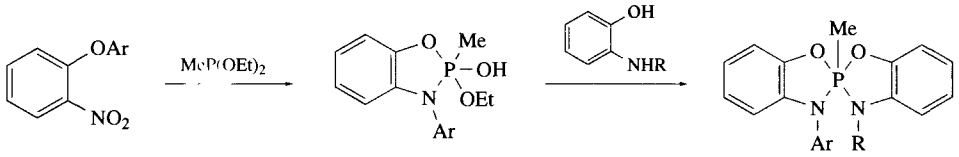
$MeP(NMe_2)_2$ with a hydrazide $RCONHNH_2$ ⟨77CB1124⟩. Also two equivalents of the Mannich base of 2-cresol were reacted with $(Et_2N)_3P$ to generate a spirophosphorane with two P—C bonds ⟨67DOK(174)846⟩. There are a number of examples of the oxidative cyclization of monocyclic hydridophosphoranes to give spirophosphoranes as shown in Equation (8) and Scheme 7 ⟨75TL497⟩. The deoxygenation of nitrobenzene derivatives by P(III) compounds can be used to make intermediate cyclic phosphoranes which react with *o*-aminophenols with migration of an aryl group from oxygen to nitrogen (Scheme 8) ⟨75JCS(P1)2376⟩. Hydrido-phosphoranes may be prepared directly from trichlorophosphine, for example (**60**; $Y = CR_2$, $Z = H$) from α-hydroxcarboxylic acids ⟨71BSF4185⟩ including tartaric, malic acid ⟨81PS(11)71⟩, and enolisable α-ketocarboxylic acids ⟨88PS(35)195⟩. Likewise, (**62**; $R = Bu^t$, $X = Y = Z = O$) was made using di-t-butylcatechol ⟨88JGU1996⟩.



(8)



Scheme 7



Scheme 8

8.41.9.1.3 Perphosphoranides

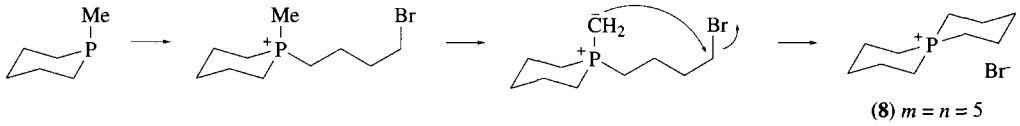
Very stable perphosphoranides may be prepared directly (**79**; $m = 0$, $n = 3$, $R = H$) from catechol and PCl_3 or $POCl_3$ ⟨76TL917⟩ or PCl_5 ⟨77JPR188⟩, (**81**; $m = 0$, $n = 3$) from PCl_3 and *N*-benzoylhydroxylamime ⟨77ZAAC(437)53⟩. White phosphorus reacts with 3,4-di-t-butylbenzoquinone in the presence of triethylamine to give (**79**; $R = Bu^t$, $m = 0$, $n = 3$) ⟨79IZV2398⟩. The phosphorus atom is invariably spiro to three identical rings.

8.41.9.2 From One Monocyclic Component

8.41.9.2.1 Spirophosphonia compounds

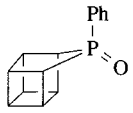
Spiro(5,5)phosphonium bromide (**1**; $m = n = 5$) was synthesized from 1-methylphosphorinan by monoalkylation with 1,4-dibromobutane followed by ylide intramolecular alkylation as shown in Scheme 9 ⟨80ZN(B)990⟩. Dilithium biphenyl reacted with the phenylphosphine oxide (**125**) to displace

the phenyl and oxygen and give the cage salt (**10**; R = H) ⟨72CC404⟩. Generation of an electrophilic centre by protonation of an allenylphosphonate was followed by cyclization to the phosphoryl oxygen to give spiro trioxonium salts as shown in Scheme 10 ⟨84PS(21)249⟩.

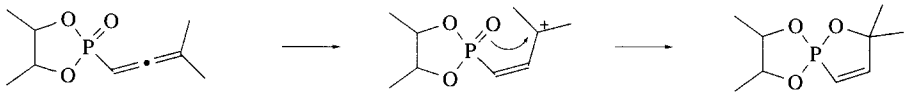


(**8**) $m = n = 5$

Scheme 9

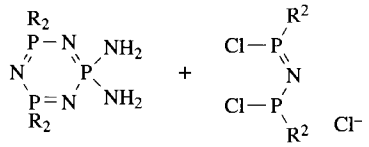


(**125**)

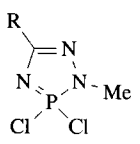


Scheme 10

A wide variety of spiro(5,5)phosphazenes may be prepared from hexachlorocyclo-triphosphazene by the replacement of two chlorine atoms by aromatic diamines or aminophenol ⟨85JA7585, 88IC1911⟩ or by a sequence of condensing reagents, for example AgNCO, ROH, MeCN ⟨87PS(30)519⟩. This approach has also been used to generate many bis spiro compounds ⟨82ZN(B)1425⟩ including 1,3-dioxaphosphorins ⟨84CC675⟩, and incorporating salicylate moieties ⟨75ICA240⟩, as well as hydrazine ⟨89ZN(B)612⟩ and thioferrocene ⟨90ZN(B)741⟩, as well as spermine bridges, for example (**29**) ⟨84JST(116)75⟩. Some reactions are accelerated by the presence of $Bu_4N^+X^-$ ⟨83MM719⟩. Alternatively the addition of a second ring may be achieved by condensation of difunctional reagents with the geminal amino groups bound to phosphorus as shown in Equation (9) ⟨76PS(6)113⟩. In the case of supermesitylmagnesium bromide, following substitution of one chlorine atom of hexachlorocyclotriphosphazene, the intermediate can be ring closed from phosphorus to one of the *t*-butyl methyl groups, under the action of $AlCl_3$, to give spirophosphazene (**15**) ⟨90JCS(D)2303⟩. Five membered phosphazenes (**126**) derived from PCl_3 and amidrazones, react with propanedithiol to produce spirophosphazene (**24**; X = S, Y = $(CH_2)_3$) ⟨76T2039⟩ and eight membered octachlorocyclotetraphosphazenes with propanediols give the corresponding spirophosphazenes ⟨91PS(55)59⟩.

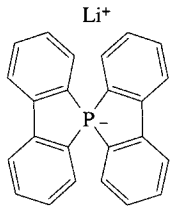


(**20**) (9)

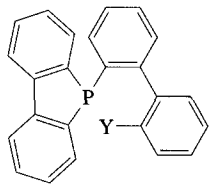


(**126**)

Lithium biphenylenephosphoranide (**127**) which may be prepared by the action of butyllithium on the fluorenylphosphine (**128**; Y = Br), is in equilibrium with the ring opened isomer (**128**; Y = Li) ⟨69CB548⟩. In most cases the phosphoranides are produced by the action of base on the corresponding hydridophosphoranes ⟨79JA4623⟩.



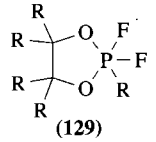
(127)



(128)

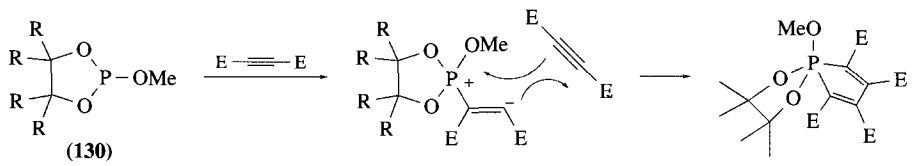
8.41.9.2.2 Spirophosphoranes

Dioxyspirophosphoranes can be prepared either by displacement of two fluorine atoms on phosphorus i.e. (**129**; R = Ph), by the dilithium salt of diols, or by cycloaddition, for example, using α-diketones ⟨70CRC(C)418, 75T797⟩ (see Section 8.41.9.3). On the other hand the catecholspirophosphoranes were prepared from difluorophosphoranes (**129**; R = Ph, Me, Bu^t, F) by condensation with trimethylsilanyl derivatives of catechol ⟨78IJ107, 78IJ143⟩. Monocyclic phosphoranes with leaving groups other than halogen can also be used (e.g., methoxy, or dimethylamino) in reactions with diols and amino alcohols ⟨72PS(2)41, 75PS(5)285⟩. These reactions can be exothermic.



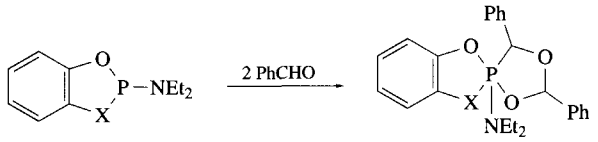
(129)

Many phosphorus(III) compounds add to two equivalents of compounds possessing electrophilic multiple bonds such as carbonyl groups and electrophilically activated double and triple bonds. The driving force for the second stage (a 1,3 polar addition) is usually the formation of a phosphorane incorporating a small ring. Whilst the reaction of triphenylphosphole with DMAD gives the spirophosphorane (**104**), it is not stable ⟨68T3437⟩. However the use of a phosphorus(III) 1,3-dioxaphospholan adds stability. Thus pinacol derived methoxyphospholan (**130**) reacts with two equivalents of DMAD to give a spirophosphorane as shown in Scheme 11 ⟨81TL3533⟩. Whilst benzaldehyde adds in the normal head to tail mode with catechol derived phospholan as shown in Equation (10) ⟨76JGU581⟩, substituted benzaldehydes with 1,3-diazaphospholan gave head to head spiro adducts (**131**) ⟨68JOC13⟩ Carbonyl compounds such as hexafluoroacetone are better able to support negative charge on carbon when attacked at oxygen in the initial step ⟨74JCS(P1)2125, 93PS(78)271, 95PS(106)65⟩. Benzophenone and PhCOCN ⟨75CR(C)225⟩ also give head to head products as shown in Scheme 12. Similar reactions occur with chloral and tribromoacetaldehyde ⟨87JGU1078⟩.

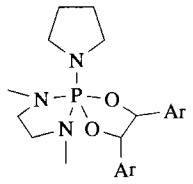


(130)

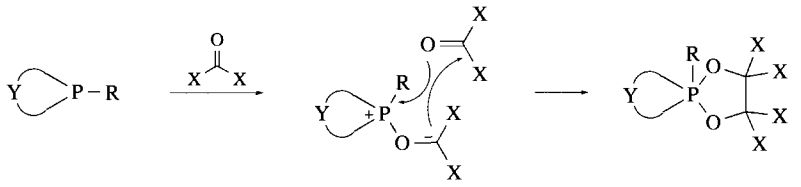
Scheme 11



(10)

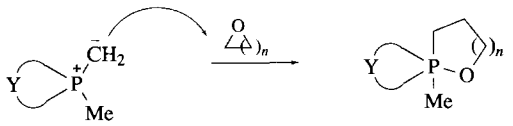


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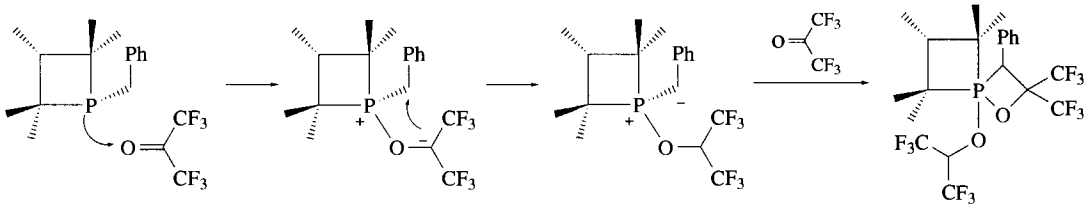


Scheme 12

Phosphonium ylides (**132**) react exothermically with oxiran but a temperature of 130 °C is required to achieve reactions with oxetan to give oxaphosphoranes shown in Equation (11) ⟨79CB501⟩. A stabilized ylide cyclized on heating at 140 °C and 150 °C to give the amides shown in Scheme 4 ⟨85PS(24)235⟩. It is possible that an ylide may be also formed in the reaction of benzylphosphetan with hexafluoroacetone in the formation of phosphoranylspiro(3,3)oxaheptane as shown in Scheme 13 ⟨73JCS(P1)1300⟩.

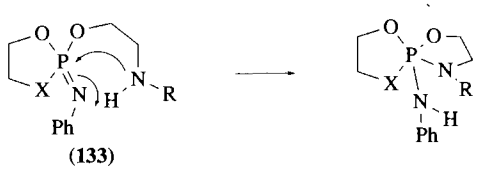


(11)



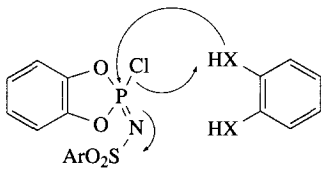
Scheme 13

Phosphazene (**133**) generated from a phospholan and phenyl azide was cyclized as shown in Equation (12) ⟨76CC730⟩. Stabilized phosphazenes, for example (**134**) have also been cyclized in this way ⟨78JGU1308⟩. The PhN=functionality can also act as a leaving group, thus phosphazene (**135**) was reacted with C_2 to C_5 diols with loss of aniline to produce spirophosphoranes (Equation (13)) (**58**; Y = Ph) ⟨79CC191⟩. An alternative approach involves the reaction of a functionalized azide, for example 2-azidophenol with cyclic phosphines to give intermediates set up for cyclization via addition to the P=N bond as in Scheme 14 ⟨80PS(8)127⟩. Similarly, phosphazene (**136**) gives spirophosphorane (**120**; $R^1 = R^2 = H$, $R^3 = R^4 = Ph$) (Equation (14)) ⟨90PS(49)385⟩. Related phosphazene intermediates were proposed in the reaction pathway shown in Scheme 15. It has two interesting features, first the use of a dialkylamino leaving group, secondly, the nitrogen to phosphorus migration to produce a phosphazene function to which the second hydroxyl group cyclizes ⟨90JGU397⟩.

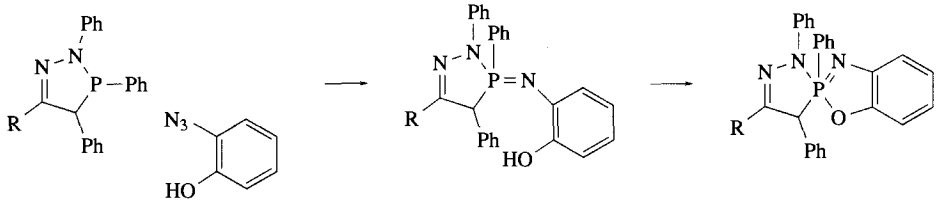


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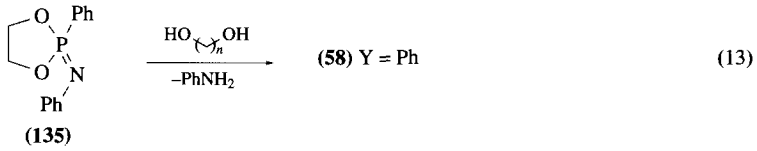
(12)



(134)

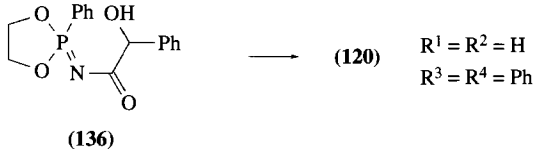


Scheme 14



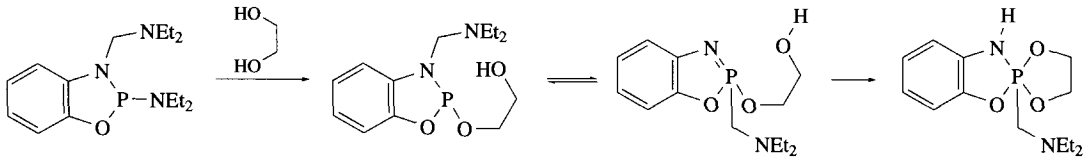
(135)

(13)



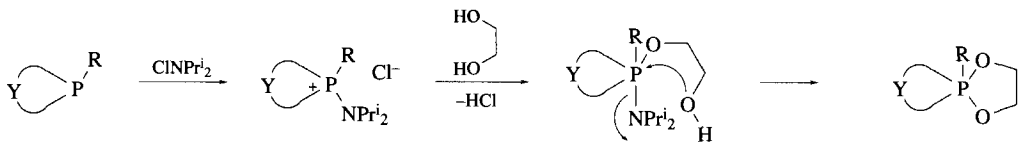
(136)

(14)



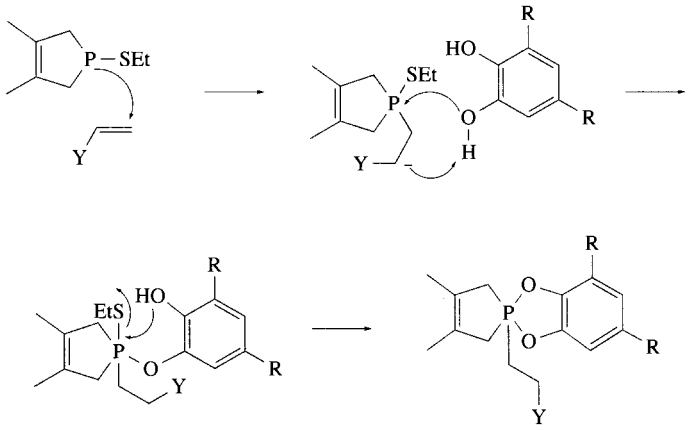
Scheme 15

The reaction of cyclic three coordinate phosphorus compounds with diols has been found to proceed smoothly in the presence of di-isopropylchloramine ($ClPr^i_2$) ⟨75TL1583⟩. This reaction would appear to involve initial formation of an amino salt which reacts with one of the alcoholic hydroxyl groups followed by cyclization and loss of amine after protonation by the liberated HCl as shown in Scheme 16. If the P(III) atom already bears a potential leaving group such as SEt, it is possible to use an activating group such as ethyl acrylate as in Scheme 17 ⟨83PS(17)283⟩. On the other hand [2 + 4] cycloaddition reactions with dichlorophosphines produce directly a phosphonium center, for example (**137**) suitable for reacting with diols and diamines etc. to give spirocompounds such as (**47**) ⟨89PS(45)255⟩. Unsaturated carboxylic acids add to cyclic P(III) compound (**138**; Ch = O) to give an hydridophosphorane which cyclizes by Michael addition of the PH group to the acrylic moiety (Scheme 18) ⟨78IZV2185⟩.

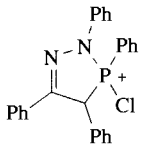


Scheme 16

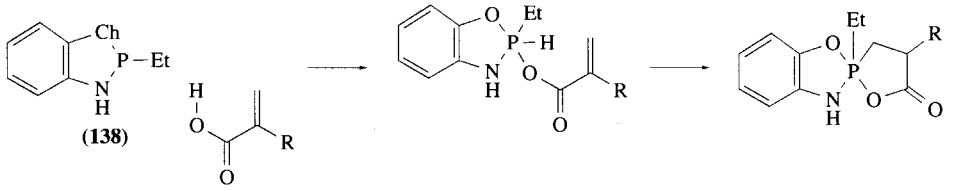
Spiro hydridophosphoranes may be prepared by a condensation reaction of P-halo or P-amino-dioxaphospholanes and 1,2-aminoalcohols (**139**; X = NH, Y = CH_2) ⟨72BSF1413, 72CR(C)419⟩ or



Scheme 17



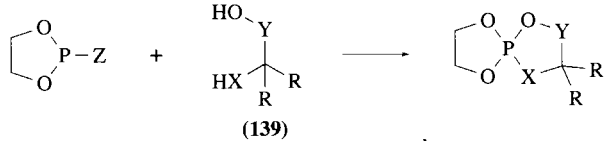
(137)



(138)

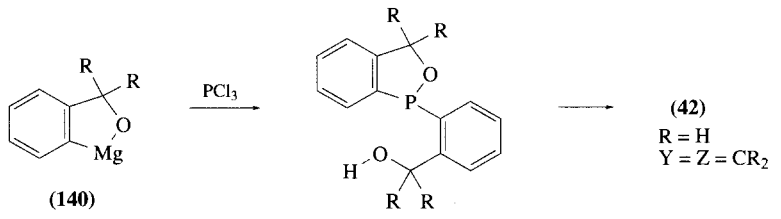
Scheme 18

amino acids (**139**; X = NH, Y = CO) ⟨77T635⟩ as in Equation (15). Alternatively routes to intermediates involve the reaction of PCl_3 with the magnesium salt of the benzyl alcohol (**140**) (Scheme 19) ⟨79JA4623⟩. The alkyl substituents R assist the electrocyclization. Similar reactions with hydrazides and amidoximes ($RC(=NOH)NH_2$) give hydridophosphoranes (**99**; X = Pnc, Y = Amo, Z = H) ⟨72CR(C)151⟩ (**99**; X = Glc, Y = Amo, Z = H) ⟨82CB2560⟩, and (**99**; X = Cat, Y = Amo, Z = H) ⟨72CRC1211⟩.



(15)

(139)

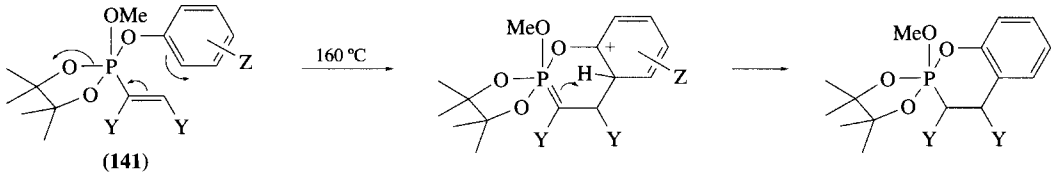


(140)

(42)
R = H
Y = Z = CR_2

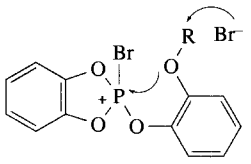
Scheme 19

There were a number of reports in the 1970s of monocyclic hydrido phosphoranes acting as intermediates in the formation of spirophosphoranes. Thus hydridophosphoranes convert to phosphoranes slowly but spontaneously when X = O, and on heating or with a mild oxidizing agent when X = NH ⟨75TL3077, 83JGV1759⟩ as shown in Equation (8). Monocyclic phosphoranes (**141**) are converted at 160 °C to spiro(4,5)phosphorane (Scheme 20). The yields are higher as the donor properties of Z increase ⟨86T3521⟩. Note that this argues against a transition state with phenoxide character for the migration and in favor of alkoxy phosphonium character to give an ylide which, after proton transfer to the ylidic carbon with rearomatization, recyclizes. An alkylarylether oxygen will cyclize to a phosphonium center with dealkylation by bromide ion as shown in Equation (16) ⟨79PS(7)57⟩. A similar ring closure was achieved with transfer of a trimethylsilyl group to a phosphoryl group as in Equation (17) ⟨76JA4330⟩.



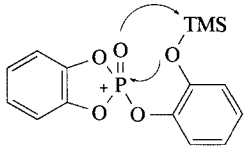
(**141**)

Scheme 20



(**99**)
X = Y = Cat
Z = Br

(16)



(**99**)
X = Y = Cat
Z = O-TMS

(17)

8.41.9.2.3 Spiroperphosphoranides

Perphosphoranides with phosphorus spiro to three rings one of which is different from the other two (e.g. **101**; X = Y = Cat, Z = Dpe) may be prepared by the reaction of a monocyclic phosphorane bearing three exocyclic dimethylamino leaving groups and a chelating ligand such as catechol ⟨75PS(5)285⟩.

8.41.9.3 By 2 + 4 Cycloaddition to Phosphorus

8.41.9.3.1 Spirophosphonia compounds

Two coordinate phosphines are able to participate as dienophiles in cycloaddition reactions with 1,3-dienes and their hetero analogues such as diimines, α-diketones, and unsaturated ketones etc. to produce four coordinate spiro compounds. Thus cyclic two coordinate phospholes, for example (**102**) add to diacetyl ⟨84TL5521⟩, diimine RN=CRCR=NR) ⟨86TL2971⟩, and to azodicarboxylic esters ⟨81CB825⟩ to give the corresponding spirophosphazenes (**23**). In the case of the product from diacetyl, a dimer is formed initially. It is also possible to have the phosphorus III atom as part of the 4 electron system adding to an activated carbonyl group as the dienophile as shown in Equation (18) ⟨82JGU189⟩.

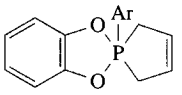


(18)

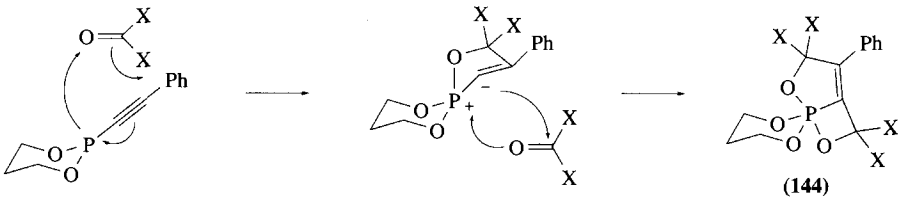
8.41.9.3.2 Spirophosphoranes

The reactions of three coordinate phosphines with 1,3-dienes and their hetero analogues such as diimines, α-diketones and unsaturated ketones etc. to produce five coordinate spiro phosphoranes has been widely exploited. Thus 1,3-butadiene reacts with catechol phosphonous esters to produce dioxaphosphoranes (**142**) ⟨69TL4693⟩, the reaction rate increasing with increasing electron accepting properties of group Y ⟨72JGU782⟩. Ortho quinones such as di-t-butylbenzoquinone ⟨94ZN(B)145⟩, phenanthraquinone ⟨68T1785⟩, and tetrachloro-ortho-quinone ⟨96S473⟩ make excellent 4p-π compounds, the increase in aromaticity and formation of stable P—O bonds strongly favoring the forward reaction. Thus these are favorite reagents for producing spirophosphoranes with three P—C bonds ⟨72JA9264, 80CB1406⟩. This reaction may be extended to α-diketones ⟨70CRC(C)418, 75T797⟩, ketoesters ⟨92JGU1172⟩, azoketones ⟨72CR(C)419⟩ and isatin ⟨85JGU1986⟩. Aliphatic spirophosphoranes, for example (**143**) with two PC bonds have been prepared from methoxyphospholenes and diacetyl ⟨89PS(44)193⟩ or benzil ⟨85JGU1514⟩. A novel approach involved cycloaddition of two equivalents of benzil to PhP (phenylphosphinidene), or its equivalent, generated either from $(PhP)_5$ at 160°C or photochemically, to give (**99**; X = Y = Dpe, Z = Ph) ⟨68CB1381, 71JCS(C)593⟩. A range of phosphoranes (**53**; R^2 = Y = H, Z = Glc) have been prepared from unsaturated aldehydes ⟨82JGU221⟩ extending previous studies of unsaturated ketones, carboxylic acids, and amides, and other phospholans. Cycloadditions to the dioxaphospholan was found to be faster than with the corresponding benzodioxaphospholan ⟨72JGU2109⟩. As above, it is also possible to have the phosphorus III atom as part of the 4 electron system adding to an activated carbonyl group as the dienophile. In the example shown in Scheme 21 the addition occurs twice to produce the bridged spirophosphorane (**144**) ⟨90JA7451⟩.

Ozone adds to dioxabenzophospholans and dioxaphosphinans to give stable spiro ozonides (**145**; Y = Cat) and (**145**; Y = Plc) ⟨84PS(20)55⟩.

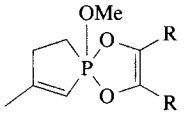


(142)

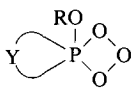


(144)

Scheme 21



(143)



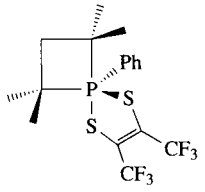
(145)

8.41.9.4 By 2 + 2 Cycloaddition to Phosphorus

8.41.9.4.1 Spirophosphoranes

The reaction of cyclic three coordinate phosphorus compounds with cyclic peroxides and disulfides gives valence expanded spirophosphoranes with a wide range of ring size possibilities as shown in Equation (19). Thus phenylphosphetan reacted with cyclic peroxides and also with a disulfide to give phosphoranes (**40**; Y = $(CH_2)_4$) ⟨77PS(3)51⟩, (**40**; R = Ph, Y = 1,3-cyclopentanylidene) ⟨83JOC2621⟩ and disulfide (**146**) ⟨72CC395⟩, and (**147**) ⟨84MI 841-02, 84MI 841-03⟩ respectively. In the

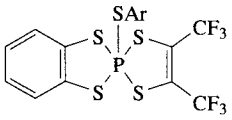
case of cyclic diselenides (**148**), one selenium is removed and the remaining fragment forms part of the spirophosphorane (**87**; Ch = Se, Y = $C(CF_3)_2$, Z = N = NMe_2) ⟨78AG(E)774⟩



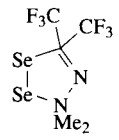
(**146**)



(19)

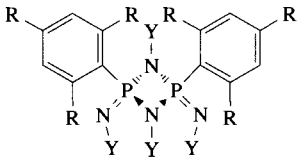


(**147**)



(**148**)

There are many examples of monocyclic phosphazenes dimerizing to give spiro(3,4)phosphoranes ⟨75CB820, 92JGU780, 92JGU970⟩. Supermesitylphosphine reacts with diazodicarboxylic ester to give diphosphazene (**149**; R = Bu^t, Y = CO_2R) which, at 110 °C, undergoes CH addition (from a methyl group) to a P=N bond at both phosphorus centers to give bis spirophosphorane (**69**) ⟨88PS(35)247⟩. There are other examples of ortho t-butyl groups reacting in this way.



(**149**)

8.41.9.5 By Ring Modification

8.41.9.5.1 Spirophosphonia compounds

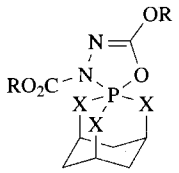
Chlorospiro-phosphoranes, under the action of Lewis acids such as $SbCl_5$, may be converted to the quasiphosphonium salt, for example (**16**) ⟨88ZAAC(561)49⟩. Hydroxyphosphorane (**42**; R = OH, Y = CMe_2) is converted to the spiroquasiphosphonium triflate (**14**) by the action of trifluoromethanesulphonic acid ⟨78JA5229⟩; this in turn can be reduced by LAH to the phosphoranide (**42**; R = electron pair, Y = CMe_2).

8.41.9.5.2 Spirophosphoranes

Phosphoranes such as phosphoranylspiro (4,4)nonane (**2**; m = n = 3, Y = Me) and the biphenylene phosphoranes (**33**) may be prepared by the reaction of lithium alkyls or lithium aryls with a spiro salt, for example (**1**; m = n = 4) ⟨77AG(E)722⟩ or (**9**) ⟨77CB693⟩. Hydridobiphenylenephosphoranes (**33**; R = H) have also been prepared by LAH or borohydride reduction of the biphenylene salt (**9**) ⟨69CB528⟩.

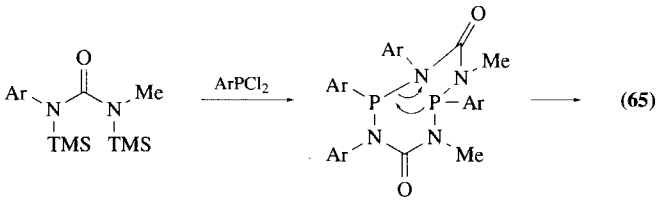
Azodicarboxylic ester can be used as an activating agent for P(III) compounds undergoing [2 + 4]

cycloaddition reactions to give phosphoranes such as (**150**) and then being replaced by reagents such as diols liberating the reduced azoester as its hydrazine ⟨80TL1449⟩. Diphenyldisulphide, PhSSPh, has also been used as a condensing agent ⟨82JOC916⟩; whilst a quasiphosphonium salt was proposed as an intermediate, a dithiophosphorane intermediate is quite possible.



(**150**)

Spirophosphorane (**65**; X^1 = MeN, X^2 = PC_6H_5, Y = CONAr) was formed in the reaction of a disilylated derivative of urea with dichloro(perfluorophenyl)phosphine, presumably the expected eight membered ring rearranging as shown in Scheme 22 ⟨79CB1365⟩. Treatment of the corresponding product from $PhPCl_2$, with Cl_2 and PCl_5 removed one of the phosphorus groups and gave spirophosphorane (**49**; Y = Ph) ⟨80CB1847⟩.



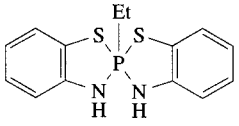
Ar = *m*-$CF_3C_6H_4$

Scheme 22

8.41.9.6 Other Methods

8.41.9.6.1 Spirophosphoranes

Aniline hydrochloride converts the azathiobenzophospholan (**138**; Ch = S) to spirophosphorane (**151**) ⟨83JGU1759⟩. Presumably the aniline releases some aminothiophenol forming a hydridophosphorane which spontaneously dehydrogenates similar to that reported in Equation (8)).



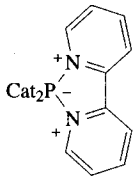
(**151**)

8.41.9.6.2 Spiroperphosphoranides

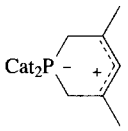
Many six coordinate spiroperphosphoranides have been obtained by addition of a nucleophile to the phosphorus atom of a spirophosophorane. Thus the nucleophiles fluoride or p-fluorophenoxy anions gave (**115**; X = Glc, Y = Pfe, Z = F/ArO) ⟨80CC157⟩, pyridine gave (**115**; X = Cat, Y = Pfe, Z = PhO, R = NC_5H_5) ⟨74JA7269⟩, and alcohols reacted with a hydridophosphorane to produce (**115**; R = H, X = Y = Cat, Z = OR) ⟨73CR(C)297⟩.

Spirophosphoranes (**99**; X = Y = Cat, Z = Hal) bearing an exocyclic leaving group (Y) such as halogen react with chelates such as bipyridyl giving (**152**) ⟨79PS(7)305⟩, 2-ketopyridines, and β-diketones giving (**153**) and with trisaminophosphazene (**154**) to give perphosphoranide (**155**) (Equation (20)) ⟨90JGU1491⟩. When spirophosphoranes have a second nucleophilic center juxtaposed to the phosphorus atom there is a potential for the formation of a perphosphoranide. Examples include

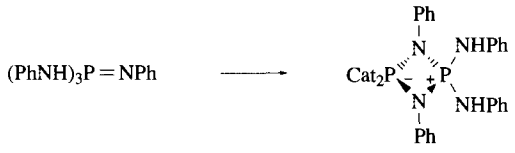
the 8-hydroxyquinoline compound (**116**) ⟨79T1825⟩. Spirophosphorus atoms participating in three different ring types, for example **101**; X = Glc, Y = Dpe, Z = Hyc) have been prepared by taking a spirophosphorane possessing two different ring types and an exocyclic leaving group ⟨75BSF1433⟩.



(**152**)



(**153**)

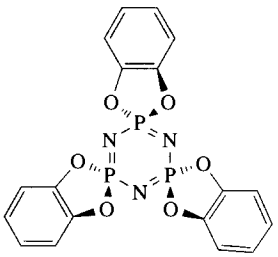


(**154**) (**155**) (20)

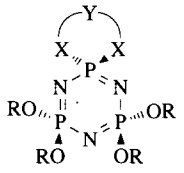
8.41.10 IMPORTANT COMPOUNDS AND APPLICATIONS

8.41.10.1 Nonmedical Applications

The tris spirocyclotriazene (**156**), prepared via condensation polymers ⟨75MI 841-01⟩, has been used to form clathrate tunnels in which alkenes can be polymerized with enhanced stereoregularity ⟨82MM697⟩. These compounds are able to form inclusion complexes with *p*-xylene thus offering a useful means of purification ⟨72BRP12570247⟩. They have also been patented in a number of countries as flame retardants ⟨75GEP(O)231350-1⟩. Attempts to polymerize spirocyclotriphosphazenes (**157**) produced ring expanded products ⟨93MM3⟩.

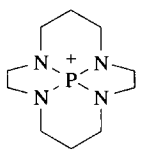


(**156**)

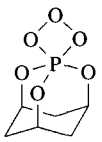


(**157**)

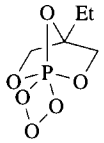
The fluoride ion in the tetraaza analogue of the fenestrane related phosphonium fluoride (**158**) is an example of a completely ionic fluoride ion ⟨81JA5265⟩. The ozonide (**159**) from an adamantyl type phosphite is a good water soluble source of singlet oxygen and is 1.4 times more stable than ozonide (**160**) ⟨75JOC1185⟩.



(**158**)



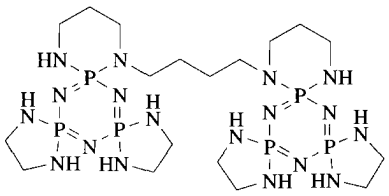
(**159**)



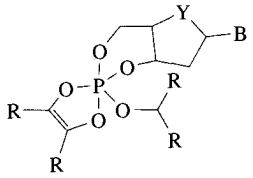
(**160**)

8.41.10.2 Compounds of Medical Interest

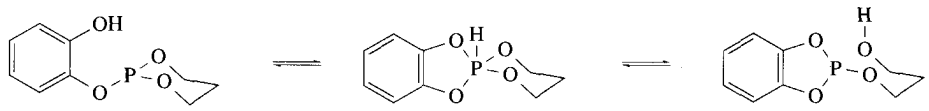
A series of bis cyclotriphosphazenyl spermines such as (**161**) have been prepared and shown to have anticancer activity in six murine tumour systems. These compounds had a higher potency and lower toxicity than related aziran derivatives ⟨87PS(29)147⟩. Spirophosphorane derivatives of thymidine such as (**162**; R = CF_3) have been used as models for the study of the stereochemistry of cyclic AMP interactions with enzymes ⟨90JA6092⟩. The base catalyzed proton transfer observed for the equilibrium shown in Scheme 23, mimics the role of the bases histidine 12 and histidine 119 in the active site of Rnase A during the hydrolysis of ribonucleic acids ⟨84PS(19)173⟩.



(**161**)



(**162**)



Scheme 23

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References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "The Tautomerism of Heterocycles," in "Advances in Heterocyclic Chemistry," Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code "MI" for miscellaneous with the whole code for books prefixed by the letter "B-".
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe–Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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