

7.01

Bicyclic 5-5 Systems: Two Heteroatoms 1 : 1

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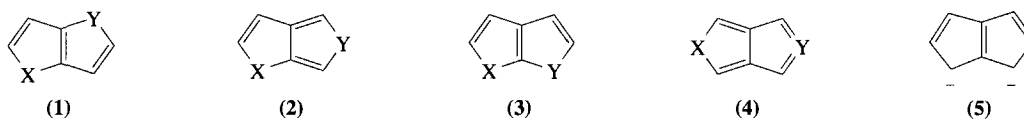
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7.01.1 INTRODUCTION

The 5:5 fused heterocyclic systems containing one heteroatom in each ring are represented by the general structures (1)–(4), wherein X and Y may be the same or different heteroatoms and represent O, NR, S, Se, and very rarely Te.



There are four possible modes of 5:5 fusion of the simple five-membered heterocycles leading to structures (1)–(4). Compounds of type (4) can only be represented by 1,3-dipolar, diradical, or hypervalent structures and only S- or Se-substituted derivatives are known. In the case of X = Y = O or N, some reduced derivatives have been reported.

The fully conjugated title compounds have a central C—C bond and are isoelectronic with the 10π -electron pentalene dianion (5). The positional isomers (1)–(4) have interesting features and their stabilities and properties are related to the positions of heteroatoms. The numbering in the parent ring systems (6)–(51) is shown in Figures 1–4. On the basis of this numbering, these four general classes of heterocycle (1)–(4) are referred to as 1,4-diheteropentalenes (1), 1,5-diheteropentalenes (2), 1,6-diheteropentalenes (3), and 2,5-diheteropentalenes (4), or generally as A,B-diheteropentalenes.

Some of the better-known systems have previously been reviewed (75ACR139, 76AHC(19)123, 77HC(30)317, 78AHC(22)183, 84CHEC-I(4)1037, 84CHEC-I(6)1027, 90CCC597). The parent compounds that were mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (84CHEC-I(4)1037) are (8), (9), (11), (12), (13), (14), (19), (25), (26), and (30)–(35). The parent compounds that are new since the first edition are (10), (17), and (21). The remainder of the parent compounds have not been synthesized, probably owing to the lack of mild synthetic methods for the preparation of these highly labile rings.

This chapter begins where two earlier ones in the first edition (84CHEC-I(4)1037, 84CHEC-I(6)1027) finished and extends the literature coverage to the end of 1994. Some earlier references have been included to cover material absent from the first edition.

7.01.2 THEORETICAL METHODS

Theoretical methods ranging from the simple Hückel (HMO) method to *ab initio* calculations have been used extensively to study the title compounds (84CHEC-I(4)1037, 84CHEC-I(6)1027). The subject of these studies was mainly the molecules (36)–(39), which cannot be represented by classical Kekulé structures. These heterocyclic systems can be represented by dipolar structures, or by

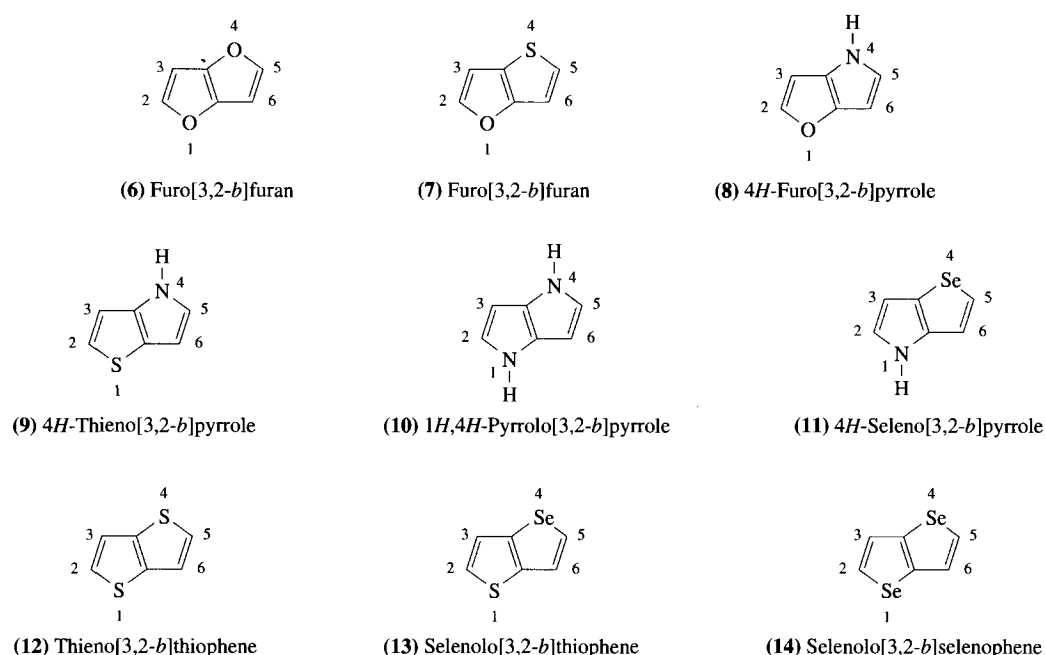


Figure 1 1,4-Diheteropentalene structures.

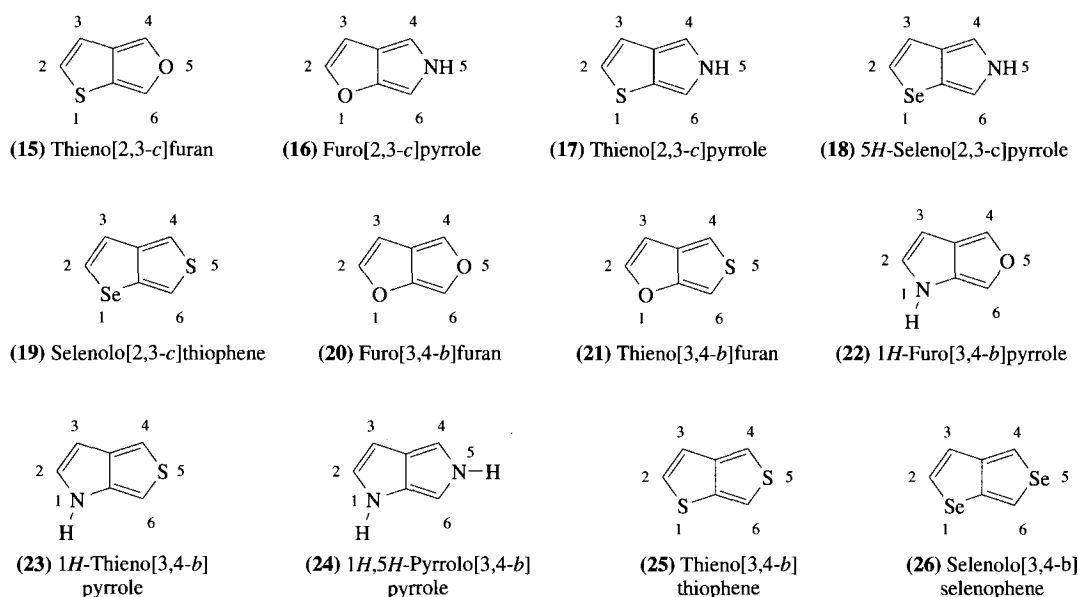


Figure 2 1,5-Diheteropentalene structures.

structures involving tetravalent sulfur atoms, and are described as conjugated mesomeric betaines or nonclassical heteropentalenes (Figure 5).

Early molecular orbital calculation using the semiempirical PPP-SCF-MO method $\langle 68T2567 \rangle$, which ignores *d*-orbital interactions, predicted a triplet ground state for thieno[3,4-*c*]thiophene (**37**). An investigation based on its photoelectron spectrum with an unrestricted version of the extended CNDO/S method predicted that the triplet was more stable than the closed-shell singlet state by 1.4 kcal mol⁻¹ (5.9 kJ mol⁻¹). With incorporation of *d*-orbitals and configuration interaction (CI), the lowest singlet emerged 31.8 kcal mol⁻¹ (133.1 kJ mol⁻¹) more stable than the lowest triplet state $\langle 76JA7187 \rangle$. A study $\langle 78JOC3893 \rangle$ based on the photoelectron, ESR, and electronic absorption spectra of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**52**) supports the prediction of a singlet ground state

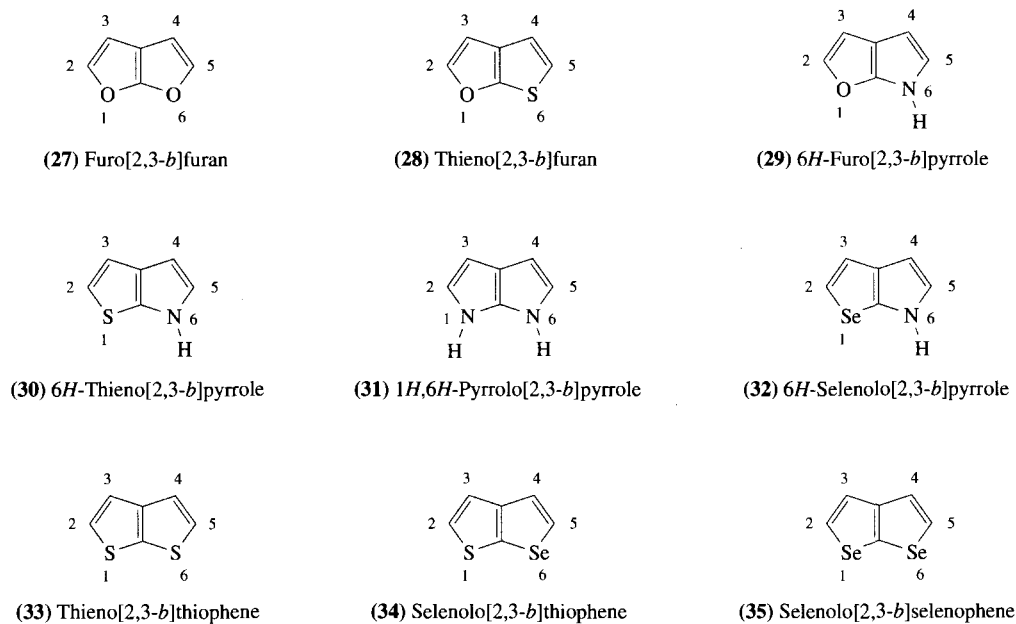


Figure 3 1,6-Diheteropentalene structures.

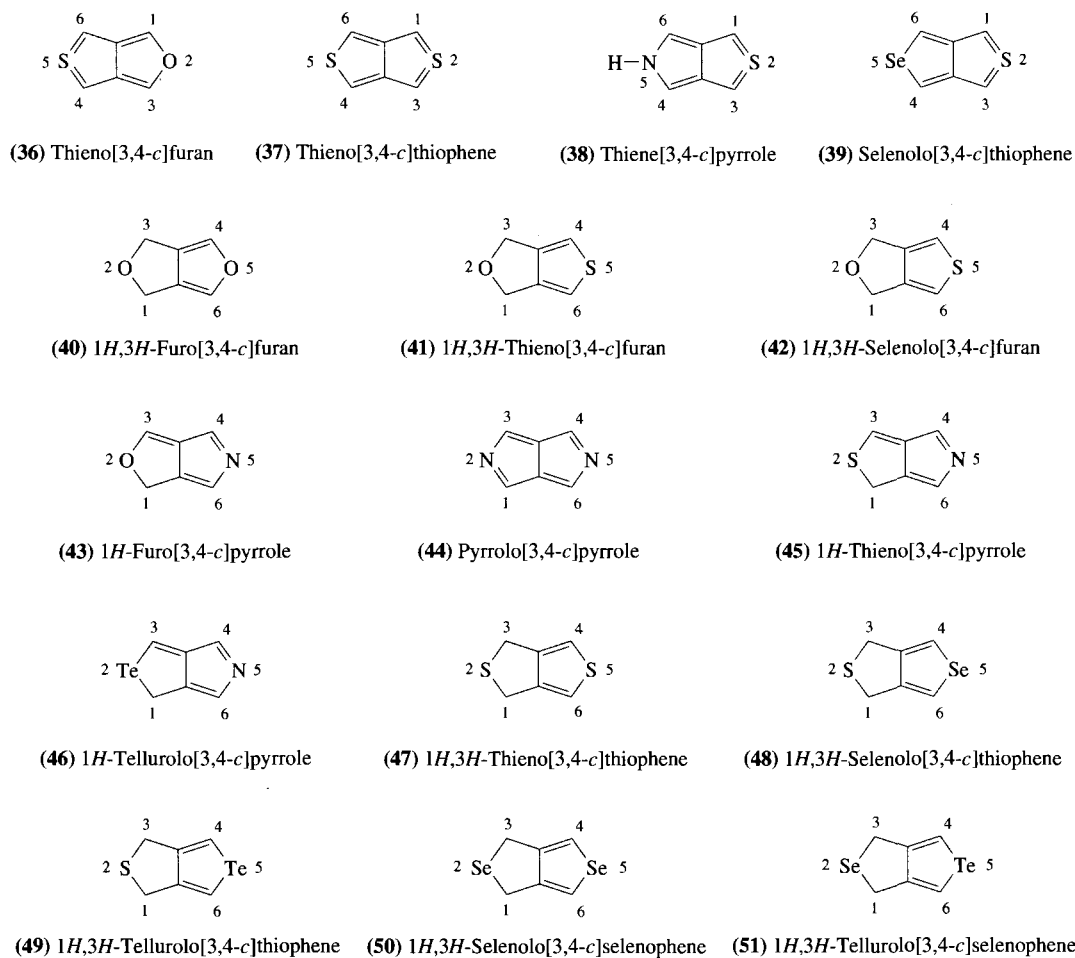
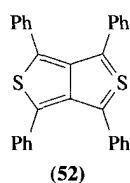


Figure 4 2,5-Diheteropentalene structures.

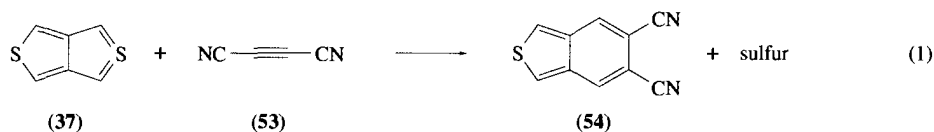


Figure 5 Resonance representations of thieno[3,4-*c*]thiophene (37).

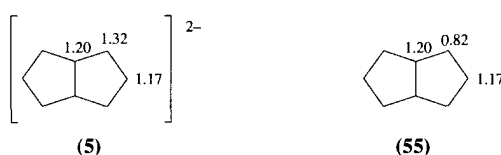
and indicates that the most appropriate representation of the π system consists of the various dipolar species implicit in the thieno[3,4-*c*]thiophene molecule. The singlet state was predicted to be more stable than the lowest triplet state $\langle 83JA1705 \rangle$ using the MINDO/3 MO method $\langle 75JA1285 \rangle$.



The reaction of thieno[3,4-*c*]thiophene (37) with dicyanoethyne (53) (Equation (1)) was examined $\langle 83JA1705 \rangle$ utilizing the MINDO/3 method. Extrusion of elemental sulfur as an atomic species from the initial 1 : 1 cycloadduct was shown to be energetically unfavorable, whereas formation of molecular sulfur (S_6 or S_8 species) resulted in a favorable energy change. A satisfactory mechanism for the extrusion of sulfur involves a thiirane species that dimerizes to a disulfide which decomposes to give the expected product, 5,6-dicyanobenzo[*c*]thiophene (54), and an intermediate that ultimately allows for the extrusion of S_6 or S_8 (Figure 6).



Gimarc $\langle 83JA1979, 86JA4303 \rangle$ proposed a rule of topological charge stabilization which states that heteroatoms prefer to be located at sites that conform to the pattern of relative electron densities determined by connectivity or topology in an isoelectronic, isostructural, homoatomic system that is called the uniform reference frame $\langle 83JA1979 \rangle$. For the series of thienothiophene positional isomers, the pentalene dianion (5) serves as the uniform reference frame ((55) represents pentalene).



The largest charge densities in dianion (5) are at equivalent positions 1, 3, 4, and 6. Accordingly, placement of electronegative heteroatoms at these positions should be favored and the introduction of electron-withdrawing groups at 1, 3, 4, and 6 positions could stabilize the thieno[3,4-*c*]thiophene. The remarkable stability of the tetrakis(alkylthio)thieno[3,4-*c*]thiophenes $\langle 88JHC559 \rangle$ can thus be rationalized by the electron-accepting conjugation of alkylthio substituents.

Table 1 lists some calculated resonance energies per electron (in β units) for thienothiophenes, pentalene, and pentalene dianion $\langle 72T3657, 75T295, 77JA1692 \rangle$. These data support the conclusions of Gimarc's proposition.

The method of the local approach in combination with a PPP Hamiltonian has been used to investigate the many-particle character of π -electron bonding in all the four isomeric diazapentalenes, i.e., pyrrolo[3,2-*b*]pyrrole (56), pyrrolo[3,4-*b*]pyrrole (57), pyrrolo[2,3-*b*]pyrrole (58) and pyrrolo[3,4-*c*]pyrrole (44) $\langle 93JPC11427 \rangle$.

In Table 2 are introduced atomic many-particle quantities and the associated mean values for pentalene (55) and pyrrolopyrroles as well as the corresponding mean values $\langle (\Delta n_{av}^2) \rangle_{corr}$, Δ_{av} , Σ_{av} averaged over all atomic sites *i*. The large π -electronic localization and strong correlation at certain centers is clearly seen. As expected the electronegative nitrogen atoms $\langle 86AG646 \rangle$ in pyrrolopyrroles

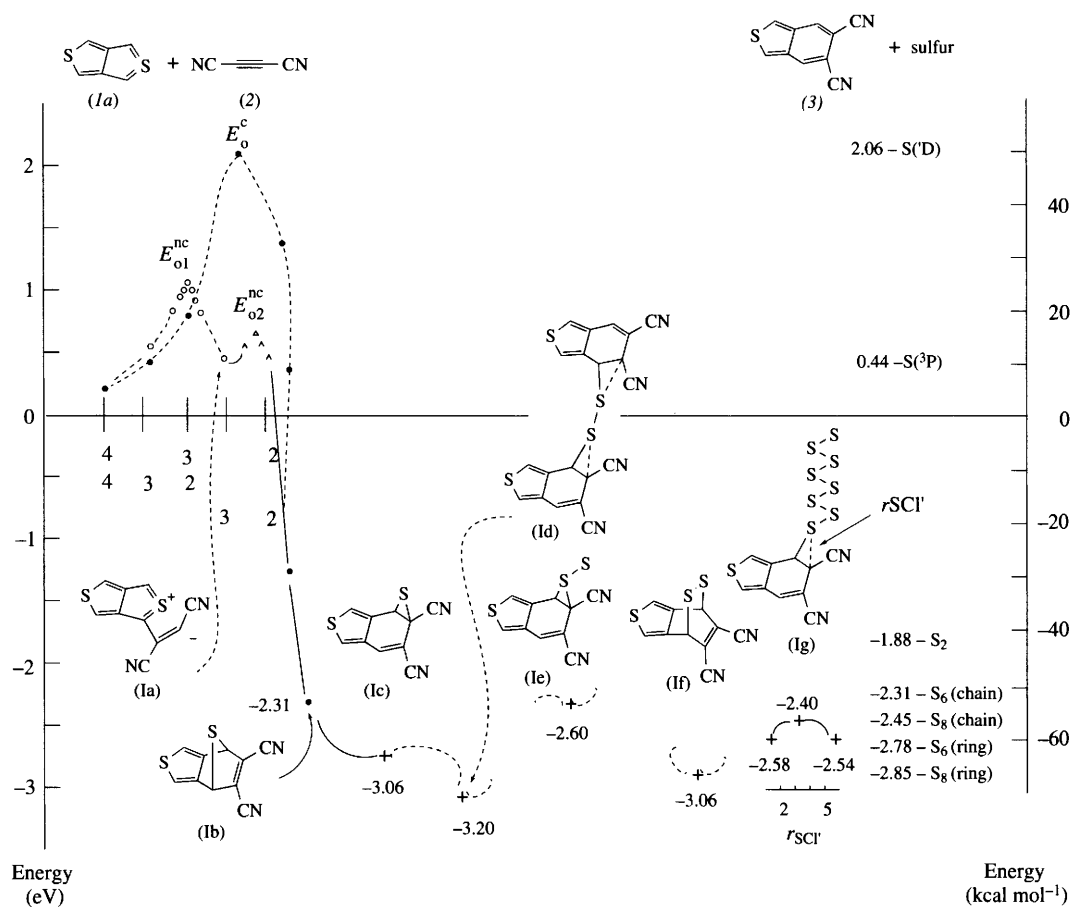


Figure 6

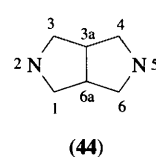
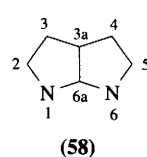
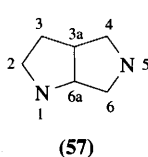
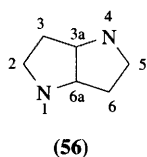
Figure 6 Theoretical reaction surface for the cycloaddition reaction of thieno[3,4-*c*]thiophene (**1a**) (**37** in this chapter) with dicyanoethyne (**2**) (**53**) to yield 5,6-dicyanobenzo[*c*]thiophene (**3**) (**54**). Energies for the hypothetical intermediates and possible products are reported per mole of atomic sulfur of the chain or ring units. (Reprinted with permission from K. I. Miller, K. F. Moschner and K. T. Potts; *J. Am. Chem. Soc.*, 1983, **105**, 1705. Copyright 1983 American Chemical Society.)

Table 1 Calculated resonance energies^a of isomeric thienothiophenes, pentalene, and pentalene dianion.

Molecule	TRE/(PE) ^b	REPE ^c
Thieno[3,2- <i>b</i>]thiophene (12)	0.031	0.022
Thieno[3,4- <i>b</i>]thiophene (25)	0.026	0.015
Thieno[2,3- <i>b</i>]thiophene (33)	0.031	0.024
Thieno[3,4- <i>c</i>]thiophene (37)	0.004	
Pentalene (55)	-0.024	-0.018
Pentalene dianion (5)	0.046	

^a Units of β . ^b Topological resonance energy (per electron).

^c Resonance energy (per π -electron) <72T3657, 75T295, 77JA1692>.



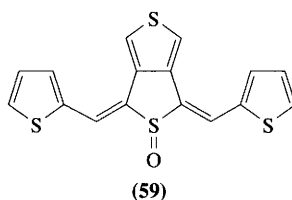
cause an enhancement in the interatomic π correlation strength. In the first place this modification is an on-site (N atoms) effect, as π electronic localization properties at the carbon atoms are roughly conserved in aza derivatives. The E_{corr} values in eV ((**55**) 0.406; (**56**) 0.591; (**57**) 0.486; (**58**) 0.493; (**44**) 0.473) show that nitrogen atoms cause an enhancement of the interatomic correlation energy in the relative order $2,5 < 1,5 < 1,6 < 1,4$. The rather high localization parameters Σ_i indicate that pyrrolopyrroles should be highly reactive as a result of their low π delocalization, which has been supported by a report <84TL5669> that attempts to prepare 1,4-pyrrolo[3,2-*b*]pyrrole (**56**) by oxidation of 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole (**10**) were unsuccessful.

Table 2 Charge fluctuation $\langle(\Delta n_i^2)\rangle_{\text{corr}}$ and correlation strength parameters Δ_i , Σ_i in pentalene (**55**) and pyrrolopyrroles (**56**), (**57**), (**58**), and (**44**) <93JPC11427>.

Structure	Atom <i>i</i>	$\langle(\Delta n_i^2)\rangle_{\text{corr}}$	Δ_i	Σ_i	$\langle(\Delta n_{\text{av}}^2)\rangle_{\text{corr}}$	Δ_{av}	Σ_{av}
(55)	C-1 = C-3 = C-4 = C-6	0.332	0.312	0.449	0.353	0.270	0.338
	C-2 = C-5	0.368	0.243	0.337			
	C-3a = C-6a	0.378	0.211	0.315			
(56)	N-1 = N-4	0.287	0.425	0.433	0.341	0.311	0.355
	C-2 = C-5	0.373	0.249	0.279			
	C-3 = C-6	0.319	0.350	0.451			
(57)	C-3a = C-6a	0.387	0.221	0.258	0.341	0.295	0.415
	N-1	0.292	0.408	0.502			
	C-2	0.376	0.234	0.300			
(58)	C-3	0.333	0.314	0.439	0.343	0.294	0.405
	C-4	0.328	0.316	0.473			
	N-5	0.313	0.351	0.508			
(44)	C-6	0.326	0.317	0.485	0.341	0.293	0.425
	C-3a	0.383	0.207	0.299			
	C-6a	0.378	0.213	0.314			
(58)	N-1 = N-6	0.288	0.414	0.536	0.343	0.294	0.405
	C-2 = C-5	0.375	0.233	0.308			
	C-3 = C-4	0.327	0.320	0.471			
(44)	C-3a	0.385	0.205	0.291	0.341	0.293	0.425
	C-6a	0.378	0.213	0.315			
	C-1 = C-3 = C-4 = C-6	0.344	0.307	0.446			
(44)	N-2 = N-5	0.316	0.347	0.493	0.341	0.293	0.425
	C-3a = C-6a	0.378	0.211	0.314			

Ab initio and/or semiempirical (PM3) quantum-chemical calculation on the parent thieno[2,3-*c*]furan (**15**) and furo[3,4-*b*]furan (**20**) systems in the ground and excited states have been performed <91CB2481>.

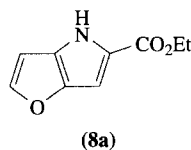
Several investigations with cyclic voltammetry and UV-vis-NIR spectroelectrochemistry (SEC) were carried out on compound (**59**), which belongs to a family of methine-bridged molecules possessing a small band gap ($E_g \sim 1$ eV) <85JCP(82)5717, 93CB1487>. The experimental data were compared with the results of electronic band structure calculated on the basis of an MNDO-optimized geometric structure by a VEH (valence effective Hamiltonian) pseudopotential method <85JCP(82)3308, 93CB1487>.



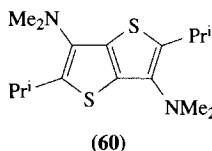
7.01.3 EXPERIMENTAL STRUCTURAL METHODS

7.01.3.1 X-ray Diffraction Studies

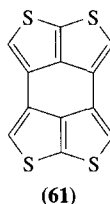
In ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (**8a**) the furan and pyrrole rings are nearly coplanar, with a dihedral angle between the rings of 1.0(2)°. The molecules are linked by N—H···O hydrogen bonds <88AX(C)2032>.



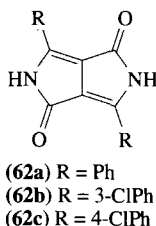
The ring system of 3,6-bis(dimethylamino)-2,5-diisopropylthieno[3,2-*b*]thiophene (**60**) has an inversion centre and is exactly planar. The two C—S bond lengths differ by a small but significant amount (3.2 pm) and are somewhat longer than standard C—S values. All other bond distances and bond angles are as expected <92AX(C)2275>.



An x-ray crystallographic analysis of benzo[1,2,3-*cd*:4,5,6-*c'd'*]bis(thieno)[2,3-*c*]thiophene (**61**) demonstrated that the molecule is planar and symmetrical but has strained bond angles. The crystal structure comprises herring-bone type column stacking with intercolumnar heteroatom interactions. Compound (**61**) showed the same oxidation potential as perilene and, like perilene, formed an iodine complex with the relatively high electroconductivity of 0.11 S cm^{-1} <93BCJ2033>.



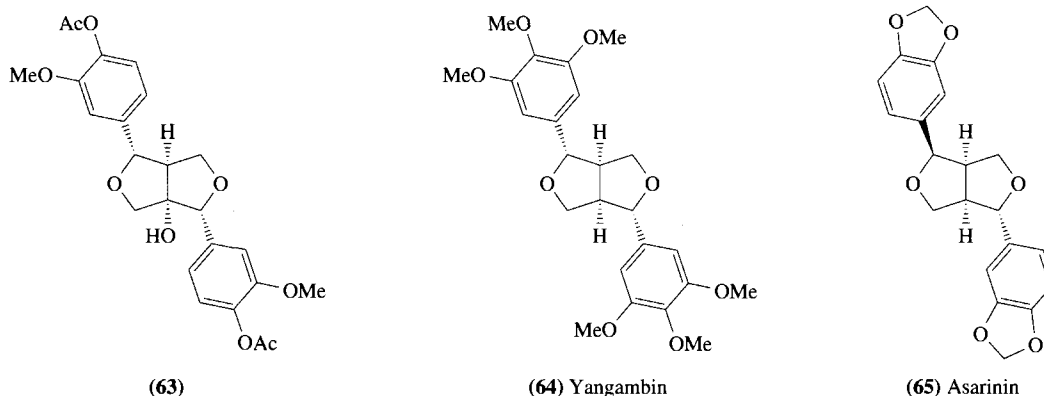
The bathochromic shift in the spectrum of 3,6-diphenyl-1,2,4,5-tetrahydropyrrolo[3,4-*c*]pyrrole-1,4-dione (**62**) in the solid state relative to solution was investigated using the semiempirical INDO/S method <94JPC1796>. On the basis of the crystal structure, the spectra for the monomer, dimers, and trimers in various geometrically different conformations were calculated. The calculated spectral changes indicate that intermolecular hydrogen bonding plays an important role in the bathochromic shift. The stabilities of the aggregated structures were established using *ab initio* calculations. The intermolecular hydrogen bond was also found to be important for the formation of planar crystal structures.



3,6-Bis(3-chlorophenyl)-1,2,4,5-tetrahydropyrrolo[3,4-*c*]pyrrole-1,4-dione (**62b**) and 3,6-bis(4-chlorophenyl)-1,2,4,5-tetrahydropyrrolo[3,4-*c*]pyrrole-1,4-dione (**62c**), are new pigments which are orange-red and red, respectively. The compounds (**62b**) and (**62c**) were synthesized from 3- or 4-chlorobenzonitrile <83EUP94911>. The latter (**62c**) has been available commercially since 1986. X-ray structure data <93AX(B)1056> indicated that differences in π - π -interaction in (**62b**) and (**62c**) result in the color of compound (**62b**) (orange red) in the solid state being different from that of its isomer (**62c**) (red), although the optical absorption spectra of these compounds are very similar in solution.

X-ray studies also have been carried out on saturated and partially saturated ring systems. For example, structures of three hexahydrofuro[3,4-*c*]furan-type lignans ((**63**), (**64**), (**65**)) have been determined <92AX(C)2240>. Compound (**63**) was obtained as colorless needles by acetylation of

(+)-1-hydroxypinoresinol from *Calamintha ashei* (Weatherby) Shinner (Lamiaceae). The two five-membered rings of yangambin (**64**) have *cis*-fused envelope conformations with the oxygen atoms at the flap positions. Yangambin (**64**) was isolated from *Rudbeckia maxima* Nutt., *R. nitida* Perdue, and *R. scabrifolia* Brown (Asteraceae). (–)-Asarinin (episesamin) (**65**) was isolated from *Pilocarpus gaudotianus*.



7.01.3.2 Proton NMR Spectroscopy

Proton NMR spectroscopy has found wide applications in the investigation and structure determination of A,B-diheteropentalenes. The results of earlier studies have been reviewed (84CHEC-I(4)1037). This chapter introduces the chemical shifts and coupling constants of the previously known parent compounds (Table 3).

Since the mid 1980s the synthesis and ^1H NMR spectral parameters for 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole (**10**) (84TL5669), 5*H*-thieno[2,3-*c*]pyrrole (**17**) (86CC310), and thieno[3,4-*b*]furan (**21**) (86TL3045), as well as for substituted furo[3,2-*b*]pyrroles (81CCC2564, 93CCC2139, 94CCC473, 94MI 701-01), have been reported.

The similarity of the ^1H NMR spectra of 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole (**10**) and of pyrrole suggests that both ring systems possess similar ring currents and aromaticity. The observed upfield shift (0.17 ppm) of the β -proton seems to reflect the influence of the fused pyrrole ring on the electron density of this system.

7.01.3.3 Carbon-13 NMR Spectroscopy

The ^{13}C NMR spectra of some parent A,B-diheteropentalenes and $J(\text{C},\text{H})$ coupling constants are summarized in Tables 4 and 5. The sensitivity of C-3 to substituent effects is the same in both thieno[2,3-*b*]thiophene (**33**) and thieno[3,2-*b*]thiophene (**12**) (76ACS(B)417). The substituted carbon atoms also show comparable sensitivity. Differences were observed for the substituent transmittance effects to similar positions in these two systems. For example the resonance effect is much more efficiently transmitted over two sulfur atoms in derivatives of compound (**12**). On the other hand, for the 6a position the system (**33**) shows a great similarity with 2-substituted thiophenes.

Carbon-13 NMR parameters for 4*H*-thieno[3,2-*b*]pyrrole (**9**) and some other furo-, thieno-, and selenolo[3,2-*b*]pyrroles have been reported (76ACS(B)391). Carbon-13 chemical shifts and $J(\text{C},\text{H})$ coupling constants of the 2-, 4-, and 6-substituted furo[3,2-*b*]pyrroles have been determined (Tables 6 and 7) (90MRC830). The largest effect of a substituent attached at C-2 was observed on the C-2, C-3, and C-6a carbons. Additional ^{13}C NMR data on furo[3,2-*b*]pyrrole derivatives have been reported (93CCC2139, 94MI 701-01).

A comparison of the spectra of thieno[2,3-*b*]thiophene (**33**) (76ACS(B)417) and selenolo[2,3-*b*]selenophene (**35**) (76CS159) reveals that the resonances of all carbons except for C-6a occur at lower field for compound (**35**).

The carbon signals of selenolo[2,3-*c*]thiophene (**19**) were assigned from the uncoupled spectrum and the values of chemical shifts and coupling constants $J(\text{C},\text{H})$ were compared with C-4 and C-6 substituted derivatives (81IZV1285).

Table 3 Proton NMR chemical shifts (δ , ppm) and coupling constants (J , Hz) of some parent A,B-diheteropentalenes.

Compound	Solvent	H-2	H-3	H-4	H-5	H-6	$J(2,3)$	$J(2,5)$	$J(3,6)$	$J(4,5)$	$J(4,6)$	$J(5,6)$	Ref.
(8)	CDCl ₃	7.44 dd	6.52 dd		6.78 dd	6.02 dd	2.1	1.2	0.9			2.9	78CJC1429
(9)	DMSO- <i>d</i> ₆	7.17 dd	7.02 dd		7.08 dd	6.37 dd	4.9	1.1	0.7			2.8	78CJC1429
(10)	CDCl ₃	6.73 dd	6.05 m		6.73 dd	6.05 m	^a	^a		^a	^a		84TL5669
(11)	DMSO- <i>d</i> ₆	7.66 dd	7.26 dd		6.99 dd	6.38 dd	5.5	1.2	0.7			2.8	78CJC1429
(12)	Acetone	7.48	7.30		7.48	7.30	5.25	1.55	0.75			5.25	70ACS105
(13)	CCl ₄	7.22	7.14		7.79	7.35	5.2	1.1	0.6			5.8	76AHC(19)123
	Acetone	7.53	7.41		8.12	7.57	5.21	1.49	0.72			5.75	70ACS1953
(17)	Acetone- <i>d</i> ₆	^b	^b	^b	^b	^b	^b	^b	^b	^b	^b	^b	86CC310
(19)	Acetone- <i>d</i> ₆	7.86	7.16	7.53		7.42	5.95		0.75		2.75		73JPR850
(21)	CDCl ₃	7.58 d	6.41 dd	6.92 d		6.74 dd	2.4		0.9		2.5		86TL3045
(25)	CCl ₄	7.17	6.74	7.05		7.15	5.5		0.7		2.5		67TL761
(26)	CDCl ₃	7.78 d	7.00 d	8.03 dd		7.84 dd	6.2		0.8		2.4		80T3317
(30)	DMSO- <i>d</i> ₆	6.94 s	6.94 s	6.30 d	7.04 d					2.8			75BSF2511
	Acetone + D ₂ O	6.88 d	6.97 d	6.35 d	7.08 d		5.0	0.8		2.9			75BSF2511
(31)	DMSO- <i>d</i> ₆	6.52 d	5.90 d	5.90 d	6.25 d		2.9			2.9			78CJC1429
(32)	DMSO- <i>d</i> ₆	7.41 dd	7.15 d	6.34 d	7.01 dd		5.5	0.9		2.9			78CJC1429
(33)	Acetone	7.42	7.23	7.23	7.42		5.23	1.20		5.23			70ACS105
(34)	Acetone- <i>d</i> ₆	7.48	7.30	7.48	8.00		5.22	1.12		5.6			70ACS1953
(35)	Acetone- <i>d</i> ₆	8.14	7.56	7.56	8.14			1.20					76CS(10)159

^a Coupling constants not reported. ^b Hard-coupled AB-spectrum centered at 7.11 ppm with a coupling of 5.4 Hz.

Table 4 Carbon-13 NMR chemical shifts (δ , ppm) of some parent A,B-diheteropentalenes.

Compound	Solvent	C-2	C-3	C-4	C-5	C-6	C-3a	C-6a	Ref.
(8)	DMSO- d_6	144.11	99.63		120.77	90.61	123.90	148.07	90MRC830
(9)	CDCl ₃	123.7	111.2		123.0	101.3	121.9 ^a	138.6 ^a	76ACS(B)391
(10)	Acetone- d_6	120.3	91.5		120.3	91.5	128.9	128.9	84TL5669
(12)	Acetone- d_6	127.9	119.9		127.9	119.9	139.9	139.9	76ACS(B)417
(14)	DMSO- d_6	131.65	125.28		131.65	125.28	140.32	140.32	74CS(5)236
(17) ^b	Acetone- d_6								86CC310
(19)	Acetone- d_6	133.0	120.8	114.9		115.2	150.7	136.4	81IZV1285
(26)	Acetone- d_6	131.4	120.7	119.8		117.9	152.2	136.9	80T3317
(33)	Acetone- d_6	129.1	120.4	120.4	129.1		147.1	137.6	76ACS(B)417
(35)	Acetone- d_6	133.84	124.21	124.21	133.84		150.35	136.15	76CS(10)159

^a The assignment may be reversed. ^b The data for (17): 106.97 (d), 107.15 (d), 116.76 (d), 124.14 (s), 125.93 (d), 133.17 (s).

Table 5 Coupling constants ($J(\text{C,H})$, Hz) of some parent A,B-diheteropentalenes.

Compound	C-2,H-2	C-2,H-3	C-3,H-3	C-3,H-2	C-4,H-4	C-5,H-5	C-5,H-6	C-6,H-6	C-6,H-5	Ref.
(8)	203.1	11.0	177.1	14.1		184.0	7.0	175.0	7.0	90MRC830
(9)	185.0	6.8	170.0	4.6		185.0	8.4	175.0	7.0	76ACS(B)391
(14)	189.0	6.8	170.5	5.8		^a	^a	^b	^b	74CS(5)236
(26)	186.8		172.1		188.0			192.0		80T3317
(35)	187.8	7.0	165.5	4.5	^b	^a	^a			76CS(10)159

^a $J(\text{C,H})$ values identical to C-2. ^b $J(\text{C,H})$ values identical to C-3.

Table 6 Carbon-13 NMR chemical shifts (δ , ppm) of substituted furo[3,2-*b*]pyrroles (8).

Compound	R ¹	R ²	R ³	C-2	C-3	C-3a	C-5	C-6	C-6a
(8)	H	H	H	144.11	99.63	123.90	120.77	90.61	148.07
(8a)	H	H	CO ₂ Et	148.69	98.92	128.88	124.14	96.82	147.95
(8b)	H	COMe	H	146.01	102.34	124.04	122.50	98.83	148.92
(8c)	H	Me	H	144.10	98.16	126.38	123.90	90.69	147.90
(8d)	H	CH ₂ Ph	H	144.04	98.66	125.78	123.52	91.33	148.20
(8e)	H	Et	CO ₂ Et	148.30	98.23	132.40	123.21	98.23	145.96
(8f)	H	Me	CO ₂ Et	148.28	97.93	133.33	123.95	97.93	145.49
(8g)	Me	H	CO ₂ Et	159.39	95.27	130.38	122.24	95.56	146.82
(8h)	Me	Et	CO ₂ Et	158.75	94.33	133.42	120.90	97.79	144.47
(8i)	CHO	Me	CO ₂ Et	156.40	107.18	132.50	130.21	97.67	149.38

Source: Dandárová *et al.* (90MRC830).

Substituents R¹, R², and R³ are attached to C-2, N-4, and C-5 respectively.

Table 7 Coupling constants ($J(\text{C,H})$, Hz) of substituted furo[3,2-*b*]pyrroles^a (8).

Compound	C-2, H-2	C-2, H-3	C-3, H-3	C-3, H-2	C-5, H-5	C-5, H-6	C-6, H-6	C-6, H-5
(8)	203.1	11.0	177.1	14.1	184.0	7.0	175.0	7.0
(8a)	202.2	10.3	178.8	14.3			180.2	
(8b)	206.0	11.0	181.1	14.0	184.0	^b	180.0	^b
(8c)	202.2	10.5	177.4	13.7	184.0	7.6	175.9	8.5
(8d)	203.0	11.0	176.8	13.8	181.2	8.0	176.1	8.3
(8e)	202.2	10.3	178.8	14.6			180.2	
(8f)	202.0	10.0	177.5	14.0			180.0	
(8g)		^c	178.7				178.7	
(8h)		^c	177.3				178.8	
(8i)		10.5	179.0			–	183.0	

Source: Darndárová *et al.* (90MRC830).

^a $J(\text{C-5, H-4}) = 4.1$ for (8) and (8d); $J(\text{C-6, H-4}) = 4.0$ for (8), 3.0 for (8a) and 4.4 for (8g); $J(\text{C-2, H-ald}) = 32$ and $J(\text{C-ald, H-ald}) = 179.0$ for (8i); $J(\text{C-5, CH}_3\text{-N}) = 3.6$ for (8c). ^b Unresolved. ^c Unresolved; C-2 is coupled with CH₃ protons.

The ^{13}C NMR spectrum of compound (10) <84TL5669> shows for C-3 and C-6 a deviation of 16.7 ppm from the chemical shift of pyrrole at the β -position: this suggests an electron density increase due to the electron-donating character of the adjacent nitrogen atom. An analogous upfield shift of C-3 and C-6 was observed in the furo[3,2-*b*]pyrrole (8).

7.01.3.4 Selenium-77 NMR Spectroscopy

Selenium-77 NMR spectra have been reported for the known classical selenolothiophenes and selenoloselenophenes (Table 8). The values of $J(\text{Se},\text{H})$ were obtained from undecoupled ^{77}Se NMR spectra or from selenium satellites in the ^1H NMR spectra. The large shift difference between Se-1 and Se-5 in compound (26) <80T3317> gives strong evidence for the more positive nature of the Se-5 than the Se-1 atom. It was found that none of the selenium signals falls into the ^{77}Se shift region of monosubstituted selenophenes <75CS(8)8>, but resonances of both (14) and (35) are found there. The resonance of Se-5 is only 6.6 ppm from that of the selenium atom in diphenyl selenoxide <75CS(8)15>, which has a partial positive charge, and the Se-1 resonance falls in the region for diarylselenides.

Table 8 Selenium-77 chemical shifts (δ , ppm) and coupling constants ($J(\text{Se},\text{H})$, Hz) of parent classical selenolothiophenes and selenoloselenophenes.

Compound	Chemical shift, δ^a	$J(\text{Se}, \text{H})$	Ref.
(13) ^b		47.6 (Se-4, H-5), 7.8 (Se-4, H-6)	70ACS1953
(14)	– 56.03 (Se-1, Se-4) ^c	47.0 (Se-1, H-2), 7.2 (Se-1, H-3), 1.8 (Se-1, H-5; Se-1, H-6)	74CS(5)236
(19)	– 173.8 ^c	^d	81IZV1285
(26)	– 176.4 (Se-1) ^c , 126.4 (Se-5) ^c	47.1 (Se-1, H-2), 7.0 (Se-1, H-3) 48.1 (Se-5, H-4; Se-5, H-3)	80T3317
(34) ^b		49.2 (Se-6, H-5), 9.4 (Se-6, H-4), ^e	70ACS1953
	– 60.0 ^{c,f}		76OMR(8)354
(35)	– 26.13 (Se-1, Se-6) ^c	48.8 (Se-1, H-2), 9.6 (Se-1, H-3), 0.8 (Se-1, H-4), 1.8 (Se-1, H-5)	76CS(10)159

^a Selenophene as external standard. ^b $J(\text{Se},\text{H})$ obtained from satellites due to the couplings of the ring protons to the ^{77}Se . ^c Upfield from selenophene. ^d Not reported. ^e Downfield from selenophene. ^f The δ value converted to selenophene as a standard.
² $J = 49.1$, ³ $J = 9.2$, ⁴ $J = 1.3$.

The signal 173.8 ppm upfield from that of selenophene in selenolo[2,3-*c*]thiophene (19) is observed also in this region <81IZV1285>. To determine the charge distribution in compound (19), calculations of the electron densities in thiophene, selenophene, thieno[3,4-*b*]thiophene (25), selenolo[3,4-*b*]selenophene (26) and selenolo[2,3-*c*]thiophene (19) were carried out <81IZV1285>. These calculations showed that in the selenolo[2,3-*c*]thiophene (19) and its derivatives, the sulfur atom is more positively charged than the selenium atom. The charge density is not determined by the character of the heteroatom but by its position in the fused heterocyclic system.

7.01.3.5 Mass Spectrometry

Mass spectra of the classical and nonclassical thienothiophenes as well as thieno[3,4-*c*]pyrrole derivatives were discussed in the first edition <84CHEC-I(4)1037>. Other A,B-diheteropentalenes were not mentioned.

The mass spectra of selenolothiophenes (13), (19), and (34) are similar, with the exception of small variations in ion intensities <73JPR850>. The spectra are characterized by an intense molecular ion (m/z 188) and identical fragmentation order, which emphasizes selenium atom elimination (m/z 108). The isomeric selenolopyrroles (11) and (32) fragment in a similar manner <78CJC1429>. The spectra contain an m/z 91 fragment ($\text{C}_6\text{H}_5\text{N}$), formed from the molecular ion (m/z 171) by loss of a selenium atom. The other significant ion occurred at m/z 63, formed by loss of m/z 28 (CH_2N^+) from m/z 91. From these examples it is evident that the selenophene ring fragments first.

In the case of the 4*H*-furo[3,2-*b*]pyrrole (8) and 4*H*-thieno[3,2-*b*]pyrrole (9) it is very difficult to specify which ring fragments first <78CJC1429>. The mass spectra of the isomeric thienopyrroles (9) and (30) are similar: their molecular ion (m/z 123) is very weak in comparison with m/z 96. The m/z 96 fragment can be formed either by loss (m/z 26) from m/z 122, which is characteristic of the thiophene ring fragmentation <B-71MI 701-01>, or by fragmentation of the pyrrole ring by loss (of

HCN or $C_2H_3\cdot$) from m/z 123. 4*H*-Furo[3,2-*b*]pyrrole (**8**) presents the same problem, although most probable is the fragmentation of the primary furan ring. The spectra of (**8**) contain a fragment at m/z 79 formed from the molecular ion (m/z 107) by loss of m/z 28 (CO) followed by specific fragmentation of the pyrrole ring. The mass spectra of the 4*H*-furo[3,2-*b*]pyrrole derivatives support these observations <81CCC2564>. The spectra of 1*H*,6*H*-pyrrolo[2,3-*b*]pyrrole (**31**) are characterized by fragments corresponding to C_2H_2 , HCN, $C_2H_3\cdot$ and $CH_2N\cdot$, i.e., the simultaneous fragmentation of both pyrrole rings occurs <78CJC1429>. In the mass spectrum of the selenolo[2,3-*b*]selenophene (**35**), the peaks centered at m/z 236 (M^+ and base peak) showed the same isotope pattern as a spectrum simulated for two selenium atoms <76CSI59>.

7.01.3.6 UV Spectroscopy

The UV spectral data of known parent A,B-diheteropentalenes are summarized in Table 9. The analogous thienothiophenes and selenolothiophenes show more absorption maxima in their UV spectra than the other systems. The known progressive shift of absorption to longer wavelengths which is observed in the simple five-membered heterocycles in the sequence furan < pyrrole < thiophene < selenophene is missing since the rings are fused.

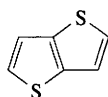
Table 9 Ultraviolet spectra of some parent A,B-diheteropentalenes.

Compound	λ_{max} (log ϵ) ^a	Ref.
(8)	248 (4.20)	78CJC1429
(9)	217 (3.85), 258 (4.10)	78CJC1429
(10)	245 (4.15) ^b	84TL5669
(11)	219 (3.81), 266 (4.09)	78CJC1429
(12)	259 (4.09), 268 (4.08), 278 (4.04), 305 (1.00)	76AHC(19)123
(13)	264 (3.58), 276 (3.61), 287 (3.65)	73JPR850
(17)	230 (4.13), 285 (3.87)	86CC310
(19)	236 (4.26), 241 (4.25), 266 (3.52), 275 (3.46), 303 (3.64)	73JPR850
(21)	216 (3.65), 221sh (3.62), 259 (3.74)	86TL3045
(25)	235 (4.23), 257 (3.53), 266 (3.56), 275.5 (3.56), 296.5 (3.73)	67TL761
(30)	212 (4.26), 250 (3.56)	78CJC1429
(31)	243 (3.94)	78CJC1429
(32)	214 (4.30), 251 (3.61)	78CJC1429
(33)	225 (4.37), 269 (3.28), 278 (2.99), 298 (1.48)	76AHC(19)123
(34)	229 (4.45), 260 (3.63), 268 (3.61), 278 (3.56) 288 (3.40)	73JPR850

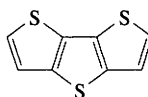
^a Solvent EtOH unless otherwise stated. ^b Solvent cyclohexane.

7.01.3.7 Photoelectron Spectrometry

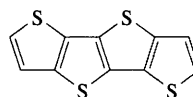
There has been a great deal of interest since the mid 1970s in photoelectron spectrometry and the ionization potentials of various A,B-diheteropentalenes have been summarized <84CHEC-I(4)1037>. The photoelectron spectrum of thieno[3,2-*b*]thiophene (**12**) was measured in the solid state as well as in the gas phase and has been investigated in comparison with linearly polycondensed polythiophenes, (**66**) and (**67**) <92JCS(P2)765>.



(**12**)



(**66**)



(**67**)

7.01.3.8 Dipole Moments

Dipole moment studies of some A,B-diheteropentalenes have been discussed <84CHEC-I(4)1037>. The dipole moments of symmetrical thieno[3,2-*b*]thiophene (**12**) and its selenium analogue (**14**) are 0.00 D (1 D = 3.336×10^{-30} C m), whereas for selenolo[3,2-*b*]thiophene (**13**) the dipole moment is

0.30 D. It was found that the [2,3-*b*]-annelated parent thienothiophenes, selenoloselenophenes, and selenolothiophenes exhibit higher dipole moment values than the [3,4-*b*]- or [2,3-*c*]-annelated systems (<84CHEC-I(4)1037>). Other parent diheteropentalene dipole moments do not appear to have been measured.

7.01.4 THERMODYNAMIC ASPECTS

7.01.4.1 Intramolecular Forces

7.01.4.1.1 Melting and boiling points

The melting points and boiling points of the known parent A,B-diheteropentalenes are presented in Table 10. The nitrogen-containing systems are solids possessing higher melting points than their thieno or selenolo analogues.

Table 10 Melting and boiling points^a of some parent A,B-diheteropentalenes.

Compound	<i>M.p.</i> , <i>b.p.</i> (°C)	Ref.
4 <i>H</i> -Furo[3,2- <i>b</i>]pyrrole (8)	39	75CR(C)(281)793
4 <i>H</i> -Thieno[3,2- <i>b</i>]pyrrole (9)	25–28 31–35 29	57JA2556 57JOC1500 78CJC1429
1 <i>H</i> ,4 <i>H</i> -Pyrrolo[3,2- <i>b</i>]pyrrole (10)	123–124	84TL5669
4 <i>H</i> -Selenolo[3,2- <i>b</i>]pyrrole (11)	38	75CR(C)793
Thieno[3,2- <i>b</i>]thiophene (12)	55.5–60	53JCS1837
Selenolo[3,2- <i>b</i>]thiophene (13)	85–86	68IZV1419
Selenolo[3,2- <i>b</i>]selenophene (14)	127.5–128	76CS(10)159
5 <i>H</i> -Thieno[2,3- <i>c</i>]pyrrole (17)	68.5–69.5	86CC310
Selenolo[2,3- <i>c</i>]thiophene (19)	25	73JPR(315)850
Thieno[3,4- <i>b</i>]furan (21)	Colorless oil	86TL3045
Thieno[3,4- <i>b</i>]thiophene (25)	7–7.5 70 (0.5 ^b)	67TL761 90SC2275
Selenolo[3,4- <i>b</i>]selenophene (26)	46–47	80T3317
6 <i>H</i> -Thieno[2,3- <i>b</i>]pyrrole (30)	42	75BSF2511
1 <i>H</i> ,6 <i>H</i> -Pyrrolo[2,3- <i>b</i>]pyrrole (31)	153	78CJC1429
6 <i>H</i> -Selenolo[2,3- <i>b</i>]pyrrole (32)	54	78CJC1429
Thieno[2,3- <i>b</i>]thiophene (33)	95 (10 ^b)	67ACS812
Selenolo[2,3- <i>b</i>]thiophene (34)	18–20.5	69ACS1823
Selenolo[2,3- <i>b</i>]selenophene (35)	56–57	76CS(10)159

^a Melting points are given in bold. ^b Torr.

7.01.4.1.2 Solubility

A,B-Diheteropentalenes have only limited solubility in water. The hydrogen donor properties of the NH site of pyrrole and the hydrogen acceptor property of the oxygen atom of the furan ring can increase the solubility of the compounds containing these heteroatoms relative to the systems with only sulfur or selenium atoms in their structure. Alkylation at the nitrogen of furo[3,2-*b*]pyrrole derivatives increases the solubility in ethanol and other organic solvents.

7.01.4.1.3 Aromaticity

The parent A,B-diheteropentalenes possess differing degrees of aromaticity based upon chemical behavior such as their ability to undergo substitution reactions with electrophilic reagents. They belong to the electron-rich heterocycles, but a quantification of their relative aromaticities is less easily resolved. The wide range of potential criteria available for this purpose has been surveyed (<84CHEC-I(4)1037>).

Most of the available criteria point to an order of decreasing aromaticity of 1,4 > 1,6 > 1,5 ring system which is influenced by the heteroatom in the order S > Se ≥ N > O. There is little evidence

for interaction between two parts of the ring system (see Section 7.01.5). Peri interactions between free lone pairs destabilize the 1,6-system. Substituents attached to the diheteropentalene structures can strongly influence the aromaticity.

The parent nonclassical heteropentalenes represented by structure (4) are unknown, but there is considerable information on characteristic reactions of their derivatives, mainly as ylides in the case of those derivatives which either have been generated *in situ* or have been isolated as stable solid compounds (see Section 7.01.5).

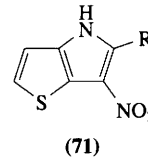
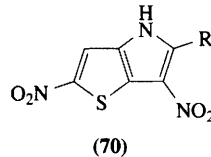
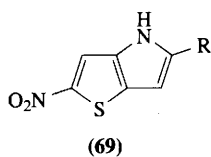
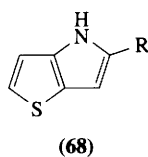
7.01.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.01.5.1 1,4-Diheteropentalene Systems (1)

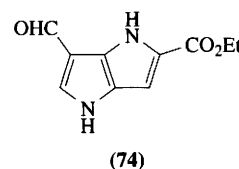
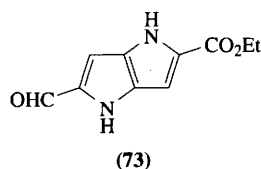
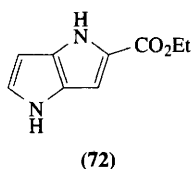
7.01.5.1.1 Electrophilic attack at carbon

The reactions and reactivities of thieno[3,2-*b*]thiophene (12) have been described in detail <84CHEC-I(4)1037>.

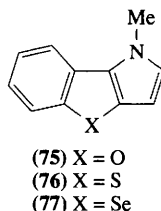
The nitration of ethyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (68; R = CO₂Et) has been carried out <84JHC215> using cupric nitrate in acetic anhydride with low yields obtained after purification by column chromatography: (69; R = CO₂Et) 34%, (70; R = CO₂Et) 42%, (71; R = CO₂Et) 3%.



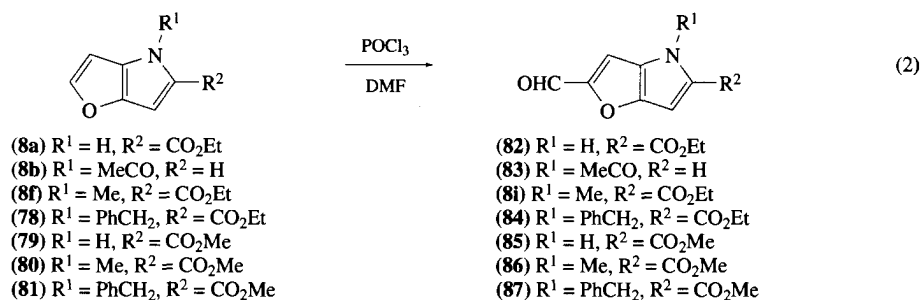
Vilsmeier reaction of ethyl 1-methyl-4*H*-pyrrolo[3,2-*b*]pyrrole-2-carboxylate (72) gave a mixture of C-5 (73) and C-6 (74) formylated products <89TL1655>.



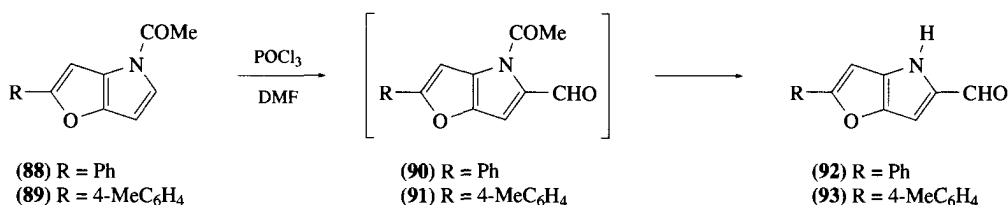
The 1-methylbenzo[*b*]furo-, benzo[*b*]thieno-, and benzo[*b*]selenolo[3,2-*b*]pyrroles (75), (76), and (77) were prepared <83JHC49> and the influence of annelation and of the heteroatom upon reactivity was tested toward acetylation and lithiation <83JHC61>. The 1-methylbenzo[*b*]furo[3,2-*b*]pyrrole (75) was acetylated at C-2.



The formylation, nitration, Mannich reaction, and diazo coupling of variously substituted furo[3,2-*b*]pyrroles and their benzo[*b*]derivatives have been studied <86CCC106, 88MI 701-01, 90CCC597, 93CCC2139>. The compounds (8a), (8b), (8f), and (78)–(81) were formylated under Vilsmeier reaction conditions (Equation (2)). When C-2 is unsubstituted, formylation takes place at this position (e.g., (8i) and (82)–(87)) at ambient or moderately elevated temperature <86CCC106, 88MI 701-01, 94MI 701-01>.

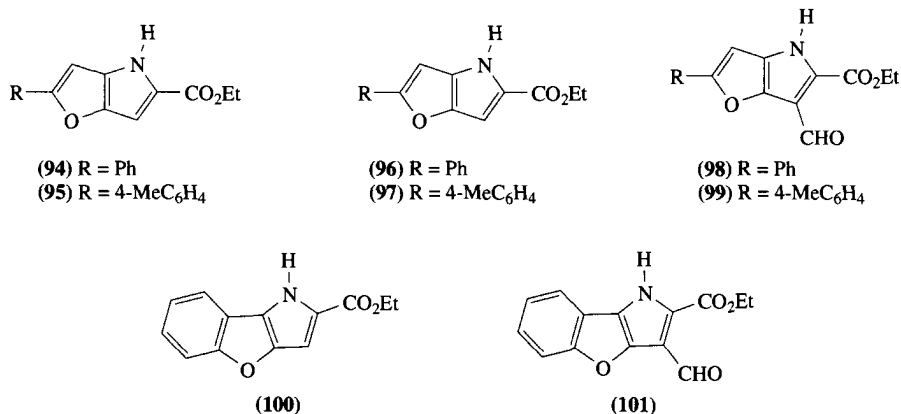


4-Acetyl-2-arylfuro[3,2-*b*]pyrroles (**88**) and (**89**) <86CCC106> yield 5-formylated products (**90**) and (**91**) which undergo spontaneous acetyl group cleavage. Heating in polar or nonpolar solvents resulted in the cleavage of the acetyl group furnishing 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carbaldehydes (**92**) and (**93**) (Scheme 1).



Scheme 1

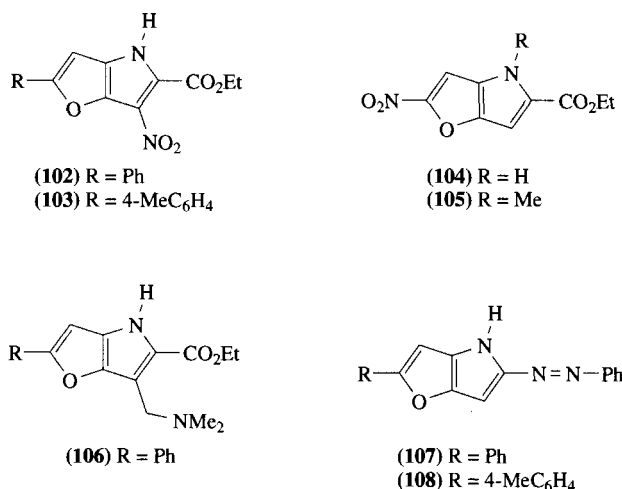
In compounds (**94**) and (**95**), where C-2 and C-5 are substituted, formylation afforded the *N*-formylated products (**96**) and (**97**). Prolonged reaction times led to the C-6 formylated products (**98**) and (**99**). In the case of ethyl 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (**100**) <82CCC3288> the C-3 formylated product (**101**) was formed <90CCC597>.



Nitration of the furo[3,2-*b*]pyrrole system, using a mixture of fuming nitric acid and acetic anhydride, was successful when C-2 and C-5 were occupied by at least one electron-withdrawing group. Nitration of ethyl 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylates (**94**) and (**95**) occurred at C-6, forming compounds (**102**) and (**103**). In the case of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (**82**) and its *N*-methyl derivative (**8i**; Equation (2)) this reaction was accompanied by *ipso* substitution of the formyl group by a nitro group, giving compounds (**104**) and (**105**), which it was not possible to obtain by direct nitration.

The Mannich reaction occurred at C-6 of ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (**94**) giving the amine (**106**). 2-Aryl-4*H*-furo[3,2-*b*]pyrroles <83CCC772> easily undergo reaction with benzenediazonium chloride at C-5 forming the azo compounds (**107**) and (**108**).

The results described above demonstrate that the preferred positions for the electrophilic attack of furo[3,2-*b*]pyrroles are C-2 and C-5, i.e., α -positions of the furan and pyrrole rings, followed by N-4 and finally C-6 (β -position of pyrrole ring). These observations were supported by MNDO calculations <B-88MI 701-02>. It was calculated that the protonation of furo[3,2-*b*]pyrrole occurs



regioselectively at the C-2 and C-5 atoms to form σ -complexes which are calculated to be 11–41 kJ mol⁻¹ more stable than cations resulting from protonation at C-3 and C-6. This is in good agreement with the experimental results <90CCC597>.

7.01.5.1.2 Electrophilic attack at nitrogen

Phase transfer catalysis was found <90CCC597> to be successful for *N*-substitution of the furo[3,2-*b*]pyrrole system. The reaction of furo[3,2-*b*]pyrroles with lithium hydride in DMF furnished *N*-lithium derivatives, which gave *N*-acetyl derivatives with acetyl chloride. The same compounds can be obtained by boiling in acetic anhydride. The treatment of furo[3,2-*b*]pyrrole derivatives with acrylonitrile in pyridine in the presence of benzyltriethylammonium hydroxide gave 4-(2-cyanoethyl)furo[3,2-*b*]pyrrole derivatives. Phase transfer catalysis has been employed for the preparation of variously substituted 4-phenylsulfonylfuro[3,2-*b*]pyrroles and 1-phenylsulfonylbenzo[*b*]furo[3,2-*b*]pyrroles <94CCC499>.

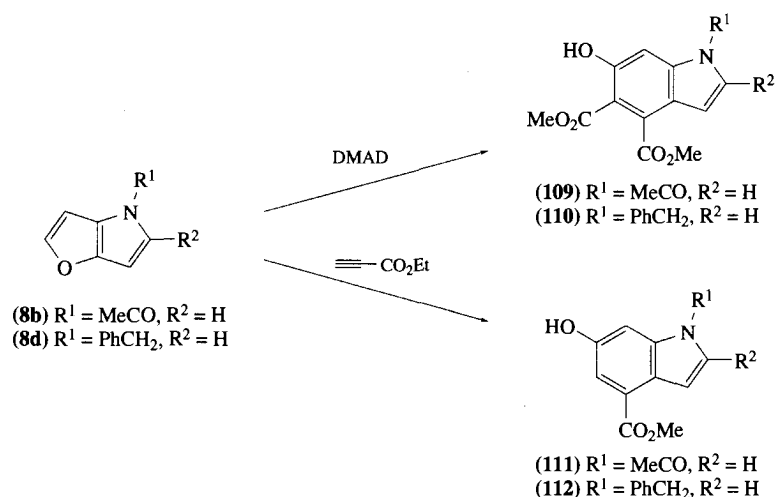
7.01.5.1.3 Addition and cycloaddition reactions

The 1,3-dipolar cycloadditions of ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (**8a**) or its 4-methyl derivative (**8f**) (Equation (2)) with *C*-benzoyl-*N*-phenylnitrone and *N,N*-diphenylnitrone proceeded regioselectively at positions 2 and 3 of the furan ring. During these reactions, exclusively *endo* cycloadducts were formed, because their transition states are stabilized by secondary orbital interactions <81CCC2421>.

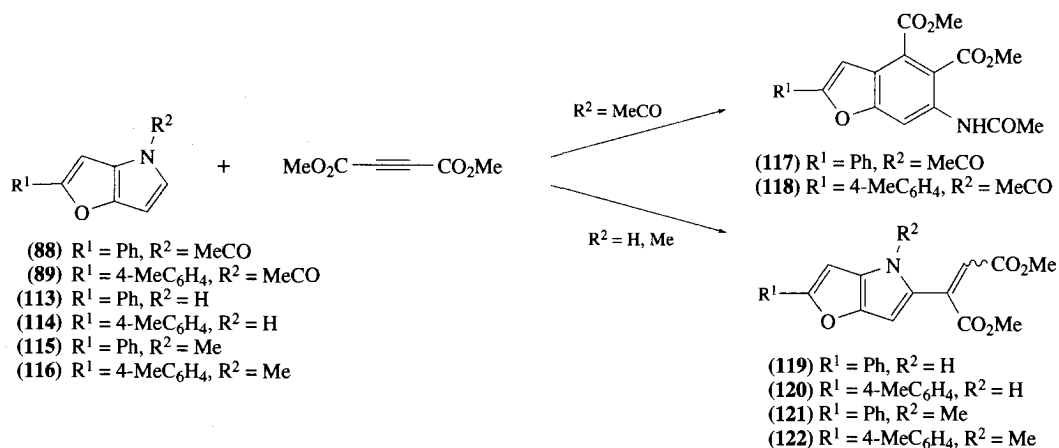
During the study of reactions of furo[3,2-*b*]pyrroles and their benzo derivatives with dienophiles it was found <90CCC597> that the reaction course is influenced by the ring substituents. The reactions of the C-2 unsubstituted furo[3,2-*b*]pyrroles (**8b**) and (**8d**) with DMAD proceed via [4 + 2] cycloaddition on the furan ring giving an adduct which is transformed into the substituted indoles (**109**) and (**110**) (Scheme 2). Regioselectivity of this reaction was observed using ethyl propynoate as dienophile. In this case only products (**111**) and (**112**) were isolated <88CCC1770, 92CCC1487>.

If C-2 is occupied and C-5 and C-6 are free, addition or cycloaddition take place on the pyrrole ring (Scheme 3) <86CCC1455>. The 4-acetyl-2-arylfuro[3,2-*b*]pyrroles (**88**) and (**89**) react with DMAD at the α and α' -positions of the pyrrole ring giving [4 + 2] cycloadducts, which by subsequent 1,5-sigmatropic rearrangement give the substituted benzo[*b*]furans (**117**) and (**118**). 2-Aryl-4*H*-furo[3,2-*b*]pyrroles (**113**) and (**114**) and their 4-methyl derivatives (**115**) and (**116**) <83CCC772> afford only the Michael addition products (**119**)–(**122**). It can be assumed that mesomeric conjugation of the acetyl group with the π -electron system of the skeleton leads to partial localization of the lone electron pair at nitrogen atom, thus enhancing the diene character of its pyrrole part.

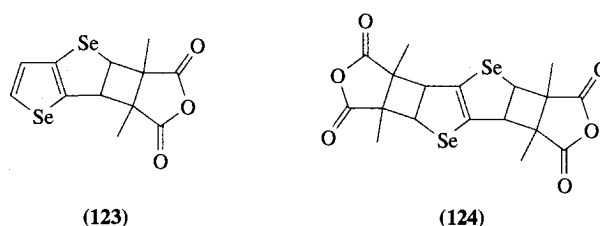
Irradiation of a benzene solution of 2,3-dimethylmaleic anhydride and the selenolo[3,2-*b*]selenophene (**14**) in the presence of benzophenone as sensitizer yielded the [2 + 2] adducts (**123**) and (**124**) <83JHC1465>.



Scheme 2



Scheme 3



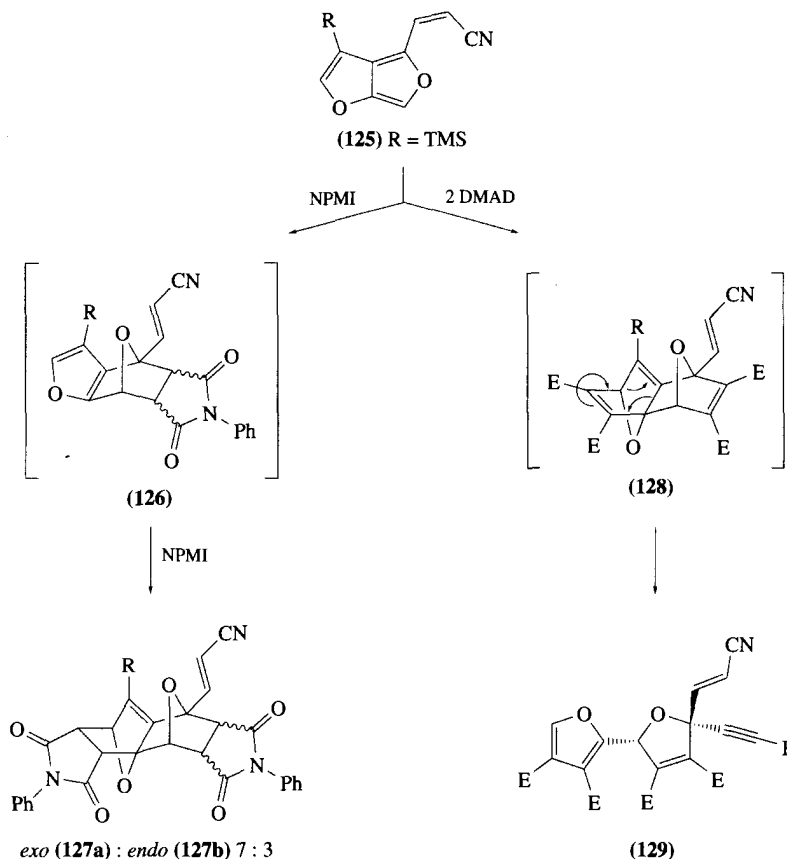
7.01.5.2 1,5-Diheteropentalene Systems (2)

The parent thieno[3,4-*b*]furan (**21**) is known <86TL3045> and some of its more stable derivatives have been prepared and their reactions studied <86JCS(P1)2223>.

7.01.5.2.1 Addition and cycloaddition reactions

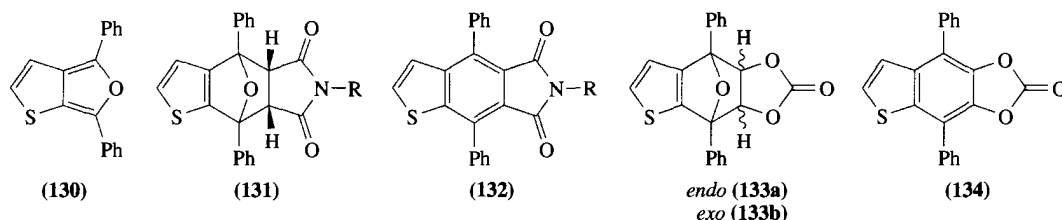
The substituted furo[3,4-*b*]furan (**125**) displays a high Diels–Alder reactivity and reacts with *N*-phenylmaleimide (NPMI) or DMAD at 20°C (Scheme 4) <88AG(E)568>. In both cases, even when using an excess of dienophile, only the 1 : 2 adducts (**127**) and (**128**) respectively (**127**) was formed via the corresponding 1 : 1 adduct (**126**). The *exo* and *endo* stereoisomers (**127a**) and (**127b**) are

obtained in a 7:3 ratio. The DMAD addition product (**128**) is not stable under the reaction conditions and undergoes a Diels–Alder reversion, providing the furyldihydrofuran derivative (**129**) (Scheme 4).



Scheme 4

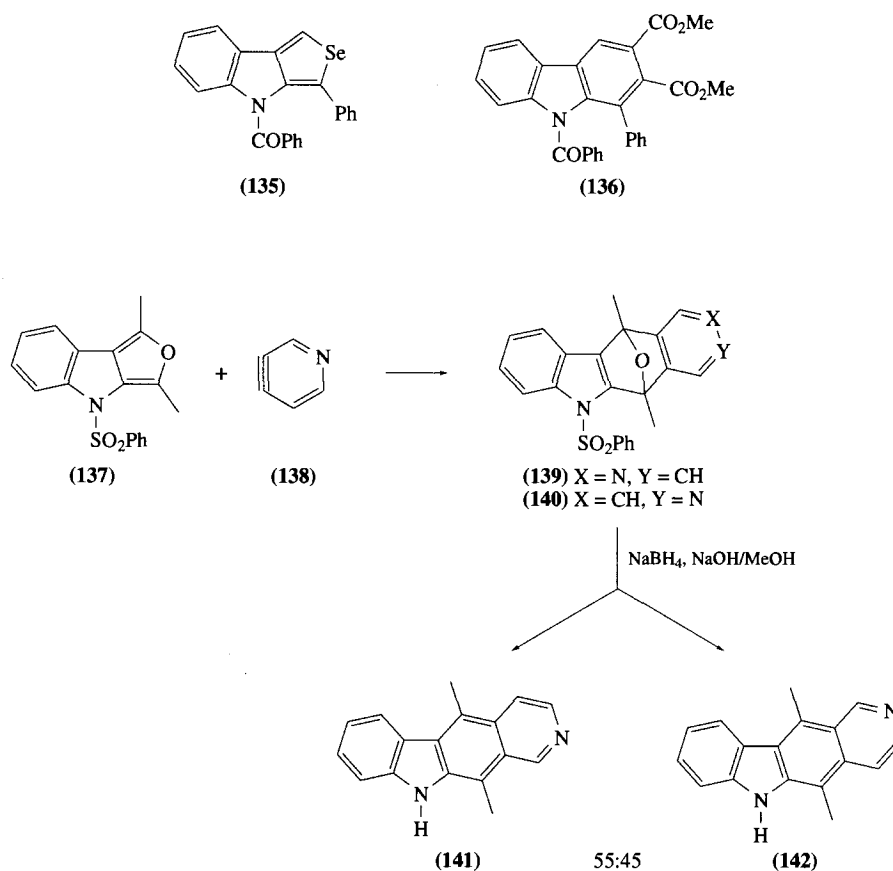
4,6-Diphenylthieno[2,3-*c*]furan (**130**) reacted with *N*-4-methylphenylmaleimide at room temperature to give in 73% yield *endo* adduct (**131**). In the presence of 4-methylbenzenesulfonic acid the substituted benzo[*b*]thiophene derivative (**132**) was obtained. Vinylene carbonate as dienophile led to an *endo/exo* mixture (**133a**) and (**133b**) in the ratio 6 : 1. The same reaction in the presence of sulfuric and acetic acids afforded compound (**134**) <89CB1119>.



The reaction of 3-phenyl-4-benzoylselenolo[3,4-*b*]indole (**135**) and DMAD afforded dimethyl 9-benzoyl-1-phenylcarbazole-2,3-dicarboxylate (**136**) <82JHC227>.

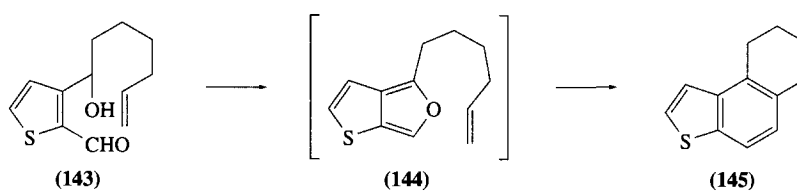
The potential utility of the 4*H*-furo[3,4-*b*]indole ring system in natural product synthesis was explored in an ellipticine (**142**) synthesis with an unexpected result <83TL5435, 84JOC4518, 91SL289>. The reaction of compound (**137**) with 3,4-pyridyne (**138**) led to a mixture of the two possible cycloadducts, (**139**) and (**140**), in approximately equal amounts (Scheme 5), which were transformed into a readily separable mixture of isoellipticine (**141**) and ellipticine (**142**).

3-(1-Hydroxy-6-hepten-1-yl)thiophene-2-carbaldehyde (**143**) under reflux with AcOH gave the



Scheme 5

intermediate 4-(5-hexen-1-yl)thieno[2,3-*c*]furan (144), which is transformed into the benzo[*b*]thiophene derivative (145) via an intramolecular Diels–Alder reaction (Scheme 6) <88TL1137>.



Scheme 6

The syntheses and Diels–Alder reactions of 5*H*-thieno[2,3-*c*]pyrrole (17) as well as benzo and *N*-alkyl derivatives of furo[2,3-*c*]pyrrole (22) have been described by Sha *et al.* <86CC310, 88CC1081, 90JOC2446, 95T193>.

7.01.5.3 1,6-Diheteropentalene Systems (3)

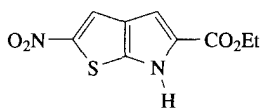
7.01.5.3.1 Electrophilic attack at carbon

The reactions and reactivities of thieno[2,3-*b*]thiophene (33) have been described in detail <84CHEC-I(4)1037>.

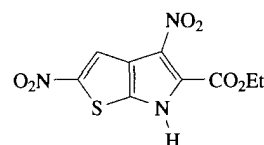
The nitration of ethyl 6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (146) has been carried out

CCOC(=O)c1c[nH]c2scccc12

(146)

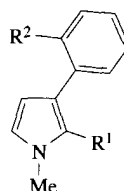


(147)



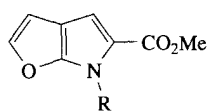
(148)

(149) $X = S$
(150) $X = Se$

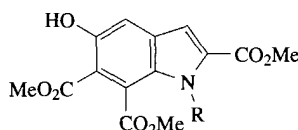


(151) $R^1 = \text{CO}_2\text{Me}$, $R^2 = \text{SeMe}$
(152) $R^1 = \text{SeMe}$, $R^2 = \text{CO}_2\text{Me}$

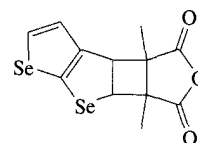
The reactions of the methyl furo[2,3-*b*]pyrrole-5-carboxylate (**153**) or its 6-methyl derivative (**154**) with DMAD proceed via [4 + 2] cycloaddition at the α, α' -positions of the furan ring, giving cycloadducts which by subsequent 1,5-sigmatropic rearrangement give trimethyl 5-hydroxyindole-2,6,7-tricarboxylate (**155**) or its 1-methyl derivative (**156**) (94UP 701-01).



(153) R = H
(154) R = Me



(155) R = H
(156) R = Me

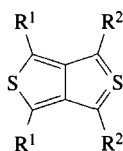


(157)

7.01.5.4 2,5-Diheteropentalene Systems (4)

Thieno[3,4-*c*]thiophene (**37**) $\langle 88\text{CC}959 \rangle$ and its 1,3-dimethyl- (**158**) $\langle 67\text{JA}3639, 73\text{JA}2558 \rangle$, 1,3-

bis(methoxycarbonyl)- (**159**) <73JA2558>, and 1,3-di-*t*-butyl- (**160**) as well as 1,3-di-*t*-butyl-4,6-dimethyl- (**161**) derivatives <90BCJ1026, 92BCJ2821> have been generated *in situ* and characterized by trapping with *N*-phenylmaleimide. On the other hand, 1,3,4,6-tetraphenyl- (**52**) <69JA3952, 73JA2561>, 1,3,4,6-tetrakis(alkylthio)- (**162**) <85JA5801, 88JA1793, 88JHC559, 89CC223, 91CC520>, and 1,3,4,6-tetra-2-thienylthieno[3,4-*c*]thiophenes (**163**) <91JOC78>, as well as 1,3-dibromo-4,6-dicyanothieno[3,4-*c*]thiophene (**164**), and compounds (**165**) and (**166**) <94JOC2223> were successfully synthesized as isolable compounds. These isolable thieno[3,4-*c*]thiophenes owe their stability to steric hindrance together with resonance and the electron-withdrawing effects of the substituents.

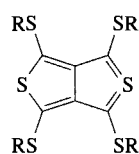


	R^1	R^2		R^1	R^2
(37)	H	H	(162)	SR	SR
(52)	Ph	Ph	(163)	2-thienyl	2-thienyl
(158)	Me	H	(164)	CN	yl
(159)	CO ₂ Me	H	(165)	CO ₂ Me	Br
(160)	Bu ^t	H	(166)	Br	Br
(161)	Bu ^t	Me			Br

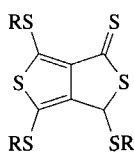
7.01.5.4.1 Cycloaddition reactions

The 1,3,4,6-tetrakis(alkylthio)thieno[3,4-*c*]thiophenes (**162**) are stable *in vacuo* for long periods. The remarkable stability of these derivatives can be rationalized in terms of the electron-accepting conjugation of the alkylthio substituents <88JHC559>. Steric influence on the stability of these compounds has also been noted: compound (**162a**) is stable in air at room temperature for several months, (**162b**) is stable for several weeks, and (**162c**) gradually decomposes.

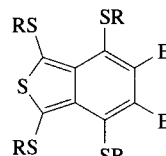
The reactions of the derivatives (**162a**)–(**162c**) with dienophiles such as *N*-phenylmaleimide (NPMI) and DMAD were carried out. The reaction of compound (**162a**) with NPMI in refluxing xylene gave the *exo* adduct (**169a**) (see Table 11) along with an 18% yield of compound (**167**). The yields of the other reactions are summarized in Table 11. The influence of the alkylthio groups is remarkable.



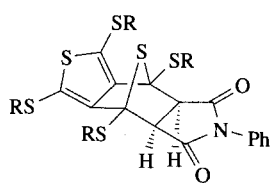
(**162a**) R = Bu^t
(**162b**) R = Prⁱ
(**162c**) R = Et



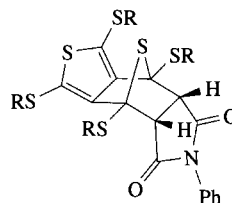
(**167**) R = Bu^t



(**168a**) R = Bu^t
(**168b**) R = Prⁱ
(**168c**) R = Et



(**169a**) R = Bu^t
(**169b**) R = Prⁱ
(**169c**) R = Et



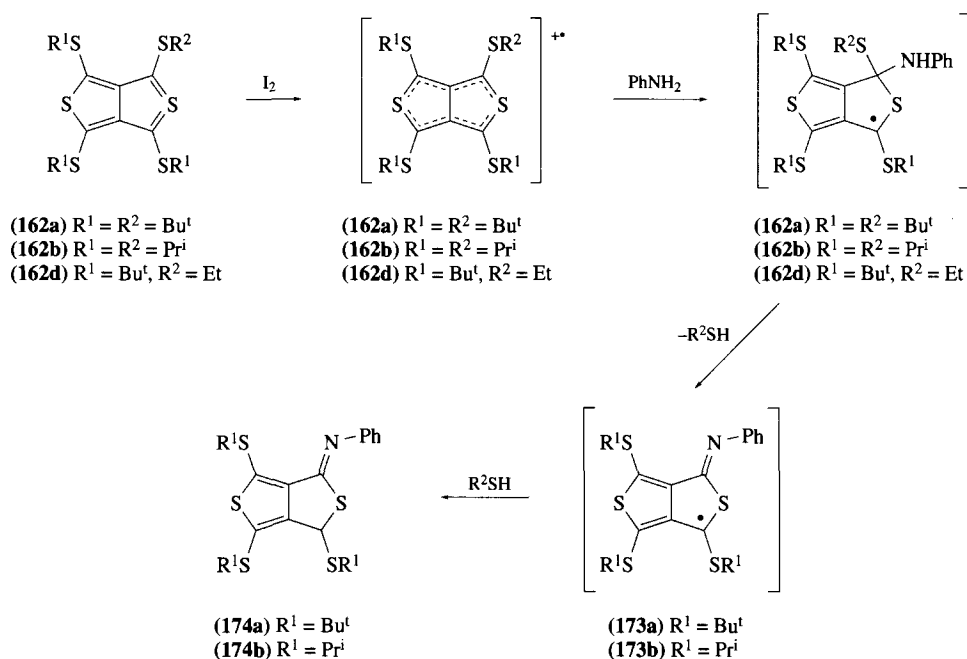
(**170a**) R = Bu^t
(**170b**) R = Prⁱ
(**170c**) R = Et

Table 11 Cycloaddition reactions of compounds (162a-c) with DMAD or NPMI <88JHC559>.

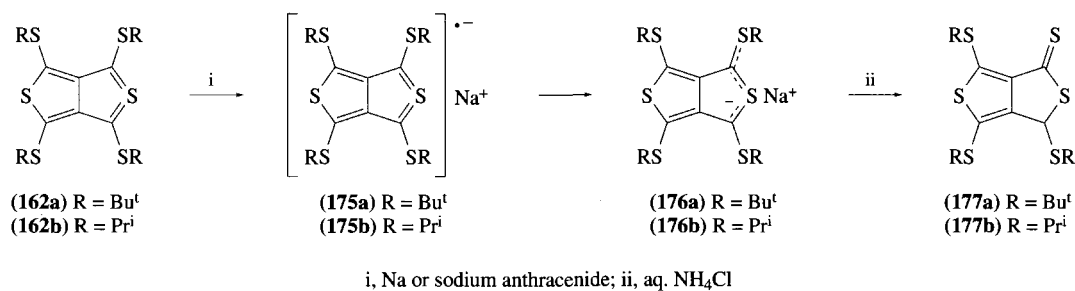
Compound	Dienophile	Temperature (°C)	Time (h)	Yield (%)		
				(168)	(169)	(170)
(162a)	DMAD	100	24	Trace		
(162b)	DMAD	100	10	49		
(162c)	DMAD	RT	27	53		
(162a)	NPMI	140	10		8	
(162b)	NPMI	80	3		77	12
(162c)	NPMI	RT	7		47	13

7.01.5.4.2 Radical reactions

1,3,4,6-Tetrakis(alkylthio)thieno[3,4-*c*]thiophenes (162a) and (162b), and 1,4,6-tris(*t*-butylthio)-3-ethylthiothieno[3,4-*c*]thiophene (162d) are oxidized by iodine in the presence of aniline in dry benzene to give 1,4,6-tris(alkylthio)-thieno[3,4-*c*]thiophen-3(1*H*)-imines (174a) and (174b) (Scheme 7). The reaction is thought <91JHC1643> to proceed via the formation of the cation radicals (171a), (171b), and (171d) by one-electron oxidation as shown in Scheme 7. The cation radicals react with aniline to give the radicals (172a), (172b), and (172d), which are converted into the radicals (173a) and (173b) by elimination of thiols. The abstraction of hydrogen from these thiols by (173a) and (173b) leads to the formation of the products (174a) and (174b). The cation radical (171d) reacted with aniline at the least hindered position and gave (173a) after EtSH elimination.

**Scheme 7**

The reaction of 1,3,4,6-tetrakis(*t*-butylthio)thieno[3,4-*c*]thiophene (162a) and 1,3,4,6-tetrakis(isopropylthio)thieno[3,4-*c*]thiophene (162b) with sodium or sodium anthracenide in HMPA proceeds through the formation of the radical anions (175a) and (175b) followed by the cleavage of an alkyl-sulfur bond to give the anions (176a) and (176b), which are converted to the products (177a) and (177b) by protonation (Scheme 8) <92JHC575>.

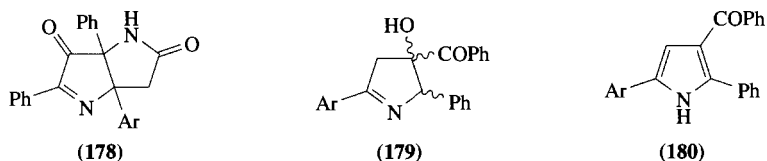


Scheme 8

7.01.6 REACTIVITY OF NONCONJUGATED RINGS

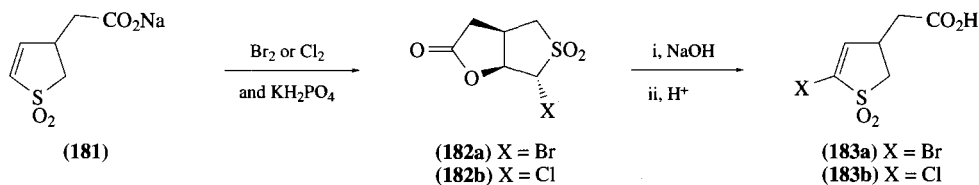
7.01.6.1 1,4-Diheteropentalene Systems

Under aqueous conditions dimethylamine, piperidine, and triethylamine catalyze the ring-opening reaction of 3a,5,6a-triaryl-3,3a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(6*aH*)-diones (**178**) <84S663> giving benzoylhydroxy-1-pyrrolines (**179**), which afford benzoylpyrroles (**180**) upon acid-catalyzed dehydration <92BCJ2611>.



7.01.6.2 1,5-Diheteropentalene Systems

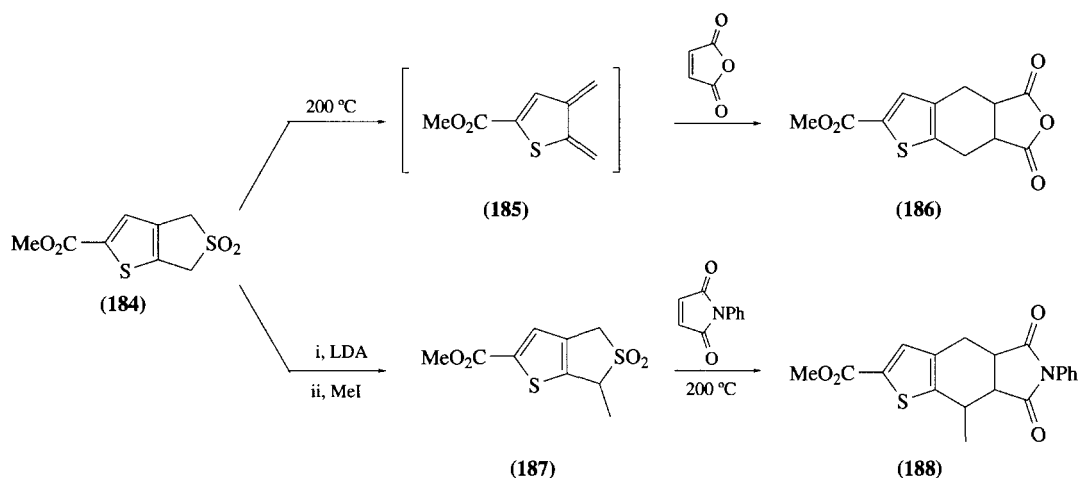
Sodium (1,1-dioxo-2,3-dihydro)-3-thienyl acetate (**181**) in the presence of KH₂PO₄ and bromine or chlorine is transformed into the 6-bromo- or 6-chloro-5,5-dioxohexahydrothieno[3,4-*b*]furan (**182a**) or (**182b**), from which, by treatment with an equimolar solution of sodium hydroxide and acidification, were isolated the acids (**183a**) and (**183b**) (Scheme 9) <87KGS1611>.



Scheme 9

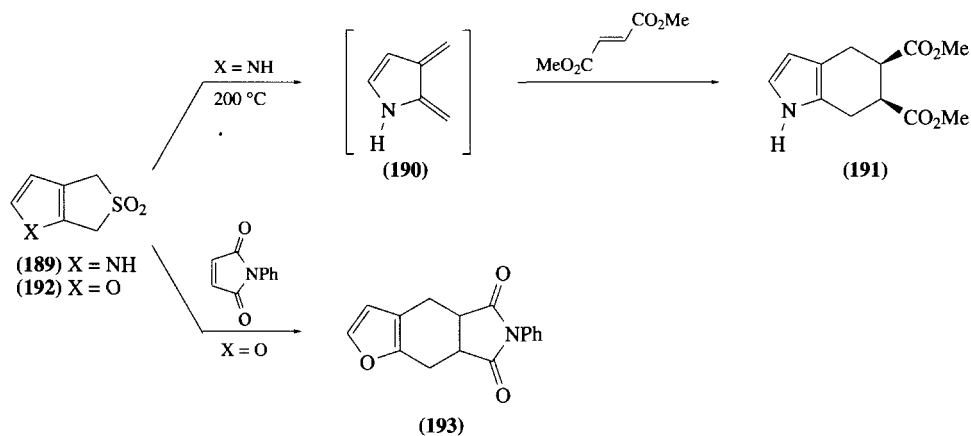
Several heterocycle-fused 3-sulfolene derivatives have long been known but only since 1990 have they been used for the generation of reactive heteroaromatic *o*-quinodimethanes <93MI 701-01>. Storr and co-workers <90TL1491, 92T8101> extruded SO₂ from methyl 5,5-dioxo-4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylate (**184**) at 200°C in the presence of the maleic anhydride and successfully obtained a high yield of the Diels–Alder adduct (**186**) via the intermediate (**185**). They also introduced a methyl group regioselectively by a deprotonation–substitution reaction sequence to obtain compound (**187**), which upon reaction with NPMI gave the product (**188**) (Scheme 10). The ease

of introduction of substituents is a unique advantage of using 3-sulfolenes as precursors for *o*-quinodimethanes.



Scheme 10

Heating 4,6-dihydrothieno[3,4-*b*]pyrrole-5,5-dioxide (189) <66JOC3363> with excess dimethyl fumarate produced, in moderate yield (38%), the Diels-Alder adduct (191), presumably via (190) (Scheme 11) <93MI 701-01>. The 4,6-dihydrothieno[3,4-*b*]furan-5,5-dioxide (192) <92H(34)663> with NPMI gave the adduct (193) (Scheme 11).

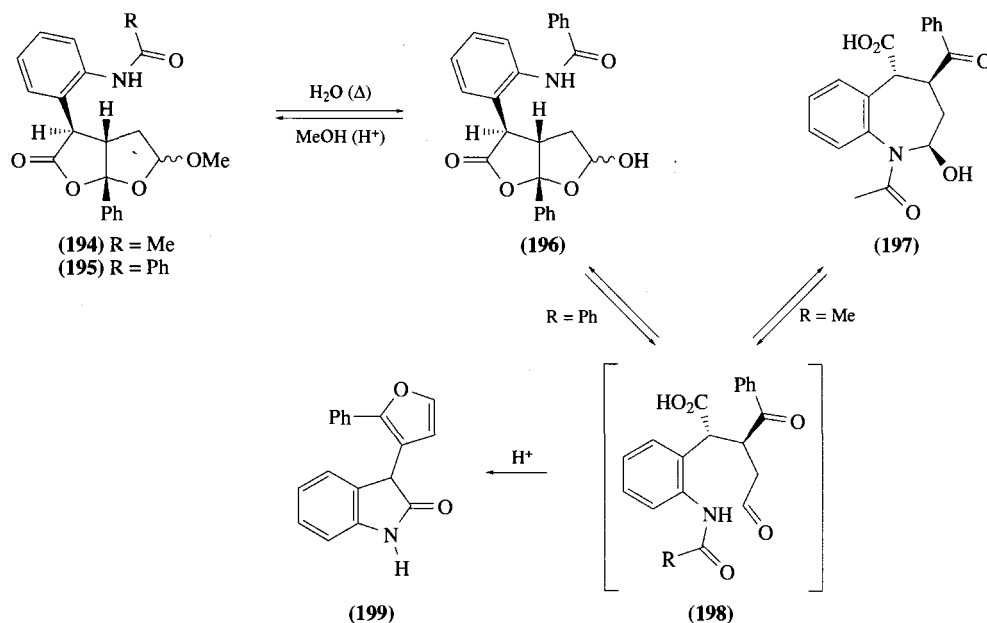


Scheme 11

7.01.6.3 1,6-Diheteropentalene Systems

An interesting equilibration between substituted hexahydrofuro[2,3-*b*]furans and benzo[*b*]azepines has been found to depend on the character of the substituent attached to an amide function in the 3-(2-acylamino-phenyl)-5-methoxyhexahydrofuro[2,3-*b*]furan-2-ones (194) and (195) (Scheme 12) <86JCR(S)84>. The isolation of benzo[*b*]azepine (197) implied an equilibrium between (196) and (197) through an open chain structure (198) <86JCR(S)84>. These rearrangements take place under mild conditions. Lengthy heating in aqueous media in the presence of acids causes

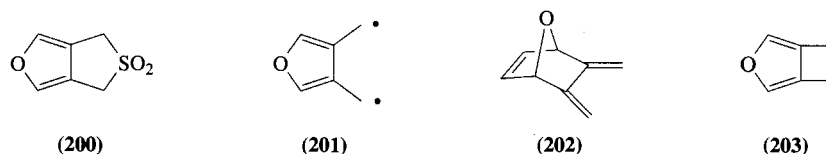
hydrolysis of the amido group. At this stage (**198**), the presence of an enolizable 1,4-dicarbonyl system can lead to a Paal–Knorr-type furan cyclization which gives 3-(2-phenyl-3-furyl)-2,3-dihydro-2-indolone (**199**) in addition to reclosure of the 2,3-dihydro-2-indolone ring.



Scheme 12

7.01.6.4 2,5-Diheteropentalene Systems

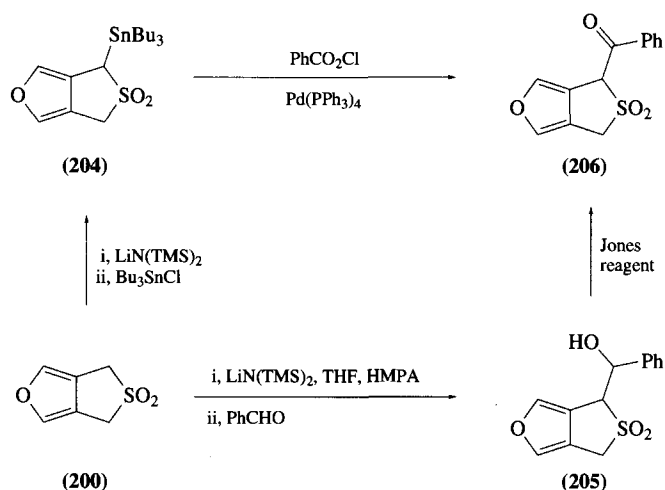
The 4,6-dihydrothieno[3,4-*c*]furan-5,5-dioxide (**200**) contains furan and sulfolene moieties <86JOC4934, 87CC332, 88CC1044, 90CC1687>, both of which can be used as the diene component in Diels–Alder reactions <91CPB2164, 91CC1765, 92CC870, 93H(35)57, 93JCS(P1)2263, 93JCS(P1)2387, 94H(37)1417>. The compound (**200**) can be regarded as a 3,4-dimethylenefuran synthon <89JA3659>. Although there is no direct evidence for the generation of 3,4-dimethylenefuran from precursor (**200**), the furan-fused sulfolene (**200**) has been found to be a useful synthetic building block. In principle, a heterocycle-fused 3-sulfolene may extrude SO₂ to give a biradical (e.g., **201**) <B-93MI 701-02>. Many years ago, the biradical (**201**) was proposed as a transient intermediate in the flash pyrolysis reaction of compound (**202**) giving ethene and (**203**) <74HCA196>. This intermediate can alternatively be formulated as a 1,3-dipole.



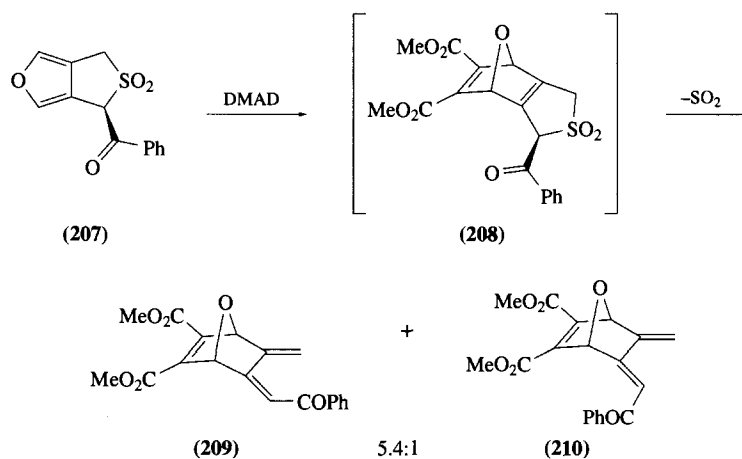
4-Benzoyl-4,6-dihydrothieno[3,4-*c*]furan-5,5-dioxide (**206**) has been prepared from compound (**200**) via the stannane (**204**) and benzoyl chloride in the presence of Pd(PPh₃)₄ as a catalyst. The aldol reaction product (**205**) is oxidized to the same product (**206**) (Scheme 13) <92CC870>.

A benzene solution of the ketone (**207**) was heated at 120°C with DMAD (3 equivalents) in a sealed tube: the Diels–Alder adduct (**208**) is formed and undergoes desulfonylation to afford the mono-adducts (**209**) and (**210**) as an inseparable mixture (5.4 : 1) in 79% yield. It is interesting that the (*E*)-isomer (**209**), with the greater steric congestion, was formed predominantly after chelatotropic desulfonylation (Scheme 14) <92CC870>.

Alkylation of compound (**200**) readily gave its 4-alkyl and 4,6-dialkyl derivatives, selectively. Reaction of 4-alkylated compounds with a variety of dienophiles led to fused furan compounds

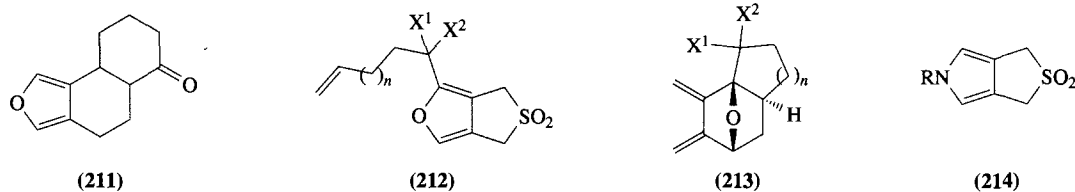


Scheme 13



Scheme 14

(e.g., **211**) in good yield (91CC1765). Compound (**200**) was converted to (alkenyl)thieno[3,4-*c*]furans (**212**; $\text{X}^1, \text{X}^2 = \text{S}(\text{CH}_2)_2\text{S}$, $n = 1, 2$), which readily cyclized to give stereoselectively the functionalized tricyclic compounds (**213**) (93JCS(P1)2263).



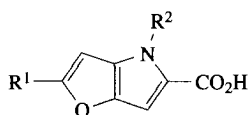
Ando *et al.* (92CC1100, 95T129) have used 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole-2,2-dioxides (**214**) with a variety of *N*-substituents as useful synthetic building blocks for the preparation of polycyclic heterocycles which are inaccessible by other methods. These cycloadditions were performed with electron-deficient dienes (e.g., DMAD) under thermal conditions in a sealed tube. Cycloaddition takes place but the SO_2 is extruded only after the pyrrole ring has undergone cycloaddition with the dienophile.

7.01.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

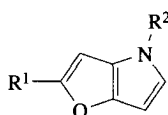
7.01.7.1 1,4-Diheteropentalene Systems

7.01.7.1.1 Carboxylic acids and derivatives

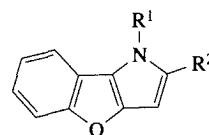
The 4*H*-furo[3,2-*b*]carboxylic acid (**215**) and substituted furo[3,2-*b*]carboxylic acids (**216**)–(**221**), as well as the benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acids (**222**) and (**223**), are decarboxylated in quinoline in the presence of copper chromite barium-promoted catalyst giving the furo[3,2-*b*]pyrroles (**8**), (**8c**), (**8d**), (**113**)–(**116**) and benzo[*b*]furo[3,2-*b*]pyrroles (**224**) and (**75**) <90CCCS97, 92CCCC1487>. During heating in boiling acetic anhydride the 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (**215**) yielded 4-acetylfuro[3,2-*b*]pyrrole (**8b**). Analogous behavior of the 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acids (**218**) and (**219**) gives (**88**) and (**89**). Since with acetic anhydride the ethyl esters of the acids furnish the *N*-acetylated product, one can presume a mechanism in which acetylation takes place in the first step. 1*H*-Benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid (**222**) under the same conditions gives not only the 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole (**225**) but also the sparingly soluble 6,7,14,15-tetrahydrodibenzo[*b*]furo[3,2-*b*]pyrrolo[1,2-*a*:1',2'-*d*]pyrazine-7,15-dione (**226**) <88MI 701-01>.



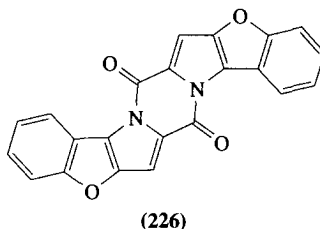
- (**215**) $R^1 = H, R^2 = H$
 (**216**) $R^1 = H, R^2 = Me$
 (**217**) $R^1 = H, R^2 = PhCH_2$
 (**218**) $R^1 = Ph, R^2 = H$
 (**219**) $R^1 = 4-MeC_6H_4, R^2 = H$
 (**220**) $R^1 = Ph, R^2 = Me$
 (**221**) $R^1 = 4-MeC_6H_4, R^2 = Me$



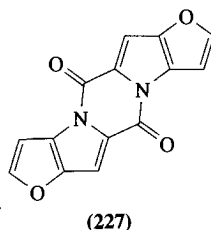
- (**8b**) $R^1 = H, R^2 = MeCO$
 (**8c**) $R^1 = H, R^2 = Me$
 (**8d**) $R^1 = H, R^2 = PhCH_2$
 (**88**) $R^1 = Ph, R^2 = MeCO$
 (**89**) $R^1 = 4-MeC_6H_4, R^2 = MeCO$
 (**113**) $R^1 = Ph, R^2 = H$
 (**114**) $R^1 = 4-MeC_6H_4, R^2 = H$
 (**115**) $R^1 = Ph, R^2 = Me$
 (**116**) $R^1 = 4-MeC_6H_4, R^2 = Me$



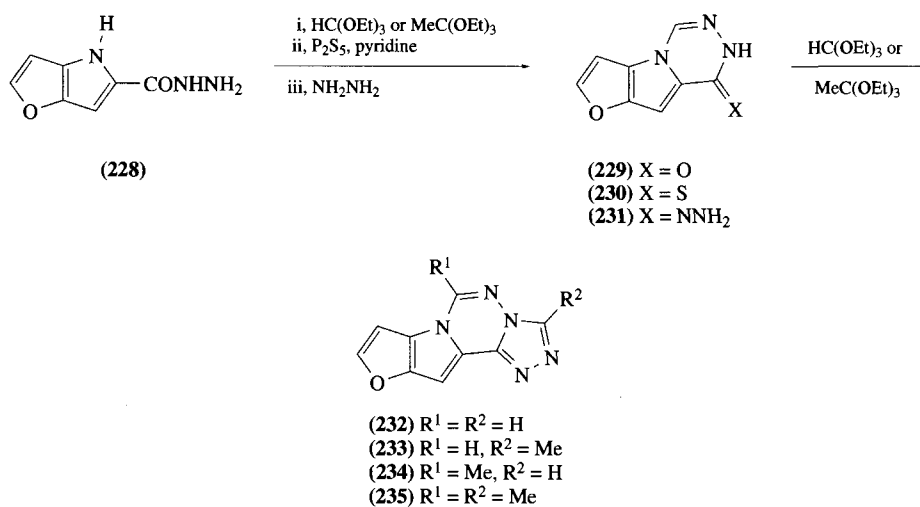
- (**75**) $R^1 = Me, R^2 = H$
 (**222**) $R^1 = H, R^2 = CO_2H$
 (**223**) $R^1 = Me, R^2 = CO_2H$
 (**224**) $R^1 = R^2 = H$
 (**225**) $R^1 = MeCO, R^2 = H$



The formation of the dimeric product (**227**) in the furo[3,2-*b*]pyrrole series was observed under conditions of flash vacuum pyrolysis of the acid (**215**) and its ethyl ester <82CC360>.

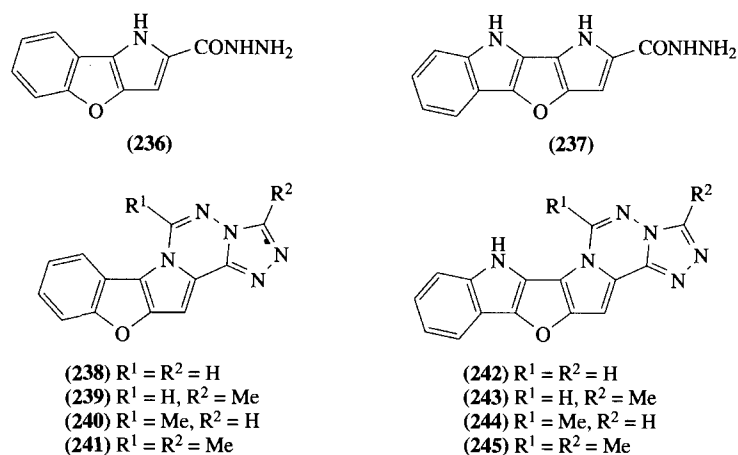


Two reaction centers of 4*H*-furo[3,2-*b*]pyrrole-5-carboxyhydrazide (**228**) (Scheme 15) <84CCC65> were utilized in cyclization reactions with either triethyl orthoformate or orthoacetate, leading to furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazine-8(7*H*)-one (**229**). Phosphorus pentasulfide treatment of this product (**229**) gave the corresponding thione (**230**) which with hydrazine hydrate gave (**231**). This compound (**231**) with triethyl orthoformate gave furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazine (**232**); the 3-methyl (**233**), 6-methyl (**234**) and 3,6-dimethyl (**235**) derivatives were also made.

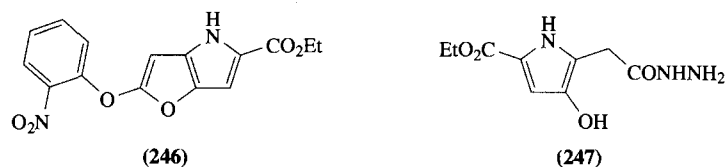


Scheme 15

Substituted derivatives <83CCC1878, 84MI 701-01> and pentacyclic (238)–(241) and hexacyclic (242)–(245) polyaza systems were prepared analogously from intermediates (236) and (237).



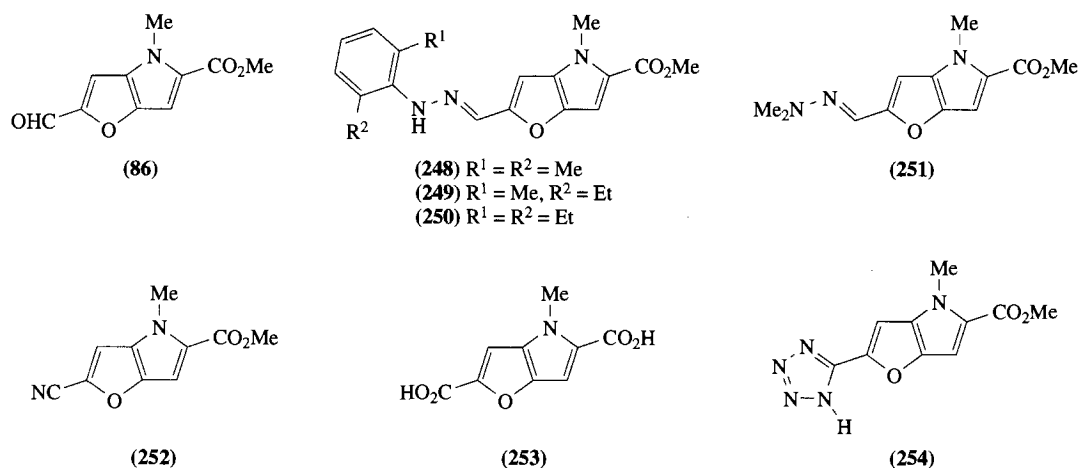
The above-mentioned hydrazides were prepared from the corresponding esters and hydrazine hydrate <90CCC597>. Ethyl 2-(2-nitrophenoxy)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (246) reacted with hydrazine in an unexpected manner. Reaction did not take place at the ethoxycarbonyl group, but instead hydrazine attacked the C-2 position, replacing the 2-nitrophenoxy group. Subsequent opening of the furan ring gave rise to the hydrazide (247).



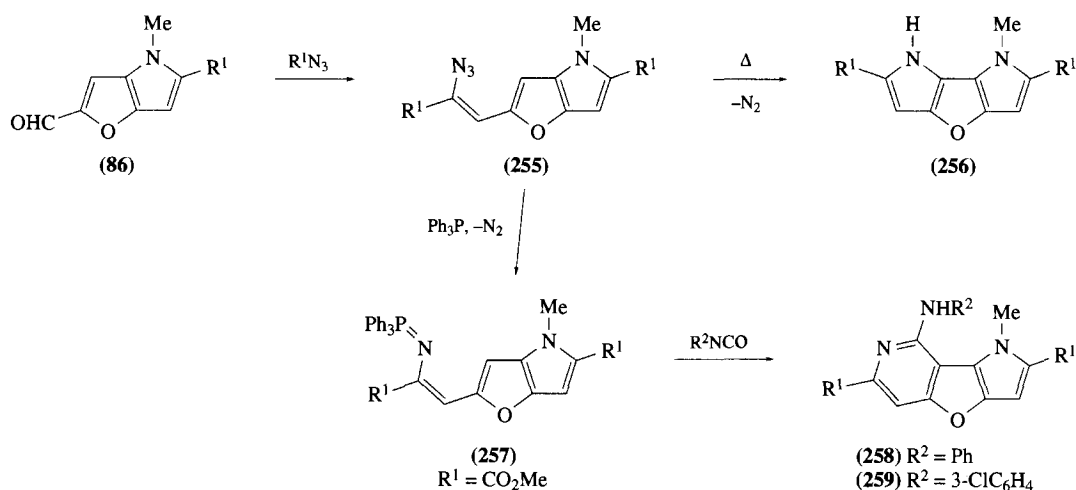
7.01.7.1.2 Aldehydes

Methyl 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (86) with 2,6-dialkylphenylhydrazines and a catalytic amount of 4-methylbenzenesulfonic acid in refluxing toluene gave the hydrazones (248)–(250). Analogously *N,N*-dimethylhydrazone (251) was made from *N,N*-dimethylhydrazine.

The reaction of compound **(86)** with hydroxylammonium chloride in acetic anhydride in the presence of pyridine gave the corresponding cyano-substituted compound **(252)**. Alkaline hydrolysis of compound **(252)** gave the diacid **(253)**, and reaction with sodium azide and ammonium chloride in DMF led to the tetrazole **(254)**. The compounds **(8i)**, **(82)**, **(84)**, **(85)**, and **(87)** reacted similarly <93CCC2139, 94MI 701-01>.



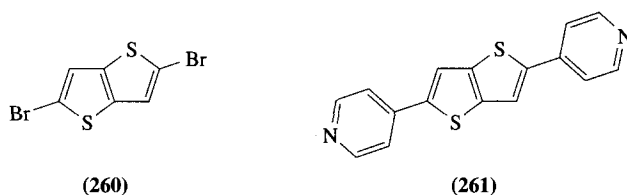
Reaction of the aldehyde **(86)** with methyl azidoacetate in the presence of sodium methoxide was found to proceed smoothly to give azide **(255)**, which upon thermolysis in boiling toluene gave dimethyl 1-methyl-7H-furo[3,2-*b*:4,5-*b'*]dipyrrole-2,6-dicarboxylate **(256)**. Compound **(255)** reacted with triphenylphosphine in dry dichloromethane to give the iminophosphorane **(257)**, which with phenyl or 3-chlorophenyl isocyanate in dry toluene under reflux gave the substituted pyrrolo-[2',3':4,5]furo[3,2-*c*]pyridines **(258)** or **(259)** via carbodiimides, which were not isolated (Scheme 16). The compounds **(8i)**, **(84)**, and **(87)** undergo similar reactions <92M807, 94H(37)1695>.



Scheme 16

7.01.7.1.3 Halogen substituents

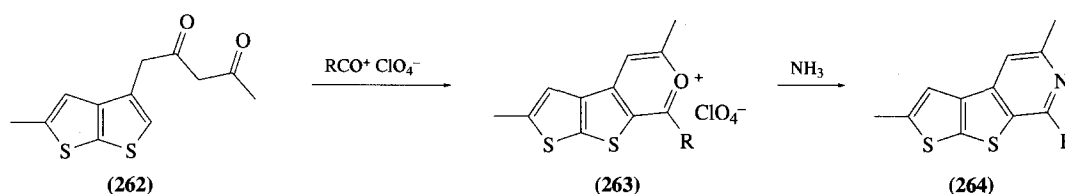
2,5-Di(4-pyridyl)thieno[3,2-*b*]thiophene **(261)** has been synthesized efficiently in a simple one-pot procedure employing a palladium-mediated cross-coupling reaction between (trimethylstannyl) pyridines and 2,5-dibromothieno[3,2-*b*]thiophene **(260)** <92BCJ1855>.



7.01.7.2 1,6-Diheteropentalene Systems

7.01.7.2.1 Alkyl groups

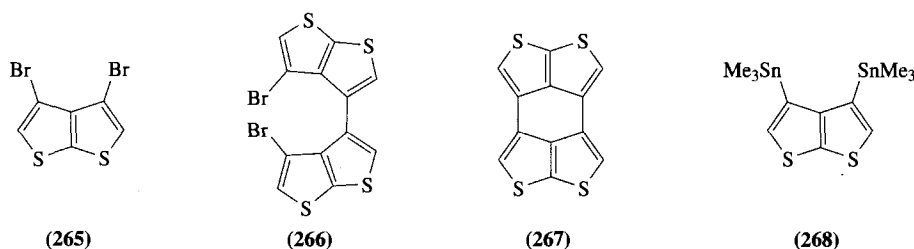
The substituted thieno[2,3-*b*]thienophene (**262**) in a mixture of an aliphatic acid anhydride and HClO_4 gave thieno[2',3' : 5,4]thieno[2,3-*c*]pyrylium perchlorates (**263**), which with an excess of ammonia are converted into the corresponding thieno[2',3' : 5,4]thieno[2,3-*c*]pyridines (**264**) (Scheme 17) <83KGS37>.



Scheme 17

7.01.7.2.2 Halogen substituents

A conventional reductive coupling of 3,4-dibromothieno[2,3-*b*]thiophene (**265**) <74BSF583> with catalytic bis(triphenylphosphine)nickel(II) chloride, excess active zinc, and tetrabutylammonium iodide in refluxing benzene gave only 4,4'-dibromo-3,3'-(bithieno[2,3-*b*]thiophene) (**266**) (maximum yield 28%) <90BCJ80>. Increasing the quantity of the nickel reagent led to formation of benzo[1,2,3-*cd* : 4,5,6-*c'd'*]bis(thieno[2,3-*c*]thiophene) (**267**), whose yield was optimized to 14%. As an alternative, the dibromide (**265**) was converted to 3,4-bis(trimethylstannyl)thieno[2,3-*b*]thiophene (**268**) in 60% yield, and a coupling of (**265**) and (**268**) in the presence of catalytic tetrakis(triphenylphosphine)palladium gave the product (**267**) in 13% yield <93BCJ2033>.



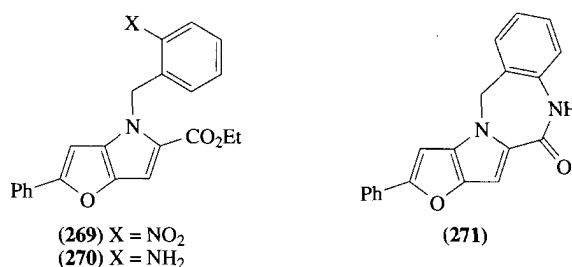
7.01.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Reactions of substituents attached to ring heteroatoms have been studied only on 1,4-diheteropentalene systems, mainly furo[3,2-*b*]pyrrole derivatives.

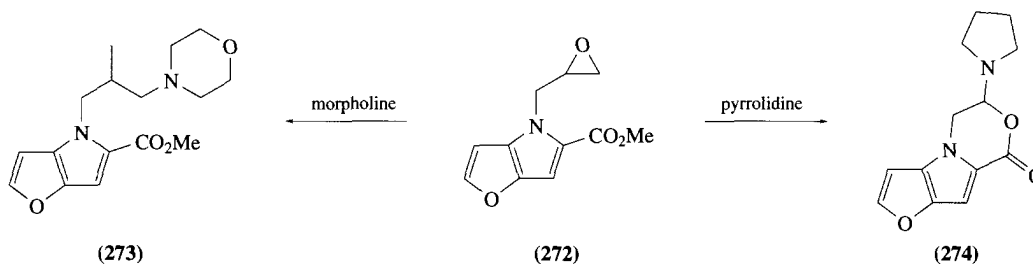
7.01.8.1 1,4-Diheteropentalene Systems

The acetyl group of the 4-acetylfuro[3,2-*b*]pyrrole (**8b**) (see Table 6) readily undergoes hydrolysis and under conditions of phase transfer catalysis with methyl iodide or benzyl chloride gave the 4-methyl (**8c**) or 4-benzylfuro[3,2-*b*]pyrrole (**8d**) via the unstable 4*H*-furo[3,2-*b*]pyrrole (**8**) <92CCCC1487>.

The reaction of ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (**94**) with 2-nitrobenzyl bromide afforded ethyl 4-(2-nitrobenzyl)-2-phenylfuro[3,2-*b*]pyrrole-5-carboxylate (**269**) under conditions of phase transfer catalysis by utilization of sodium carbonate and tetrabutylammonium bromide. This product (**269**) was hydrogenated using palladium-on-charcoal catalyst to give the amine (**270**), which cyclized in the presence of 2-hydroxypyridine to give 2-phenylfuro[2',3':4,5]pyrrolo[2,1-*c*]benzo[1,4]diazepin-11-one (**271**) <92CCCC1487>.



4-(2-Oxiranylmethyl)furo[3,2-*b*]pyrrole-5-carboxylate (**272**) with morpholine undergoes oxirane ring opening to form the *N*-substituted derivative of methyl 4-(3-amino-2-hydroxypropyl)furo[3,2-*b*]pyrrole-5-carboxylate (**273**). Using pyrrolidine as nucleophile the fused *aza*-lactone (**274**) is formed (Scheme 18) <95UP 701-01>.



Scheme 18

7.01.9 RING SYNTHESES

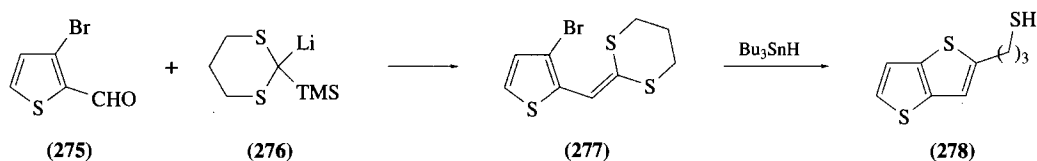
A wide variety of methods for the preparation of the general systems (1)–(4) have been reviewed <84CHEC-I(4)1037> and can be categorized into a few main types, according to the number of new bonds formed during the annelation. The methods for the synthesis of various annelated thienopyrroles <85S143> have been classified according to the ring to be constructed and according to starting materials. In this chapter, synthetic routes have been classified according to starting compounds, i.e., syntheses by construction of the second heterocyclic ring on to an existing heterocycle by intramolecular cyclization, intramolecular cycloadditions, and syntheses from acyclic precursors.

7.01.9.1 Syntheses of 1,4-Diheteropentalene Systems (1)

7.01.9.1.1 Synthesis by construction of the second heterocyclic ring on to an existing heterocycle

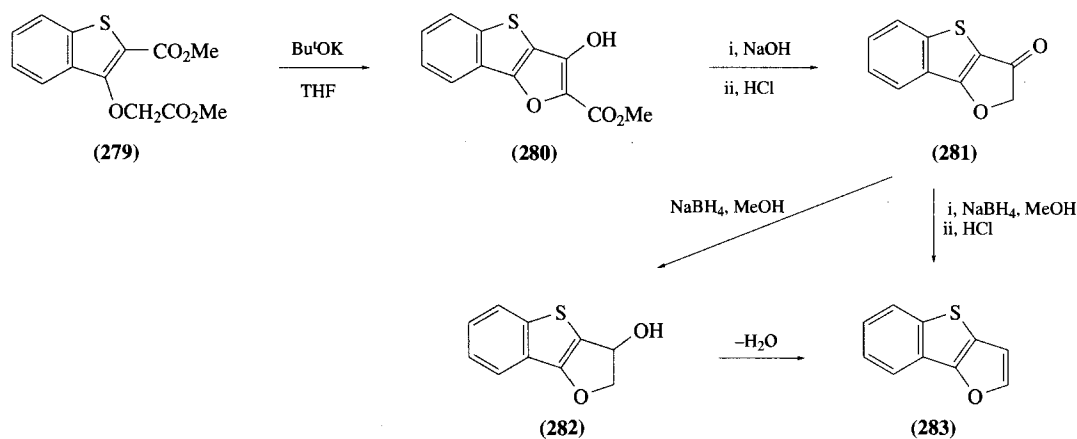
(i) Intramolecular cyclization of carbonyl and carboxylic acid intermediates

The ketenethioacetal (**277**), prepared from the aldehyde (**275**) and 2-lithio-2-trimethylsilyl-1,3-dithiane (**276**), upon treatment with tributyltin hydride gave, via a radical tandem cyclization, the 2-(3-thiol-1-propyl)thieno[3,2-*b*]thiophene (**278**) (Scheme 19) <93TL5653>.



Scheme 19

The benzo[*b*]thieno[3,2-*b*]furan (283) has been prepared in a four-step synthesis (Scheme 20) <93CCC2983>. Reaction of methyl thiosalicylate with methyl chloroacetate gives methyl 3-[(methoxycarbonyl)methoxy]benzo[*b*]thiophene-2-carboxylate (279), which on cyclization using potassium *t*-butoxide gives methyl 3-hydroxybenzo[*b*]thieno[3,2-*b*]furan-2-carboxylate (280). Subsequent base-catalyzed hydrolysis and decarboxylation forms benzo[*b*]thieno[3,2-*b*]furan-3(2*H*)-one (281); reduction with NaBH₄ gives compound (282), which undergoes dehydration to give compound (283).

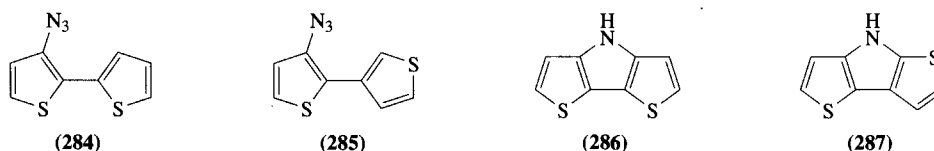


Scheme 20

(ii) Intramolecular cyclizations involving nitrene intermediates

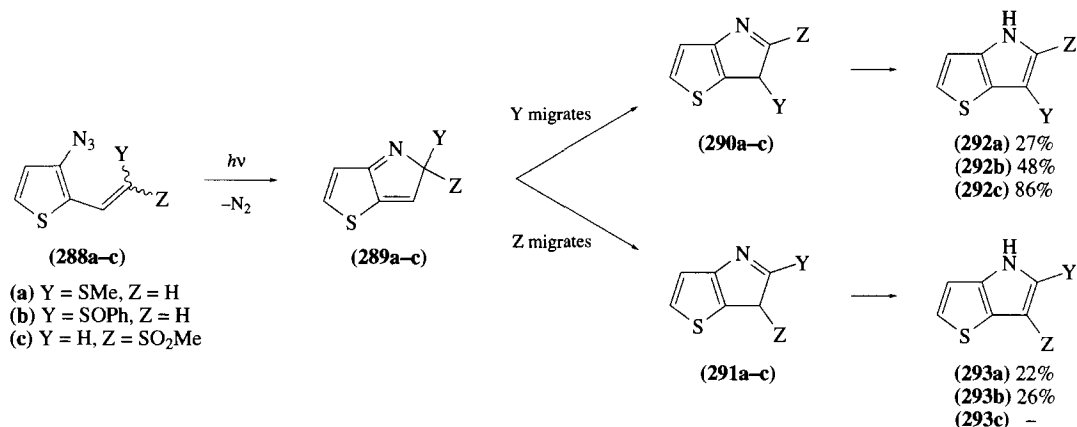
Pyrolysis of an azide frequently produces the reactive nitrene, which immediately attacks a nearby position on an adjacent ring. The azide is usually heated in an inert high-boiling solvent, although cyclization may occur without a solvent. Photochemically induced cyclization of an azide can often give a good yield of product.

Thermal decomposition of 3-azido-2,2'-bithienyl (284) and 3-azido-2,3'-bithienyl (285) gave 4*H*-dithieno[3,2-*b*:2',3'-*d*]pyrrole (286) and 4*H*-dithieno[2,3-*b*:2',3'-*d*]pyrrole (287) in yields of 87% and 89%, respectively. Other isomers gave polymers or intractable materials <83JCS(P1)2551>.



The 5*H*-thieno[3,2-*b*]pyrroles (289a)–(289c) are not stable enough to be isolated. They are formed in photochemical conversions of the 3-azido-2-vinylthiophenes (288a–c) into thieno[3,2-*b*]pyrroles (292a–c) and (293a–c). The final products are formed via the nonaromatic fused intermediates (290) and (291) (Scheme 21) <85CC1818>. A mechanism has been proposed involving formation and 1,5-electrocyclization of a corresponding nitrene, followed by a sigmatropic shift of one or both of the

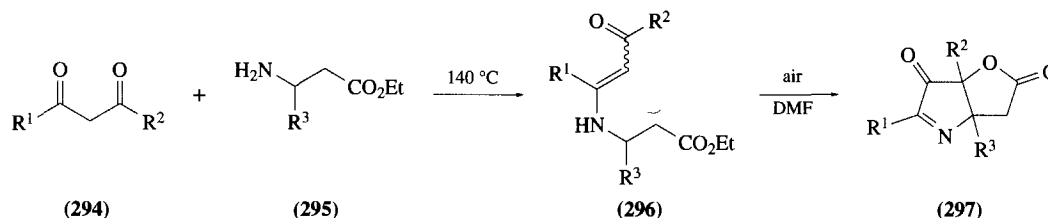
C-5 substituents of the intermediates (**290a–c**) or (**291a–c**). For the Y and Z groups studied, the order of migratory aptitude was found to be $\text{RSO} > \text{RS} \sim \text{H} > \text{RSO}_2 > \text{RCO} > \text{EtO}_2\text{C}$ <86JCS(P1)497, 86JCS(P1)501>.



Scheme 21

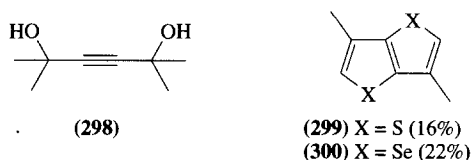
7.01.9.1.2 Synthesis from acyclic precursors

The 2,6-dioxo-3,3a,6,6a-tetrahydrofuro[3,2-*b*]pyrroles (**297**) were formed by reaction of the 1,3-diketones (**294**) with ethyl 3-aminopropanoates (**295**). The reaction proceeds via the intermediate enamines (**296**) (Scheme 22) <84S663>.



Scheme 22

Heating a mixture of 2,5-dimethyl-3-hexyne-2,5-diol (**298**) with elemental sulfur or selenium provides a one-pot synthesis of 3,6-dimethylthieno[3,2-*b*]thiophene (**299**) or 3,6-dimethylselenolo[3,2-*b*]selenophene (**300**) respectively <94H(38)143>.

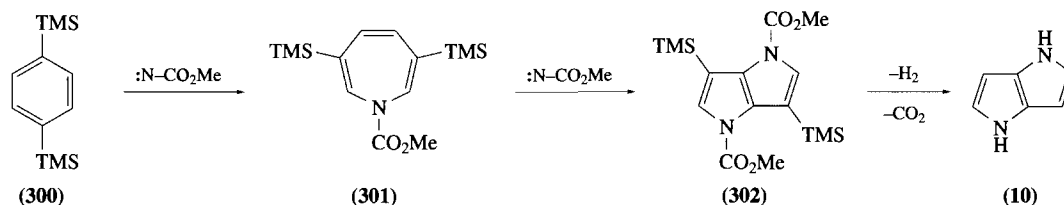


7.01.9.1.3 Other methods

The chemistry of pyrrolopyrroles has not been explored because of synthetic barriers. The synthesis of 1,4-dimethyl and 3,6-di-*t*-butyl-1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole has been described <75AG(E)347, 83CL743>.

The parent 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole (**10**) has been synthesized <84TL5669> (Scheme 23) from 1,4-bis(trimethylsilyl)benzene (**300**) and methyl azidoformate via the azepine intermediate (**301**)

and the tetrahydropyrrolo[3,2-*b*]pyrrole (**302**). Dehydrogenation and simultaneous desilylation by treatment with *ddq* and further hydrolysis and decarboxylation using methanolic potassium hydroxide gave compound (**10**).



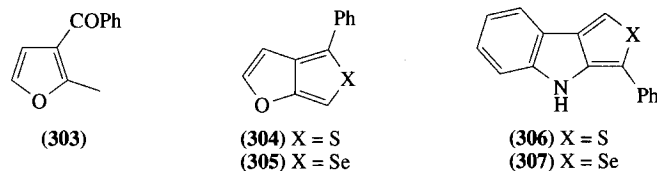
Scheme 23

7.01.9.2 Syntheses of 1,5-Diheteropentalene Systems (2)

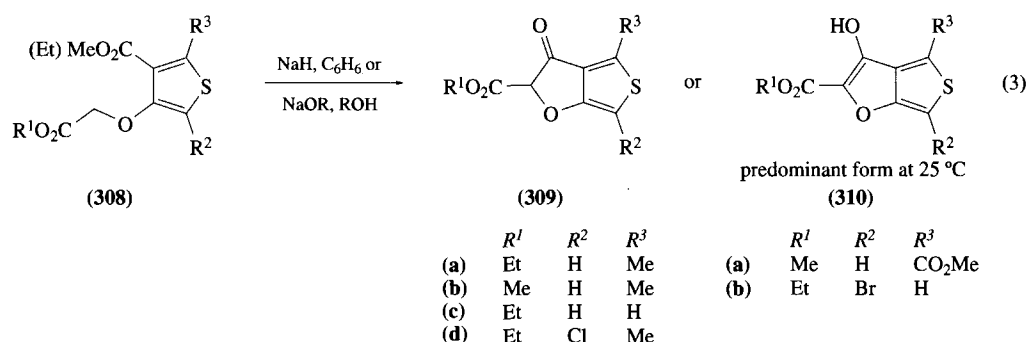
7.01.9.2.1 Synthesis by construction of the second heterocyclic ring on to an existing heterocycle

(i) Intramolecular cyclization of carbonyl and carboxylic acid intermediates

Starting from readily available 2-methyl-3-benzoylfuran (**303**), 4-phenylthieno[3,4-*b*]furan (**304**) and 4-phenylselenolo[3,4-*b*]furan (**305**) were prepared <82JHC227>. Shafiee and Sattari <82JHC227> prepared 3-phenylthieno[3,4-*b*]indole (**306**) and 3-phenylselenolo[3,4-*b*]indole (**307**).

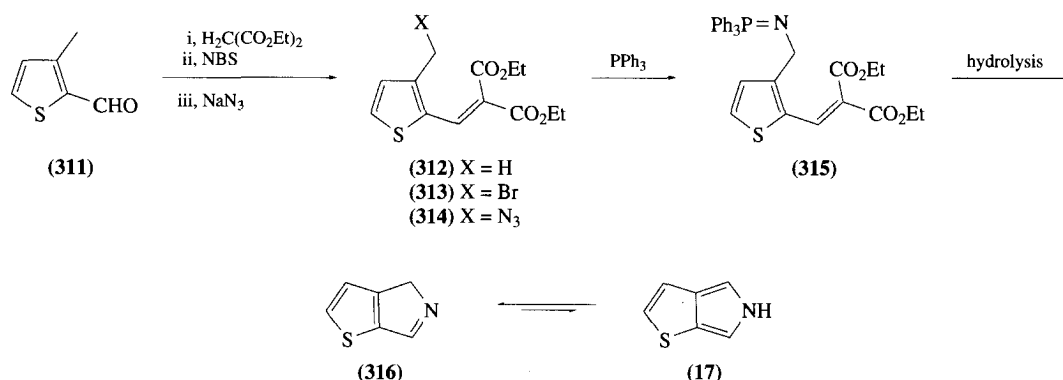


Cyclization of suitably substituted thiophenes (**308**) to yield thieno[3,4-*b*]furans (**309**) or (**310**) was achieved by utilization of the Dieckmann condensation (Equation (3)) <86JCS(P1)2223>.



Synthesis of the parent 5*H*-thieno[2,3-*c*]pyrrole (**17**) is summarized in Scheme 24 <86CC310>. Knoevenagel condensation of the aldehyde (**311**) with diethyl malonate gave compound (**312**) (98% yield) and bromination (NBS–dibenzoyl peroxide) afforded the bromide (**313**) (80% yield). Treatment of this bromide (**313**) with sodium azide in aqueous ethanol at room temperature produced the azide (**314**) (92% yield), which with triphenylphosphine in THF formed (**315**), hydroly-

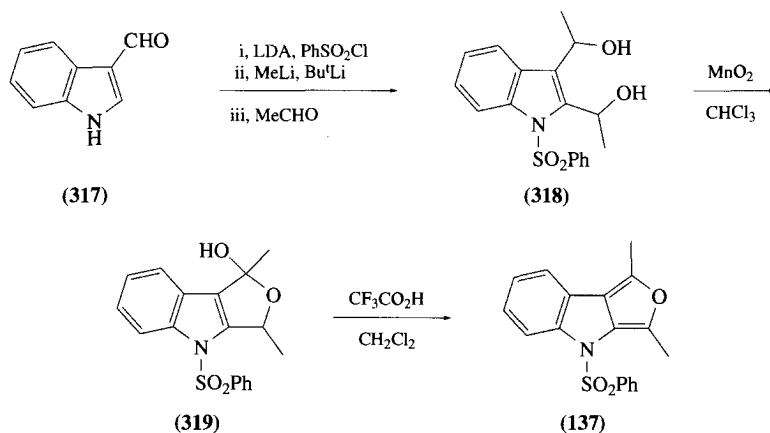
sis of which gave compound (316). Upon silica gel chromatography, compound (316) was transformed into the tautomer (17) (78% yield) (Scheme 24).



Scheme 24

The 3-indolecarbaldehyde (317) was protected as the 1-phenylsulfonyl derivative and transformed by sequential treatment with methyllithium, *t*-butyllithium, and ethanal into the diol (318). Compound (318) was then oxidized to give the butenolide (319) and dehydrated to give the 1,3-dimethyl-4-phenylsulfonylfuro[3,4-*b*]indole (137) (Scheme 25) <83TL5435, 84JOC4518, 91SL289>.

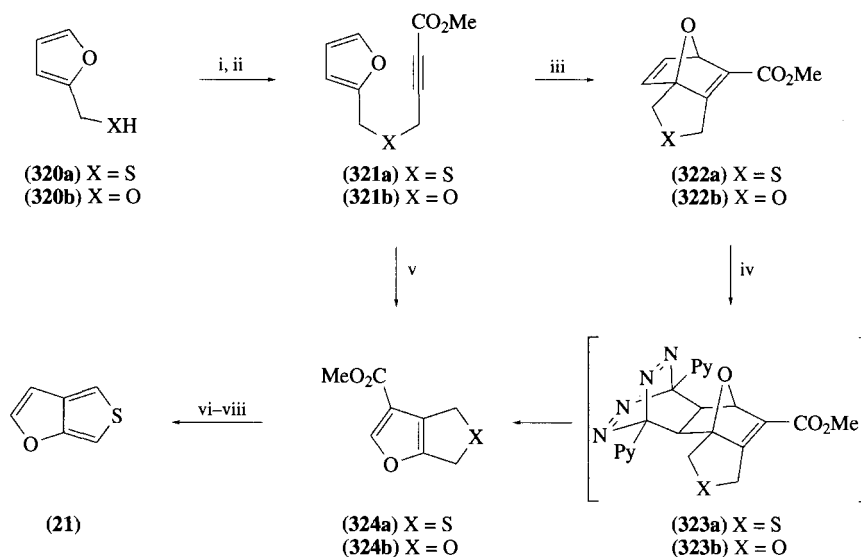
Interesting recent advances in the synthesis of pyrrolo[3,4-*b*]indoles have been summarised <84CC1552, 87ZN(B)473>.



Scheme 25

(ii) Intramolecular cycloadditions

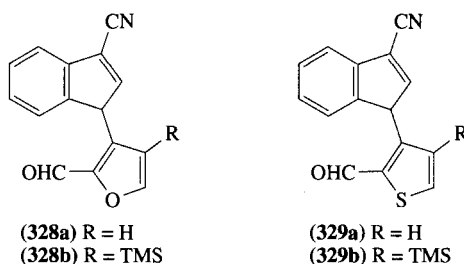
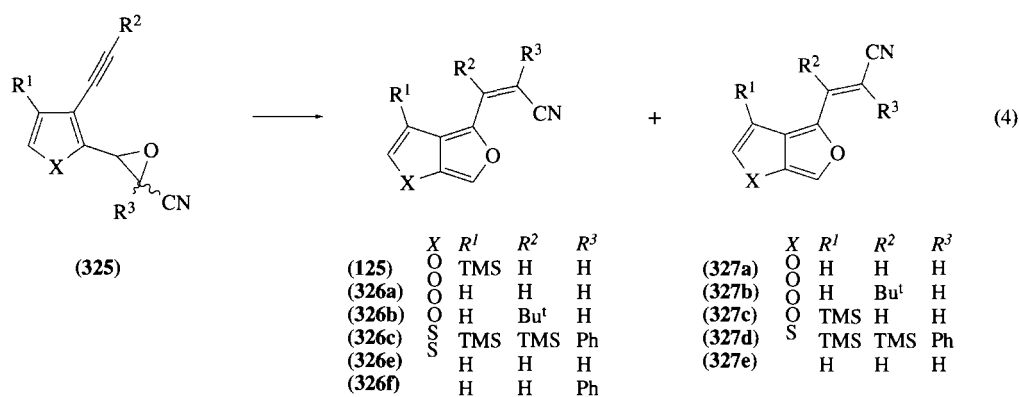
The parent thieno[3,4-*b*]furan (21) has been prepared by an elegant route involving as the key step intramolecular Diels–Alder addition of the ethoxycarbonylthynylfuran (321a) which is readily prepared from the thiol (320a). This compound (321a) in refluxing toluene solution affords the intramolecular adduct (322a), which with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, via the cycloaddition–cycloreversion sequence (322a → 323a → 324a) gave the ester (324a). The intramolecular cycloaddition and cycloreversion steps can also be carried out by heating the alkyne (321a) with 1 equivalent of the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine in toluene. Finally, the parent system (21) is formed by oxidative hydrolysis and decarboxylation (Scheme 26) <86TL3045>. Attempts to synthesize the analogous furo[3,4-*b*]furan (20) stopped at the intermediate (324b) due to failure to find sufficiently mild conditions to enable isolation of the very sensitive two-oxygen-containing 1,5 system.



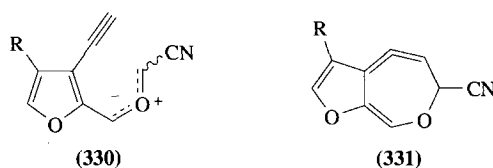
i, NaH, THF, propargyl chloride; ii, EtMgBr, THF, ClCO₂Me; iii, toluene; iv, 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, CHCl₃; v, 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, toluene; vi, DDQ, CH₂Cl₂; vii, HO⁻, then H⁺; viii, Cu chromite, quinoline

Scheme 26

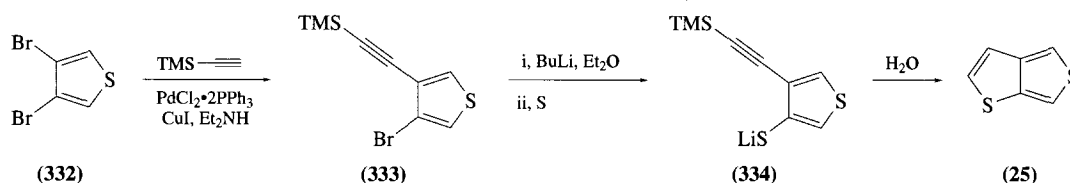
The series of known 1,5 ring systems has been extended to substituted thieno[2,3-*c*]furans (15) <86H(24)307>. A general route for the synthesis of substituted furo[3,4-*b*]furans and thieno[2,3-*c*]furans (326) and (327) has been developed (Equation (4)) <85H(23)2797, 86T2221, 87TL2685, 88AG(E)568, 93CB975>. The reaction is based on the rapid thermolysis of suitably structured epoxyhexenynes (325). Index derivatives (228a), (328b), (329a) and (329b) are form as by-products.



A mechanistic explanation of this transformation of the epoxyhexenynes (325) to furo- and thienofurans (326) and (327) has been proposed <93CB975>. The reaction pathway leading to the products (326) and (327) presumably proceeds via the carbonyl ylides (330) which undergo a 1,7-dipolar cyclization to the allene derivatives (331). These are subsequently transformed into the furo[3,4-*b*]furans via a pathway involving diradical and carbene intermediates.



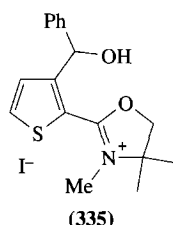
Thieno[3,4-*b*]thiophene (**25**) has been obtained (> 50% yield) from 3,4-dibromothiophene (**332**) by a sequence involving Pd(II)–Cu(I) catalysed cross-coupling with trimethylsilylthyne giving (**333**), bromine–lithium exchange, thiolation with elemental sulfur (**334**) and ring-closure in aqueous medium (Scheme 27) <90SC2275>.



Scheme 27

(iii) Other methods

The 2-[3-(α -hydroxybenzyl)-2-thienyl]-3,4,4-trimethyl-2-oxazolinium iodide (**335**) reacted with phenylmagnesium bromide to give 4,6-diphenylthieno[2,3-*c*]furan (**130**) (85% yield) <89CB1119>.



7.01.9.3 Syntheses of 1,6-Diheteropentalene Systems (3)

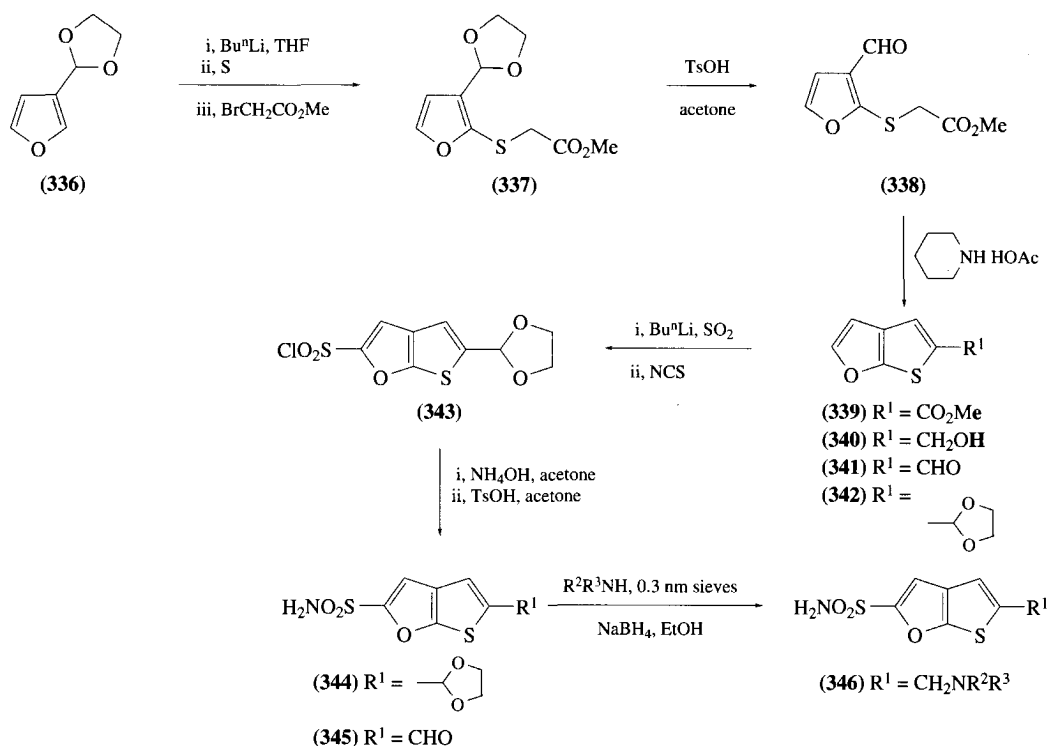
7.01.9.3.1 Synthesis by construction of the second heterocyclic ring on to an existing heterocycle

(i) Synthesis from furan derivatives

The thieno[2,3-*b*]furan-2-sulfonamides (**346**) (Scheme 28) have been prepared and evaluated as topical carbonic anhydrase inhibitors <91JMC1805>.

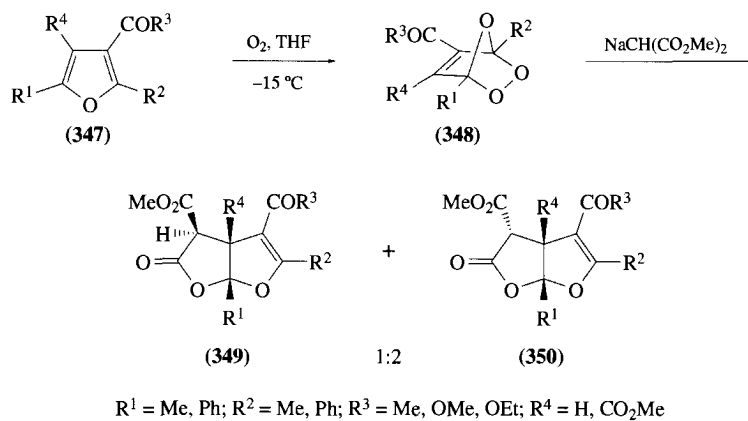
The synthesis of the derivatives (**339**)–(**346**) was carried out as shown in Scheme 28. Metalation of the acetal (**336**), followed by thiolation and alkylation, gave the ester derivative (**337**). Acetal deprotection to form (**338**) and subsequent treatment under Knoevenagel conditions with piperidinium acetate in benzene afforded the desired ester (**339**). Reduction of compound (**339**) gave alcohol (**340**), which was converted to aldehyde (**341**) and protected as its acetal (**342**) under standard conditions. Deprotonation was effected by BuⁿLi in THF at –78°C and subsequent conversion to the sulfonyl chloride was carried out by sequential treatment with sulfur dioxide and *N*-chlorosuccinimide. Treatment of the sulfonyl chloride (**343**) with concentrated NH₄OH in acetone provided the sulfonamide (**344**), which was deprotected (**345**) and subjected to reductive amination to provide compounds in the aminomethyl sulfonamide series (**346**).

Synthesis of the 2,3,3a,6a-tetrahydrofuro[2,3-*b*]furan-2-ones (**349**) and (**350**) was realized by



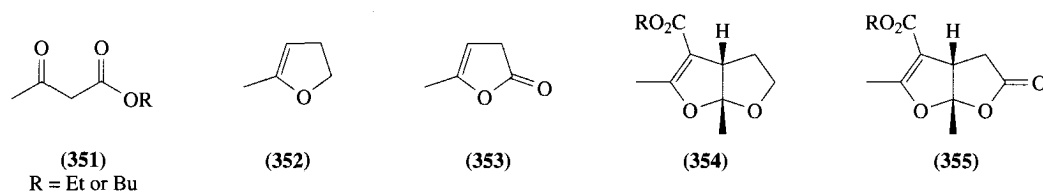
Scheme 28

reaction of dimethyl malonate with the *endo*-peroxides (348), which are formed by photosensitized oxidation of the furans (347) using singlet oxygen in THF at -15°C (Scheme 29) <84S64>.



Scheme 29

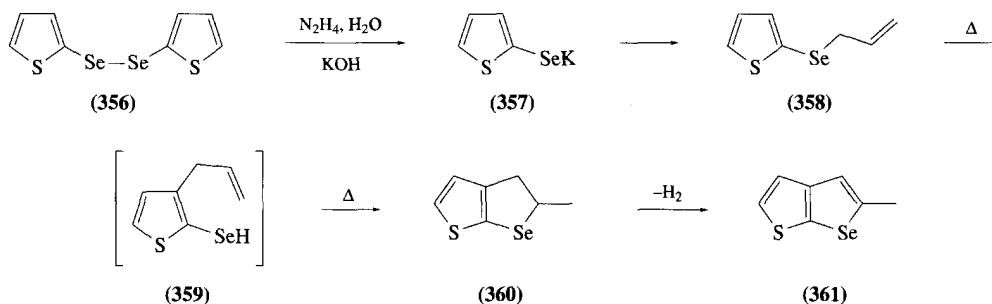
Manganese acetate-promoted oxidative addition of 1,3-dicarbonyl compounds (351) to *endo*-cyclic enol ethers (352) and enol lactones (353) gives 2,3,3a,6a-tetrahydrofuro[2,3-*b*]furan derivatives (354) and (355) <87CL223, 91TL711, 91TL7107>.



(ii) Synthesis from thiophene derivatives

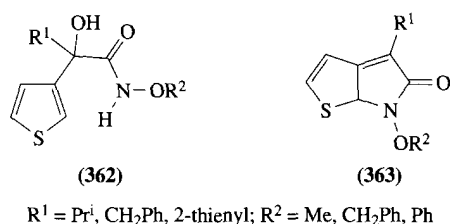
A series of 5-substituted thieno[2,3-*b*]thiophene-2-sulfonamides was prepared <91JMC1805> from thiophene-3-carbaldehyde in a manner analogous to that described for the corresponding thieno[2,3-*b*]furan-2-sulfonamides (346) (Scheme 28) <92JMC3027>.

Allyl-2-thienyl selenide (358) was prepared from the diselenide (356) via (357) and was quantitatively converted into compound (360) <91KGS1312>; a thio-Claisen rearrangement gives the intermediate (359) which, by an intramolecular cyclization, gave compound (360), which was then aromatized to 5-methylselenolo[2,3-*b*]thiophene (361) (Scheme 30).



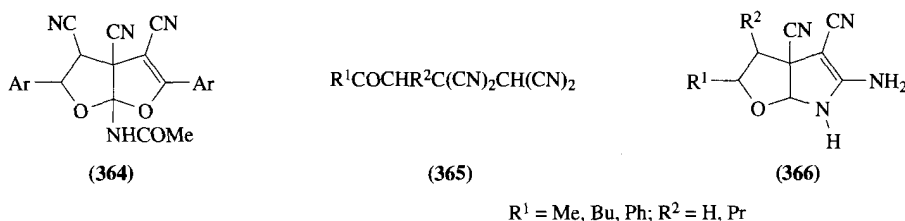
Scheme 30

The *O*-alkyl glycolohydroxamic acids (362) are converted (DCC) into 5,6-dihydro-6a*H*-thieno[2,3-*b*]pyrrol-5-ones (363), formation of which depends on the nature of the C-2 substituents <93PHA801>.



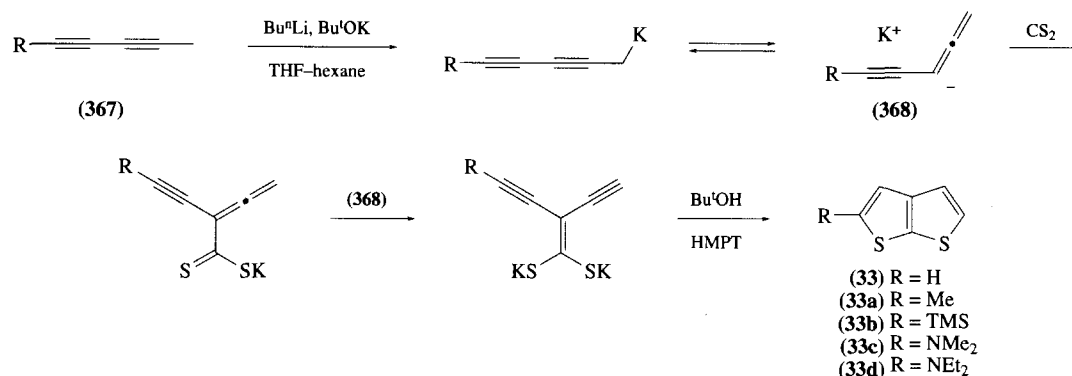
(iii) Synthesis from acyclic precursors

Bromomalononitrile and ω-cyanoacetophenones in the presence of alkoxides give the substituted tetrahydrofuro[2,3-*b*]furans (364) in one step <88JOC5341>. Reduction of β,β,γ,γ-tetracyanoketones (365) with sodium borohydride gives 2,3,3a,6a-tetrahydrofuro[2,3-*b*]pyrroles (366) <92KGS277>.



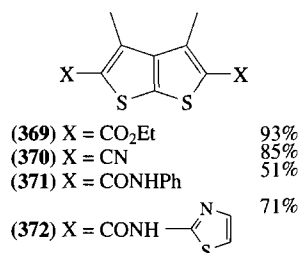
Thieno[2,3-*b*]thiophene (33) and the derivatives (33a-d) have been obtained in fair yields in a one-pot procedure using the substituted diynes (367) and carbon disulfide as building blocks (Scheme

31) <91SC145>. An important condition for the successful synthesis of thienothiophenes is that the intermediate potassium salt reacts mainly or exclusively in the allenic form (368).



Scheme 31

The synthesis of some new substituted thieno[2,3-*b*]thiophenes (369)–(372) has been achieved <93BCJ2011> in a one-pot reaction employing solid–liquid phase transfer catalysis (PTC) conditions (K₂CO₃, benzene, tetrabutylammonium bromide catalyst) and starting from acetylacetone, CS₂, and α -chloro compounds in 1:1:2 molar ratio. The reaction of acetylacetone and CS₂ with ethyl chloroacetate, chloroacetonitrile, 2-(chloroacetyl-amino)thiazole, or chloroacetanilide was carried out under PTC conditions by stirring the reactants; reaction times and temperatures were optimized. The corresponding thieno[2,3-*b*]thiophenes (369)–(372) were obtained in excellent yields (51–93%).



7.01.9.4 Syntheses of 2,5-Diheteropentalene Systems (4)

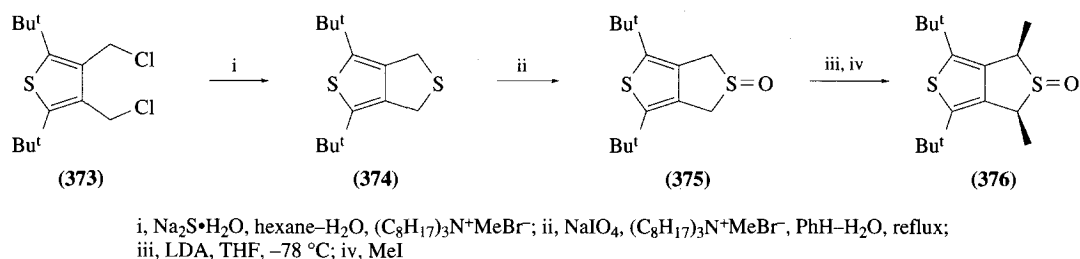
7.01.9.4.1 Thieno[3,4-*c*]thiophenes

The unstable parent thieno[3,4-*c*]thiophene (37) and its unstable derivatives (158)–(161) have been synthesized and characterized *in situ* by trapping experiments <67JA3639, 73JA2558, 88CC959, 90BCJ1026, 92BCJ2821>. On the other hand, some derivatives such as 1,3,4,6-tetraphenyl- (52) <69JA3952, 73JA2561>, 1,3,4,6-tetrakis(alkylthio)- (162) <85JA5801, 88JA1793, 89CC223, 91CC520>, 1,3,4,6-tetra-2-thienyl- (163) <91JOC78> 1,3-dibromo-4,6-dicyano- (164), 1,3-dibromo-4,6-dimethoxycarbonyl- (165) and 1,3,4,6-tetrabromo- (166) <94JOC2223> thieno[3,4-*c*]thiophenes have been successfully synthesized as isolable compounds.

(i) Synthesis from thiophene derivatives

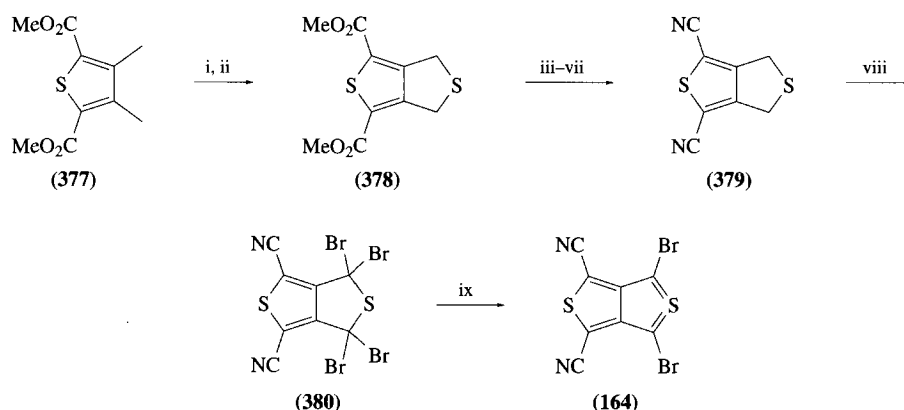
The 1,3-di-*t*-butyl-4,6-dimethylthieno[3,4-*c*]thiophenes (160) and (161) <92BCJ2821> were generated by Pummerer dehydration of the corresponding sulfoxides in boiling acetic anhydride and were characterized by trapping with *N*-phenylmaleimide. From these results it was concluded <92BCJ2821> that the steric protection afforded by two *t*-butyl and two methyl substituents is not sufficient to make the thieno[3,4-*c*]thienophene system unreactive enough to be isolable. The 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (373) <56IZV495, 90BCJ1026> was chosen as the starting

material for the synthesis of the derivatives (160) and (161) (Scheme 32). The reaction of compound (373) with Na₂S afforded (374), which was oxidized (NaIO₄) to give the sulfoxide (375). Dilithiation with LDA at -78 °C followed by treatment with iodomethane gave 4,6-di-*t*-butyl-1,3-dimethyl-1*H*,3*H*-thieno[3,4-*c*]thiophene-2-oxide (376) in 56% yield. By Pummerer dehydration the sulfoxide (376) gave 1,3-di-*t*-butyl-4,6-dimethylthieno[3,4-*c*]thiophene (161) as an unstable compound which was characterized as its maleimide adduct <92BCJ2821>.



Scheme 32

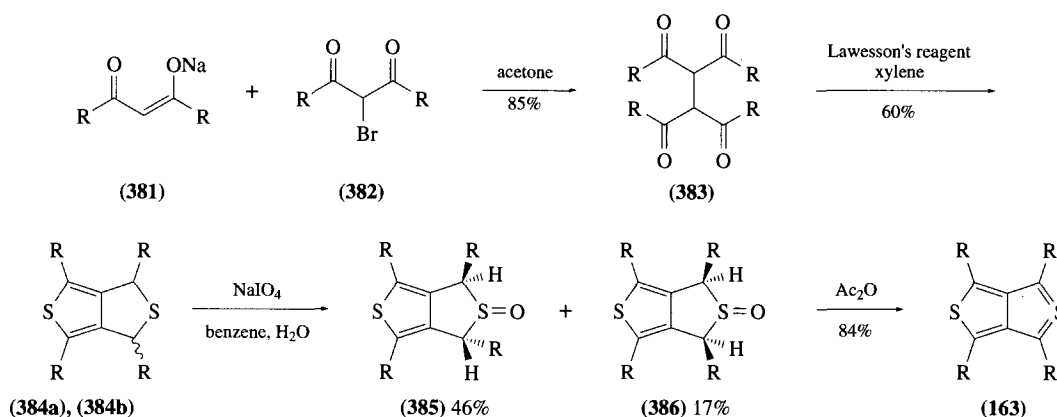
The dimethyl ester of 3,4-dimethyl-2,5-thiophenedicarboxylic acid (377) was converted into 4,6-dicyano-1*H*,3*H*-thieno[3,4-*c*]thiophene (379) via the known intermediate (378) <64JOC1919>. Compound (379) was tetrabrominated photochemically, leading to 4,6-dicyano-1,1,3,3-tetrabromo-1*H*,3*H*-thieno[3,4-*c*]thiophene (380), which lost bromine upon heating in DMF, or with sodium iodide in acetone to give 1,3-dibromo-4,6-dicyanothieno[3,4-*c*]thiophene (164) <94JOC2223> (Scheme 33).



Scheme 33

(ii) Synthesis from acyclic precursors

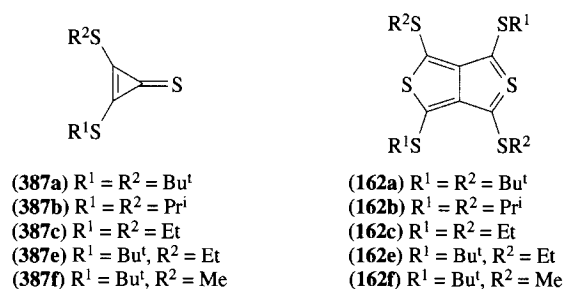
For the synthesis of the 1,3,4,6-tetra-2-thienylthieno[3,4-*c*]thienophene (163), a method which has been used for the tetraphenyl derivative (52) <73JA2561> was applied with a small modification (Scheme 34) <91JOC78>. The reaction of the sodium salt of di-2-thienylmethane (381) and bromodi-2-thienylmethane (382) in acetone gave 1,1,2,2-tetra-2-thienylethane (383). Treatment with Lawesson's reagent <78BSB223, 85T5061> in refluxing xylene yielded two isomeric 1,3-dihydrothieno[3,4-*c*]thiophenes (384a) and (384b). The separation of these isomers was difficult and the mixture was oxidized (NaIO₄) to give the sulfoxides (385) and (386), which were separated by chromatography. Pummerer dehydration of a mixture of the sulfoxides (385) and (386) afforded compound (163; R = 2-thienyl) (Scheme 34).



Scheme 34

(iii) Other methods

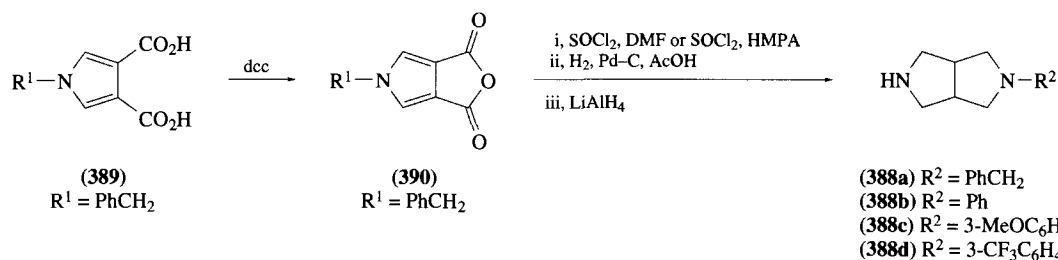
A remarkable dimerization of 2,3-bis(alkylthio)cyclopropenethiones (**387**) in benzene in the presence of tributylphosphine or triphenylphosphine was found to give the 1,3,4,6-tetra-kis(alkylthio)thieno[3,4-*c*]thiophenes (**162**) in yields of 24–68% (85JA5801, 88JHC559). Compounds bearing bulky substituent groups, for example, (**162a**), (**162b**), and (**162e**), are more stable to air. The considerable stability of the derivatives (**162**) to oxygen seems to depend not only on the steric hindrance of alkylthio groups but also on their electronic effect.



7.01.9.4.2 Other systems

(i) Synthesis from pyrrole derivatives

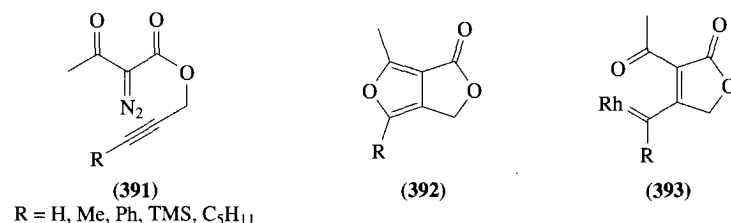
2-Benzyl- (**388a**), 2-phenyl- (**388b**) 2-(3-methoxyphenyl)- (**388c**) and 2-(3-trifluoromethyl-phenyl)octahydropyrrolo[3,4-*c*]pyrrole (**388d**) have been prepared in five steps from 1-benzylpyrrole-3,4-dicarboxylic acid (**389**) through an intermediate anhydride (**390**) (Scheme 35) (83JHC321).



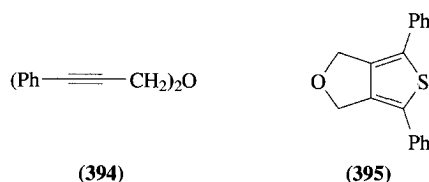
Scheme 35

(ii) Synthesis from acyclic precursors

2-Alkynyl-2-diazo-3-oxobutanoates (**391**) when treated with catalytic amounts of rhodium(II) acetate were found to produce 1,3-dihydrofuro[3,4-*c*]furans (**392**) in good yield. The reaction proceeds by addition of a rhodium-stabilized carbenoid on to the alkynic π bond to give a vinyl carbenoid (**393**) which subsequently cyclizes on to the neighboring carbonyl group to produce the furan ring $\langle 93\text{JOC}21 \rangle$.

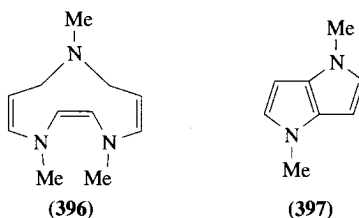


Di(3-phenyl-2-propyn-1-yl)ether (**394**) yielded 4,6-diphenyl-1,3-dihydrothieno[3,4-*c*]furan (**395**) in the presence of equimolar amounts of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ and aliquat-336 $\langle 93\text{PS}(79)87 \rangle$.



7.01.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

It has already been mentioned $\langle 84\text{CHEC-I}(4)1037 \rangle$ that vapor-phase pyrolysis of 1,4,7-trimethyl-1,4,7-triazonine (**396**) yields 1,4-dimethylpyrrolo[3,2-*b*]pyrrole (**397**) with the loss of methylamine.

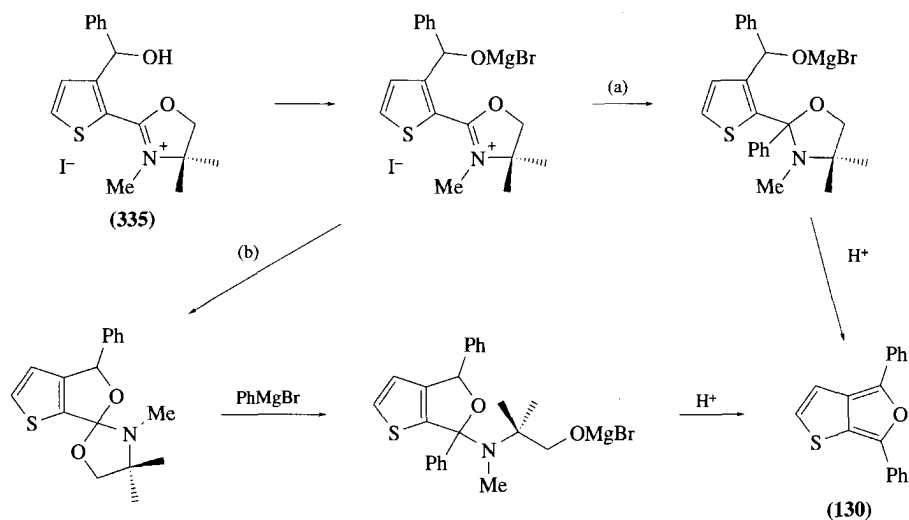


The 4,6-diphenylthieno[2,3-*c*]furan (**130**) has been obtained by reaction of 2-[3-(α -hydroxybenzyl)-2-thienyl]-3,4,4-trimethyl-2-oxazolinium iodide (**335**) with phenylmagnesium bromide. Two possible pathways (a) and (b) have been proposed for the mechanism of this useful reaction (Scheme 36) $\langle 89\text{CB}1119 \rangle$.

7.01.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

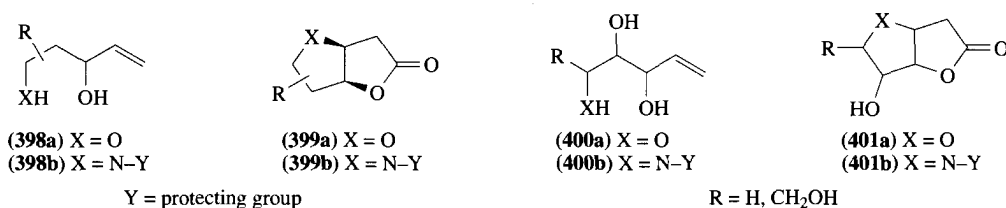
Saturated furofuran and fuopyrrolidine fragments appear in a number of interesting natural products and are versatile intermediates for synthesis. A very powerful process for the construction of stereochemically defined bicycles is palladium(II)-promoted bicyclization of monoalkenes $\langle 90\text{T}3321 \rangle$. Alkene-diols (**398a**) $\langle 85\text{TL}3207, 91\text{JOC}1099 \rangle$ and amino alcohols (**398b**) $\langle 85\text{TL}4479, 88\text{JOC}5731 \rangle$ undergo palladium(II) chloride-catalyzed intramolecular oxygen- or nitrogen-cyclization, respectively, and CO-addition to form corresponding bicycles (**399a**) and (**399b**) with *cis* selectivity.

The applications of this reaction to unprotected optically active $\langle 86\text{AG}(E)87, 87\text{T}2059, 89\text{TL}1517, 91\text{S}769 \rangle$ and carbohydrate-derived alkenitols (**400a**) and aminoalkenitols (**400b**) $\langle 87\text{S}801, 93\text{UP} 701-01 \rangle$ demonstrate that bicyclization to afford furo-2-furanones (anhydroaldonolactones) (**401a**) $\langle 91\text{S}1108 \rangle$



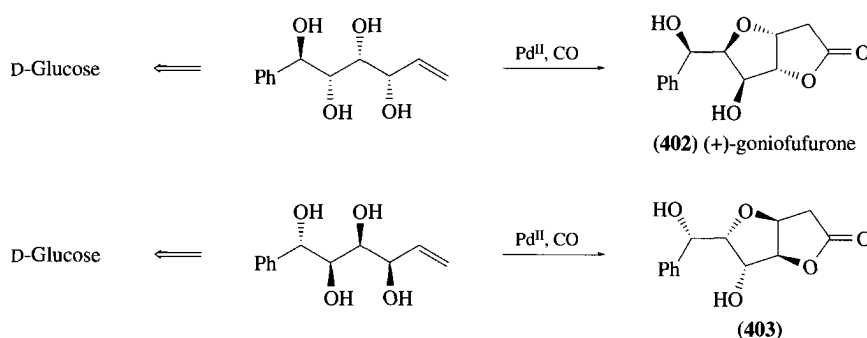
Scheme 36

or furo-2-pyrrolidines (**401b**) <90AG(E)1171, 93UP 701-01> with high *regio*-preference and excellent *threo*-selectivity (concerning the newly formed stereocenter) is the dominating process.



Very simple experimental conditions (palladium(II) chloride (catalyst, 0.1 equivalent) copper(II) chloride (oxidant, 3 equivalents) and sodium acetate (buffer, 3 equivalents) in acetic acid under carbon monoxide at normal pressure and temperature) are necessary for this asymmetric route to saturated fused heterocycles with defined stereochemistry.

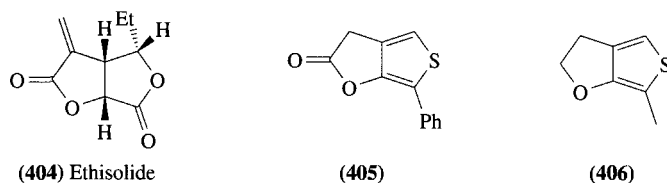
The total synthesis of both enantiomers (**402**) (natural) <94SL1359> and (**403**) (unnatural) <92SL191> of naturally occurring cytotoxic (+)-goniofufurone from D-glucose, using palladium(II)-catalyzed oxycarbonylation as a key step has been reported (Scheme 37).



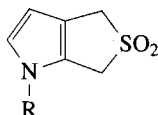
Scheme 37

A total synthesis of the mold metabolite ethisolide <86TL445> (**404**) has been described. Two reduced thieno[3,4-*b*]furan systems have been prepared to test their value as food flavorings (**405**) <70GEP(O)1964803> and as antiinflammatory agents (**406**) <73GEP(O)2238204>.

A short and novel synthetic route toward pyrrolo-3-sulfolene (**189**) and its *N*-mesyl derivative (**407**), precursors for the corresponding pyrrolo *o*-quinodimethanes, has been developed. The syn-

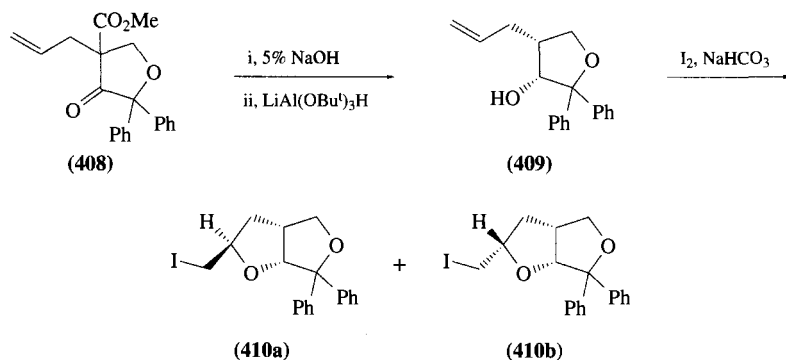


thesis involves ultrasonic zincation of 5-bromo-3-chloro-2-sulfolene and *N*-protected 2-amino-aldehyde, intramolecular conjugate addition, dehydration, and isomerization <93MI 701-01>.



(189) R = H
(407) R = MeSO₂

A facile, one-pot synthesis of an alkylated tetrahydrofuranone intermediate was applied to the synthesis of a novel hexahydrofuro[3,4-*b*]furan derivative <83TL2335>. Reaction of methyl acrylate with methyl sodium benzoate in DMSO gave the intermediate 3-oxo ester carbanion, which was alkylated with allyl bromide to yield the tetrahydrofuranone derivative (408). Subsequent hydrolysis and decarboxylation of (408), followed by reduction with lithium tri-*t*-butoxyaluminum hydride gave compound (409), which with excess iodine and Na₂CO₃ afforded an 85:15 mixture of the epimers (410a) and (410b) in 95% yield (Scheme 38).



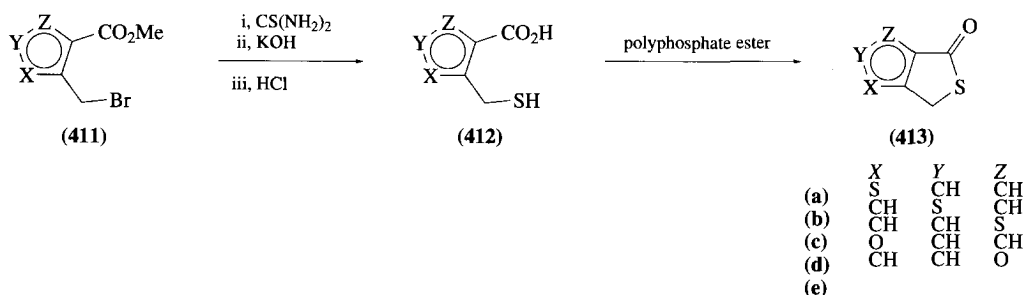
Scheme 38

Thiophene- or furan-2- or -3-carboxylic acids possessing a neighboring thiomethyl group (412) are easily accessible from the corresponding bromomethyl-substituted methyl esters (411) and readily furnish thieno[3,4-*b*]thiophene- or furan-4(6*H*)-ones (413a) and (413d) and thieno[3,4-*b*]thiophene- or furan-4(6*H*)-ones (413c) and (413e) as well as thieno[3,4-*c*]thiophene-1(3*H*)-one (413b) (Scheme 39). The reaction can be effected with polyphosphate esters (PPE) in organic solvents in 75–90% yield <92SC2057>.

7.01.12 IMPORTANT COMPOUNDS AND APPLICATIONS

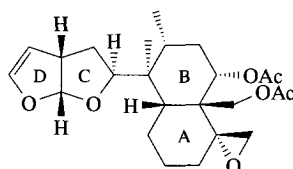
The thieno[2,3-*b*]furan-2-sulfonamides (11), thieno[2,3-*b*]thiophene-2-sulfonamides, and thieno[3,2-*b*]thiophene-2-sulfonamides were prepared and found to be a new class of topically active ocular hypotensive carbonic anhydrase inhibitors <91JMC1805, 92JMC3027>.

The partially hydrogenated furo[2,3-*b*]furan ring is embodied in a large number of natural products, particularly in some antifeeding compounds such as clerodin (414) <86TL3715>. Clerodin type compounds have attracted much interest over the last few years on account of their useful insect antifeedant activity <86RTC513> and challenging structures. Some models of clerodin (414),



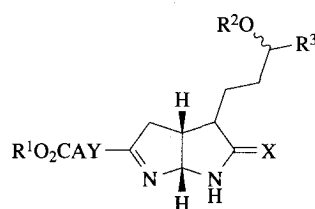
Scheme 39

including either the A/B *trans*-decalin system <83CC503, 86T6519, 89T5595> or the C/D furo[2,3-*b*]furan system <86T489, 86TL3715, 88TL2179, 91T5953, 91TL5957>, have been synthesized. Other approaches are known <84TL3939, 85JOC5167, 85JOC5875, 85TL6465>.



(414) Clerodin

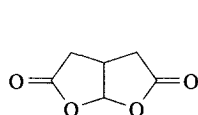
The preparation of hexahydropyrrolo[2,3-*b*]pyrrole derivatives of the general structure (415) as antiulcer agents has been described <92JAP(K)04270283>.



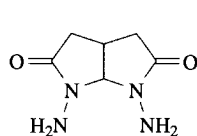
(415)

X = O, S; Y = O, S, SO; A = alkylene; R¹ = H; R² = H, OH, protecting group; R³ = alkyl

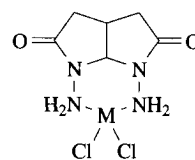
In vitro ICL₅₀, ICT₅₀, and *in vivo* antitumour activities have been determined for the platinum(II) and palladium(II) complexes (418) and (419) of 1,6-diaminotetrahydropyrrolo[2,3-*b*]pyrrole-2,5(1*H*,4*H*)-dione (417) <89JCR(M)631>. Compound (417) can be obtained in 63% yield by slow addition of hexahydrofuro[2,3-*b*]furan-2,5-dione (416) to boiling 80% hydrazine hydrate <93CB2159>.



(416)



(417)



(418) M = Pt
(419) M = Pd

7.02

Bicyclic 5-5 Systems: Three Heteroatoms 1 : 2

VING J. LEE

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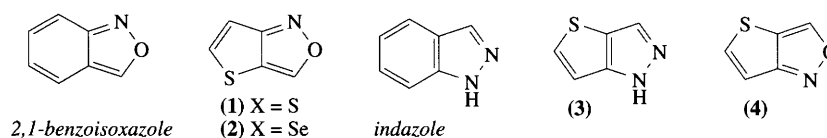
7.02.1 INTRODUCTION

Since the chemistry of the bicyclic [5-5]-heterocycles with 2:1-heteroatom orientation is diverse, there is substantial challenge in assembling a compendium on these heterocycles. This author has attempted to cite key references which are instructive for the reader. Various aspects of the chemistry of these systems were discussed in part in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(4)741, 84CHEC-I(5)32, 84CHEC-I(6)333, 84CHEC-I(6)973, 84CHEC-I(6)1027>. In spite of the topological similarity of many of these heterocycles, their reactivity varies. Further, the diverse reactivity of the fully unsaturated heterocycles compared to their partially (or fully) saturated members has prompted the author to use a modified format for this chapter. For conciseness and continuity, the sections on the synthesis and reactivity of the nonconjugated heterocycles have been combined.

7.02.2 THEORETICAL METHODS

While there are no extensive reports on the relative aromaticity of the heterocycles covered in this chapter, the general reactivity of these systems can be predicted based on first principles. By assuming that these fused systems are comprised of a five-membered π -excessive heterocyclic system and a five-membered π -deficient heterocyclic system, electrophilic agents are expected to react on the π -excessive subunit. *Ab initio* calculations on the thienothiazoles and furothiazoles predicted that electrophilic substitutions should occur exclusively on the furan or thiophene subunit with the regioselectivity being a function of the resonance-stabilization of the reactive intermediates <76KGS1202>. *A priori*, C-H deprotonation by a nonnucleophilic base should occur preferentially on the π -deficient heterocyclic component.

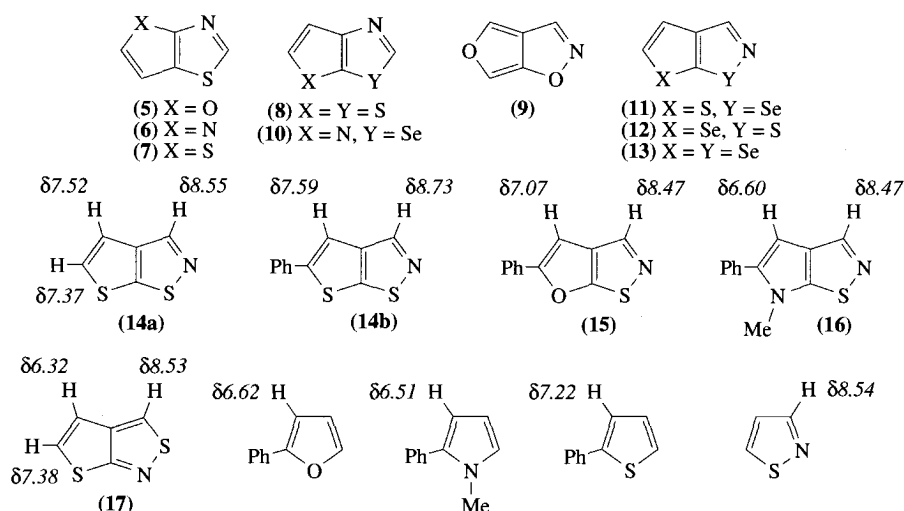
Within a given series of heterocycles, differences in reactivity and stability are found compared to their corresponding benzo analogues (see Section 7.02.5). For example, 2,1-benzisoxazoles are stable in mineral acids, while thieno[3,2-*c*]isoxazoles (1) and selenolo[3,2-*c*]isoxazoles (2) are not. Further, 2,1-benzisoxazoles react with activated methylene synthons to afford quinoline *N*-oxides <67TL2337> whereas compounds (1) and (2) are inert. The isomer distribution from the pH dependent bromination of thieno[3,2-*c*]pyrazole (3) is similar to that found for indazole, while thieno[3,2-*c*]isoxazole (4) is relatively inert <76CSI65, 77CSI1>.



7.02.3 EXPERIMENTAL STRUCTURAL METHODS

No single reference exists which discusses the comparative spectroscopic properties of the heterocycles covered in this chapter. However, extensive ^1H and ^{13}C NMR and UV data on furo[2,3-*d*]thiazoles (5) <86CCC1678>, pyrrolo[2,3-*d*]thiazoles (6) <92JCS(P1)973>, thieno[2,3-*d*]thiazoles (7) <73JPR539, 83JHC113, 88JPR866, 92JCS(P1)973, 92T7689>, thieno[3,2-*d*]thiazoles (8) <78JHC81, 79KGS474, 80BSF(2)151, 90ZC18>, and furo[3,4-*d*]isoxazoles (9) <91CB2481> have been reported. Similarly, ^1H , ^{13}C , and ^{77}S NMR spectral data of pyrrolo[3,2-*d*]selenazoles (10) <79JHC1563>, thieno[3,2-*d*]isoselenazoles (11), selenolo[3,2-*d*]isothiazoles (12), selenolo[3,2-*d*]isoselenazoles (13), thieno[3,2-*d*]isothiazoles (14), and their [2,3-*d*] analogues have been reported <77KGS1495, 80BSB773, 82OMR(19)74>.

The electron-withdrawing effect of the isothiazole unit is evident in the proton chemical shifts of H-3 and H-4 in 5-phenylfuro[3,2-*d*]isothiazole (15), *N*-methyl-5-phenylpyrrolo[3,2-*d*]isothiazole (16), thieno[3,2-*d*]isothiazole (14a), and 5-phenylthieno[3,2-*d*]isothiazole (14b) when compared with the parent monocyclic heterocycles <80BSB773, 85KGS223>. As expected, changing the orientation of the isothiazole subunit (i.e., thieno[2,3-*c*]isothiazole (17)) *vis-à-vis* the thiophene subunit has little effect on the chemical shift of H-4 (see structures (14a) and (17)) <82AJC385>.



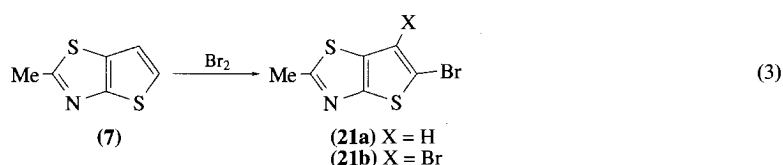
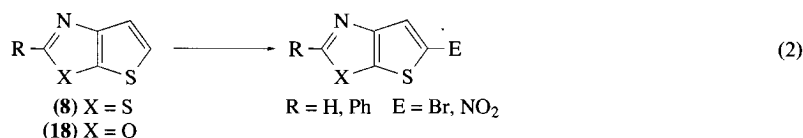
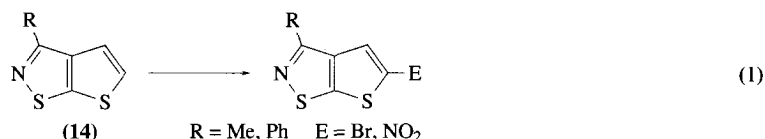
7.02.4 THERMODYNAMIC ASPECTS

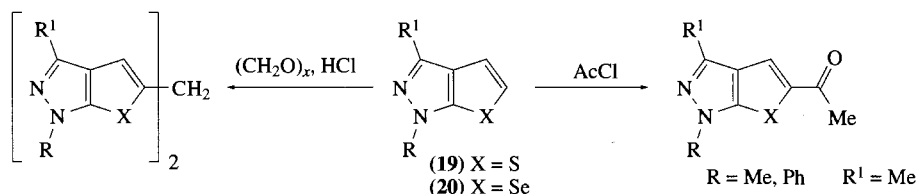
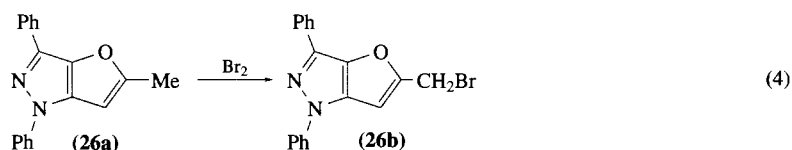
Nothing is known about the relationship between the thermodynamic aspects of these heterocycles and their physicochemical properties (b.p., m.p., volatility, chromatographic behavior).

7.02.5 REACTIVITY OF FULLY CONJUGATED RINGS

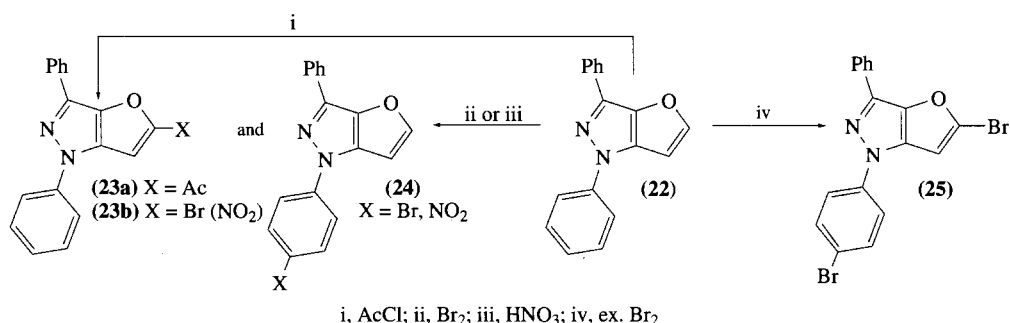
7.02.5.1 Electrophilic Attack on Carbon and Nitrogen

Since these heterocycles are readily obtained from appropriately substituted monocyclic heterocyclic precursors, methods for direct functionalization of the parent heterocycles are rarely required. Electrophilic substitution reactions have been performed on various isomeric systems, but the product distribution varies with the 10π -reactant, the electrophile, and the reaction conditions employed. For example, bromination, nitration, formylation (acylation), or chloromethylation occur exclusively (or preferentially) at C-5 of thieno[3,2-*d*]isothiazoles (**14**) (Equation (1)) <82AJC393, 89AJC1291>, thieno[3,2-*d*]thiazoles (**8**) (Equation (2)) <77CS1, 79KGS474>, thieno[3,2-*d*]oxazoles (**18**) (Equation (2)) <79KGS474>, thieno[2,3-*d*]thiazole (**7**) (Equation (3)) <87KGS410>, and 1,3-disubstituted-1*H*-thieno(selenolo)[2,3-*c*]pyrazoles (**19**) and (**20**) (Scheme 1) <69ZOR1498, 72ZOR1750, 73ZOR2201>. Further bromination of the 5-bromo adduct (**21a**) affords the 5,6-dibromo adduct (**21b**) (Equation (3)). Koshelev and co-workers reported that the relative rates of formylation for 3-methyl-1-phenylthieno[2,3-*c*]pyrazole (**19**; R = Ph, R¹ = Me) compared to thiophene is 0.6:1.0, which is due to the electron-withdrawing effects of the pyrazole nucleus <73ZOR2201>.



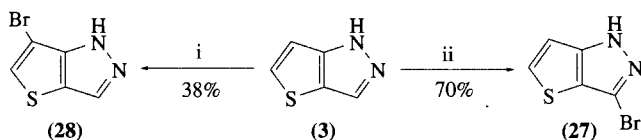


Scheme 1



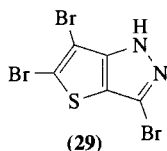
Scheme 2

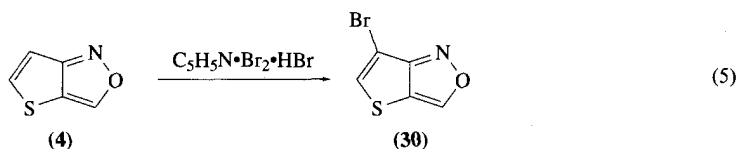
Other subtle electronic effects have also been observed. For example, acylation of 1,3-diphenylfuro[3,2-*c*]pyrazole (**22**) affords 5-acyl adducts (**23a**) while bromination (or nitration) affords mixtures of the 5-substituted adducts (**23b**) and 4'-substituted adducts (**24**) (Scheme 2) <78YZ204>. The 4'-substitution is a result of long-range nitrogen delocalization and excess bromine affords the dibromo product (**25**). Bromination of 5-methyl-1,3-diphenylfuro[3,2-*c*]pyrazole (**26a**) affords the 5-bromomethyl product (**26b**) (Equation (4)) <78YZ264>. In an extreme example, the bromination of thieno[3,2-*c*]pyrazole (**3**) is sensitive to the pH conditions used. For example, bromine–2N sodium hydroxide affords 3-bromothieno[3,2-*c*]pyrazole (**27**), while bromine–sulfuric acid–silver sulfate affords the 6-bromo isomer (**28**) (Scheme 3); excess bromine affords 3,5,6-tribromothieno[3,2-*c*]pyrazole (**29**) <77CS1>. In contrast, exhaustive bromination (pyridinium perbromide hydrobromide) of thieno[3,2-*c*]isoxazole (**4**) affords exclusively 6-bromothieno[3,2-*c*]isoxazole (**30**) (Equation (5)) <76CS165>. These results infer that the thieno[3,2-*c*]pyrazoles are more reactive than the thieno[3,2-*c*]isoxazoles. The order of site reactivity parallels data from NMR studies in D₂SO₄ (ambient temperature) in which H-6 undergoes instantaneous deuterium exchange in compound (**3**) while there was only ca. 50% exchange after two weeks for compound (**4**) <77CS1>.



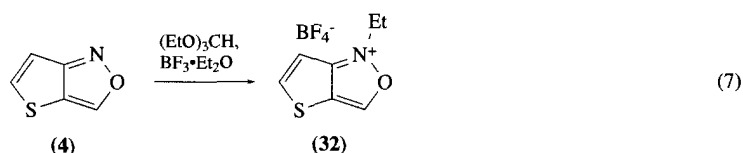
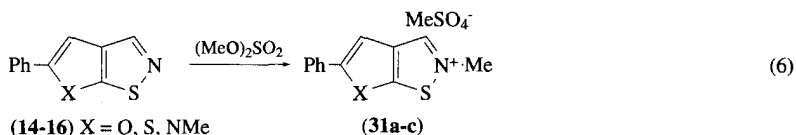
i, Br₂, H₂SO₄, Ag₂SO₄; ii, Br₂, NaOH

Scheme 3



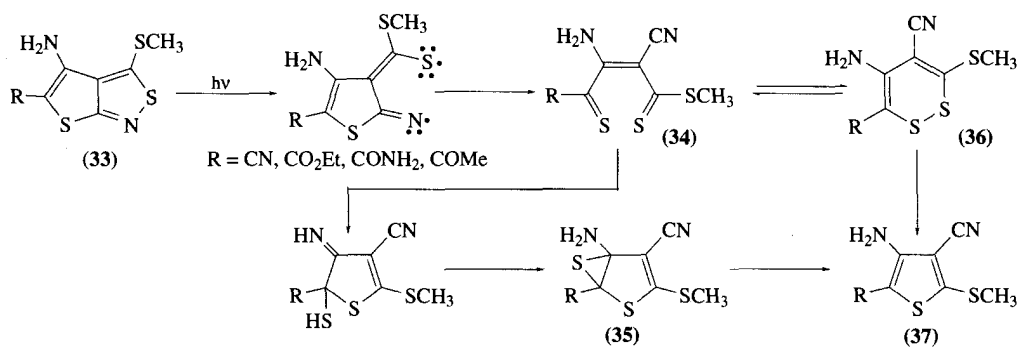


Direct alkylation has been reported for thieno[3,2-*c*]isoxazole (**4**) and 5-phenylfuro(pyrrolo or thieno)[3,2-*d*]isothiazoles (**14**)–(**16**) to afford the hydrolytically sensitive *N*-methyloisothiazolium salts (**31**) (Equation (6)) <85KGS223> and *N*-alkylisoxazolium salt (**32**) (Equation (7)) <76CS165>. In contrast, thieno[2,3-*c*]isothiazole (**17**) is a weak base and does not react with alkyl halides <82AJC385>.



7.02.5.2 Photochemistry and Thermolysis

Few examples of photochemical transformations of the 10π heterocycles in this series have been reported. Notable is the conversion of thieno[2,3-*c*]isothiazoles (**33**) to thiophenes (**37**) by homolytic cleavage of the nitrogen–sulfur bond (Scheme 4). The enedithione (**34**) which arises from the initial diradical may undergo (a) cyclization via the bicyclic thiirane (**35**) or (b) electrocyclization to the 1,2-dithiine (**36**) <88H(27)2539>. Since similar rearrangements do not occur with isothiazoles, benzoisothiazoles, or the isomeric thieno[3,2-*d*]isothiazoles, this unique transformation is a direct consequence of the thieno[2,3-*c*]annellation. However, substituent effects on the efficiency of the transformation have not been explored.

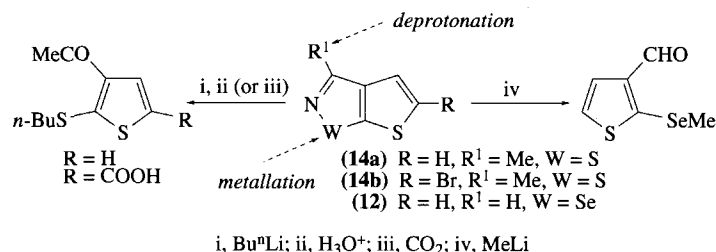


Scheme 4

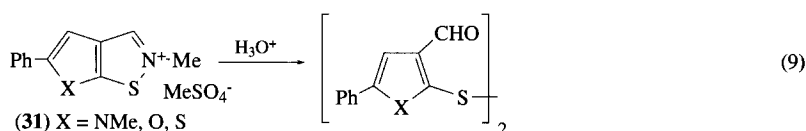
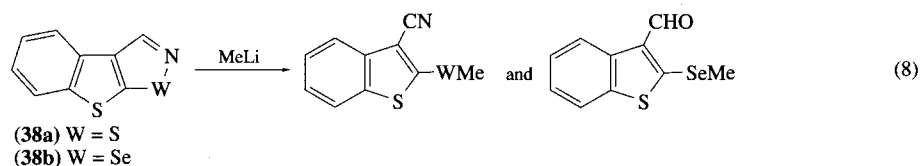
7.02.5.3 Metallation

Few examples of metallation reactions of these heterocycles have been reported. Notable are the bimodal reactions of organolithiums with thieno[3,2-*d*]isothiazoles (**14**) and thieno[3,2-*d*]isoseleazoles (**12**) which occur with (a) nucleophilic attack on the nitrogen–sulfur or nitrogen–selenium bond, and/or (b) deprotonation at C-3 (nitrile formation) (Scheme 5) <82AJC393, 83BSB53, 89AJC1291>. The rate of bond cleavage is influenced by the relative strength of the nitrogen–sulfur bond compared to the nitrogen–selenium bond. Since the isothiazole and isoseleazole nucleus is highly electron-

withdrawing, the electrophilicity of H-3 towards strong bases is enhanced. The presence of C-3 substituents precludes the deprotonation pathway and ensures nucleophilic attack. With the benzo-fused analogues (**38**), the acidity of C(3)—H is further enhanced (Equation (8)). The enhanced electrophilicity of C-3 is also evident in the hydrolytic instability of the *N*-methylisothiazolium salts (**31**) (Equation (9)) <85KGS223>.

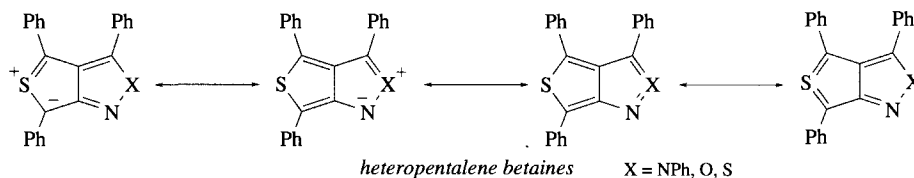


Scheme 5

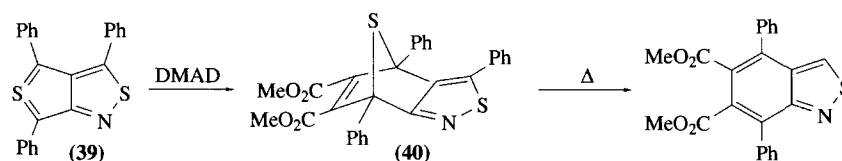


7.02.5.4 Cycloadditions and Dipole-mediated Transformations

Several of the 10 π heterocycles (e.g., thieno[3,4-*c*]isothiazole (**39**), thieno[3,4-*c*]pyrazoles (**41**)) in this chapter are also referred to in the literature as mesomeric heteropentalene betaines of type A. They cannot be represented by a classical, noncharge separated structure and have an appreciable dipolar character due to contribution of a hypervalent heteroatom (Scheme 6). These heterocycles react exclusively as thiocarbonyl ylides in [3 + 2] cycloadditions with dipolarophiles to afford initially 7-heterabicyclo[2.2.1]heptanes (or heptenes) (**40**), (**42**), which in some cases undergo aromatization under more forcing conditions (Schemes 7 and 8) <74JA4276, 74TL2163, 79CB260, 79CB266, 80JOC90, 88CB95>. The pyrrolo[3',4':2,3]pyrazolo[1,5-*a*]pyridine (**43**) and thieno[3',4':2,3]pyrazolo[1,5-*a*]pyridine (**44**) show similar reactivity (Scheme 9) <79JOC622>.

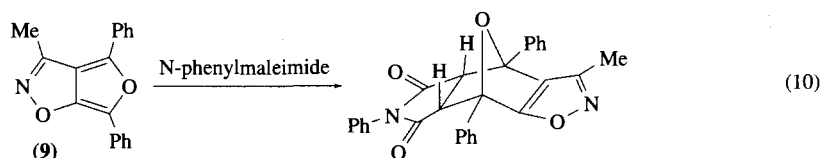
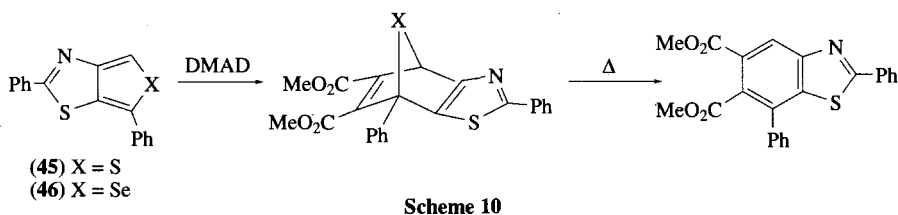
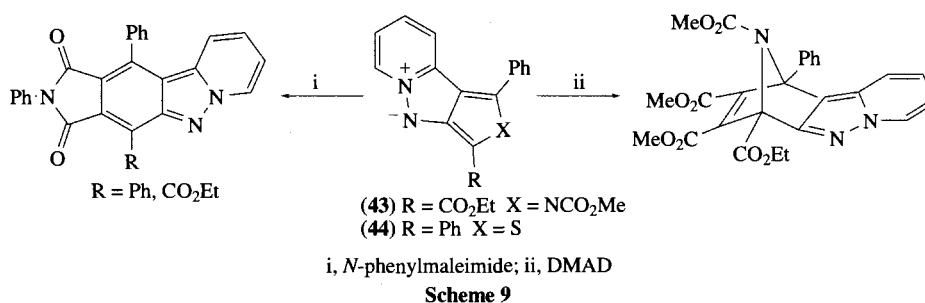
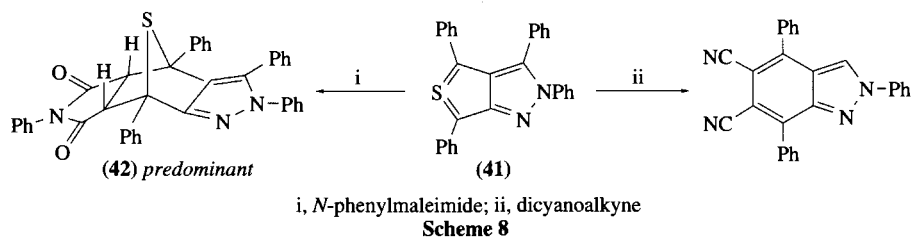


Scheme 6



Scheme 7

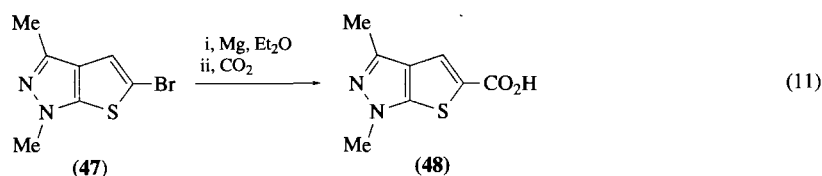
The isomeric thieno[3,4-*d*]thiazoles (**45**), selenolo[3,4-*d*]thiazoles (**46**), and furo[3,4-*d*]isoxazoles (**9**), which show diene character, participate in Diels–Alder reactions (Scheme 10 and Equation (10)), <78JHC1455, 91CB2481>.



7.02.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.02.6.1 Metal–Halogen Exchange

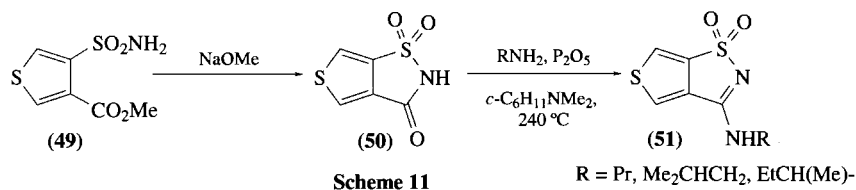
Metal–halogen exchange has been reported to occur with no complications for a few halides of these heterocycles. For example, the bromothiopyrazole (**47**) was converted to the thienopyrazole carboxylic acid (**48**) via the Grignard reagent (Equation (11)) <73ZOR2201>.



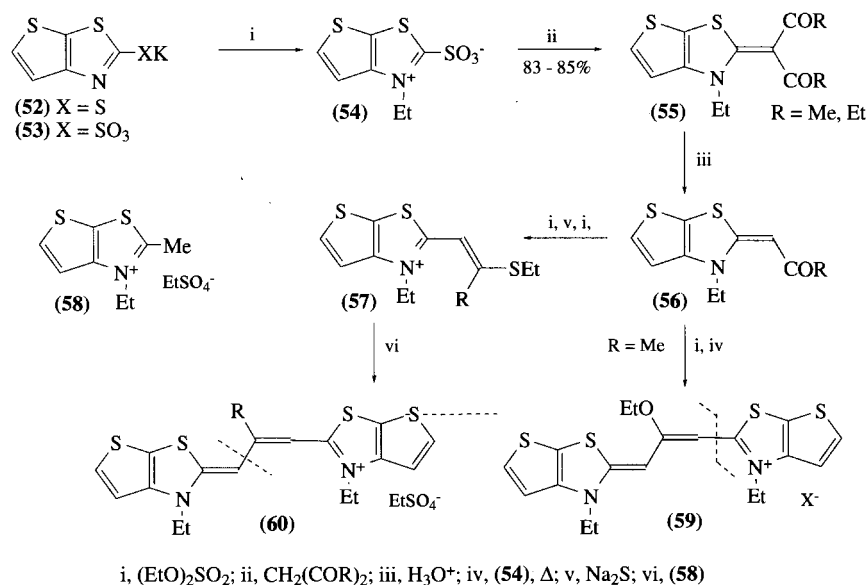
7.02.6.2 Direct Substitution

Few examples of substitution reactions on intact heterocycles have been reported. Notable is the synthesis of 3-aminothieno[3,4-*d*]isothiazole 1,1-dioxides (**51**) by the fusion of thieno[3,4-*d*]iso-

thiazolin-3-one 1,1-dioxide (**50**) with primary (or secondary) amine hydrochlorides and a mixture of phosphorus pentoxide and *N,N*-dimethylcyclohexylamine (Scheme 11) <80JOC617>. The isothiazolin-3-one (**50**) is readily obtained from the 3-methoxycarbonyl sulfonamide (**49**) in the presence of sodium methoxide.



Another notable example is the chemistry of the 2-sulfo-3-alkyl[3,2-*d*]thiazolium betaines (**54**) which are obtained in two steps from potassium thieno[3,2-*d*]thiazole-2-thiolate (**52**). Potassium permanganate oxidation of compound (**52**) affords the sulfonate (**53**) which on subsequent *N*-alkylation affords the betaine (**54**). These react with 1,3-diketones to afford 2-acylmethylene-3-ethylthieno[3,2-*d*]thiazolines (**56**) which are further converted to the ethoxycarbocyanines (**59**) using intermediate (**54**) (Scheme 12) <74DOK(219)870>. Alternatively, the 2-(ethylthiovinyl)thieno[3,2-*d*]thiazolium salt (**57**) is coupled with the 2-methylthieno[3,2-*d*]thiazolium salt (**58**) to give the carbocyanine (**60**).



Scheme 12

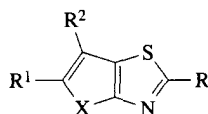
7.02.7 RING SYNTHESIS OF FULLY CONJUGATED SYSTEMS

The synthetic approaches to these systems are discussed and exemplified in the following sections and a compilation of known derivatives is given in Tables 1–14.

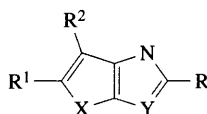
7.02.7.1 Annulations onto π -Excessive Heterocycles

7.02.7.1.1 Oxidative [5 + 0] and [4 + 1] cycloamination

This approach is used exclusively for the synthesis of the isomeric annelated isothiazoles and isoselenazoles. The first reported example was the phosphorus pentasulfide-mediated cyclization of α -ketoester (**61**) to the thieno[2,3-*c*]isothiazole (**17**) (Scheme 13) <82AJC385>. A wide variety of oxidative cyclization conditions, some including an amination step, have been employed for the

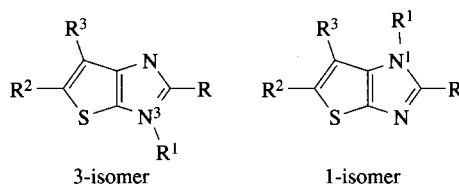
Table 1 Thieno[2,3-*d*]thiazoles (*X* = S), furo[2,3-*d*]thiazoles (*X* = O), selenolo[2,3-*d*]thiazoles (*X* = Se).

No.	R	R ¹	R ²	X	m.p. (°C)	Ref.
1	H	H	H	S	air unstable	83JHC113
2	Me	H	H	S	78°/13 mm	83JHC113
3	NH ₂	H	H	S	103–104°	83JHC113
4	CH ₃ CONH	H	H	S	272°	83JHC113
5	SH	H	H	S	170–171°	76KGS1355
6	SH	C ₆ H ₅	H	S	210–212°	79KGS477
7	SEt	C ₆ H ₅	H	S	160–165°/2 mm	79KGS477
8	-S) ₂	C ₆ H ₅	H	S	194–195°	79KGS477
9	SO ₃ K	C ₆ H ₅	H	S	> 300°	79KGS477
10	SO ₃ H	C ₆ H ₅	H	S	256–266°	79KGS477
11	OH	C ₆ H ₅	H	S	166–167°	79KGS477
12	Me	C ₆ H ₅	H	S	118–119°	70KGS1624
13	Me	4-MeOC ₆ H ₄	H	S	123–124° (180–200°/3 mm)	87KGS410
14	SH	CH=CH—CH=CH		S	233–235°	75KGS1607
15	Me	CH=CH—S		S	111–112°	76KGS1039
16	Me	CH=CH—CH=CH		S	85–86°	77KGS1495
17	Me	CH ₂ CH ₂ CH ₂ CH ₂		S	35–36°	87KGS410
18	Me	Br	H	S	89–90°	87KGS410
19	Me	Br	Br	S		87KGS410
20	NH ₂	Me	Me	S	187–188°	74KGS1204
21	CH ₃ CONH	Me	Me	S	281.5–282.5°	74KGS1204
22	C ₆ H ₅ CONH	Me	Me	S	239.5–240.0°	74KGS1204
23	NH ₂	CH ₂ CH ₂ CH ₂ CH ₂		S	169–170°	74KGS1204
24	CH ₃ CONH	CH ₂ CH ₂ CH ₂ CH ₂		S	271.5–273.0°	74KGS1204
25	C ₆ H ₅ CONH	CH ₂ CH ₂ CH ₂ CH ₂		S	185–186.0°	74KGS1204
26	H	CO ₂ Et	H	S	71–72°	92JCS(P1)973
27	Me	CO ₂ Et	H	S	102–103°	88JPR866
28	Me	CO ₂ Et	Me	S	90–91°	88JPR866
29	H	CO ₂ Et	NH ₂	S	159–160°	80JCS(P1)1029
30	H	CO ₂ Et	NHCHO	S	147–148°	80JCS(P1)1029
31	Me	CO ₂ Et	C ₆ H ₅	S	110–111°	88JPR866
32	Me	CO ₂ Et	4-Me ₂ NC ₆ H ₄	S	163–165°	88JPR866
33	Cl	CO ₂ Et	NH ₂	S	181–182°	80JCS(P1)1029
34	HS	CO ₂ Et	Me	S	196–198°	88JPR866
35	MeS	CO ₂ Et	Me	S	84–85°	88JPR866
36	H	CO ₂ H	H	S	155–156°	92JCS(P1)973
37	H	CONH ₂	NH ₂	S	134–135°	80JCS(P1)1029
38	SMe	CONH ₂	NH ₂	S	235–236°	80JCS(P1)1029
39	OPr ⁱ	CONH ₂	NH ₂	S	106–107°	80JCS(P1)1029
40	NH ₂	Me	H	S	118–120°	73JPR539
41	NH ₂	C ₆ H ₅	H	S	205–208°	73JPR539
42	NH ₂	CH=CH—CH=CH		S	238–240°	73JPR539
43	NH ₂	CH ₂ CH ₂ CH ₂ CH ₂		S	153–158°	73JPR539
44	NH ₂	CO ₂ Et	Me	S	255–257°	73JPR539
45	Me ₂ N	CO ₂ Et	H	S	117–118°	92JCS(P1)973
46	CH ₃ CONH	Me	H	S	280–282°	73JPR539
47	CH ₃ CONH	C ₆ H ₅	H	S	330–332°	73JPR539
48	CH ₃ CONH	CO ₂ Et	Me	S	237–238°	73JPR539
49	4-Me ₂ NC ₆ H ₄ N=N	CO ₂ Et	Me	S	243–245°	73JPR539
50	Me	CH=CH—CH=CH		O	51–52°	77KGS1495
51	C ₆ H ₅ CONH	CO ₂ Me	H	O	273–275°	86CCCC1678
52	C ₆ H ₅ CONH	CO ₂ Bu ⁿ	H	O	177–178°	86CCCC1678
53	CH ₃ CONH	CO ₂ Me	H	O	270° (dec)	86CCCC1678
54	CH ₃ CONH	CO ₂ Bu ⁿ	H	O	156–157°	86CCCC1678
55	2-furoylNH	CO ₂ Me	H	O	271–273°	86CCCC1678
56	2-furoylNH	CO ₂ Bu ⁿ	H	O	189–190°	86CCCC1678
57	C ₆ H ₅ CONH	CO ₂ H	H	O	250° (dec)	86CCCC1678
58	CH ₃ CONH	CO ₂ H	H	O	230° (dec)	86CCCC1678
59	2-furoylNH	CO ₂ H	H	O	260° (dec)	86CCCC1678
60	Me	H	H	Se	107–110°/7 mm	77KGS1495
61	Me	CH=CH—CH=CH		Se	73–74°	71KGS37
62	NH ₂	H	H	Se	115–116°	83JHC113

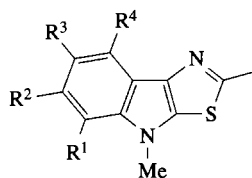
Table 2 Thieno[3,2-*d*]thiazoles ($X = Y = S$), thieno[2,3-*d*]oxazoles ($X = S$, $Y = O$), pyrrolo[3,2-*d*]thiazoles ($X = N$, $Y = S$), pyrrolo[3,2-*d*]selenazoles ($X = N$, $Y = Se$), and selenolo[3,2-*d*]thiazoles ($X = Se$, $Y = S$).

No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	H	H	H	S	S	64–75° 75–85°/1 mm	90ZC18, 78JHC81
2	Me	H	H	S	S	35–36°	90ZC18
3	C ₆ H ₅	H	H	S	S	150–151°	79KGS474
4	Cl	H	H	S	S	NA	80BSF(2)151
5	H	Br	H	S	S	122–123°	78JHC81
6	H	NO ₂	H	S	S	ca. 200°	78JHC81
7	NH ₂	H	H	S	S	107.0–107.5°	78JHC81
8	C ₆ H ₅ CONH	H	H	S	S	218–218.5°	78JHC81
9	MeCONH	H	H	S	S	214.5–215.5°	78JHC81
10	EtO ₂ CNH	H	H	S	S	215°	78JHC81
11	OH	H	H	S	S	144–145°	79KGS477
12	SH	H	H	S	S	194–195°	79KGS477
13	S ₂	H	H	S	S	175–176°	79KGS477
14	SEt	H	H	S	S	34–35° (163–165°/8–10 mm)	79KGS477
15	SO ₃ H	H	H	S	S	235–236°	79KGS477
16	SH	CH=CH–CH=CH	H	S	S	239–240°	76KGS1355
17	C ₆ H ₅	CO ₂ H	H	S	S	269–271°	79KGS474
18	C ₆ H ₅	HCO	H	S	S	174–175°	79KGS474
19	MeS	C ₆ H ₅ CO	OH	S	S	135°	90ZC18
20	MeS	CO ₂ Me	OH	S	S	152–154°	90ZC18
21	MeS	CN	OH	S	S	210°	90ZC18
22	Me	CO ₂ Et	Me	S	S	127–130°	80JCS(P1)1029
23	Me	OCCH(CO ₂ Et)SCH ₂	H	S	S	136–138°	80JCS(P1)1029
24	CH ₃ CONH	MeO ₂ C	H	S	S	273–275°	78JHC81
25	CH ₃ CONH	H	H	Se	S	249°	80BSF(2)151
26	NH ₂	H	H	Se	S	118°	80BSF(2)151
27	C ₆ H ₅	H	H	S	O	106–107°	79KGS474
28	C ₆ H ₅	CO ₂ H	H	S	O	259–260°	79KGS474
29	C ₆ H ₅	CO ₂ Me	H	S	O	188–190°	79KGS474
30	H	CO ₂ Et	H	NH	S	136–138°	79JHC1563
31	CH ₃	CO ₂ Et	H	NH	S	217–219°	79JHC1563
32	C ₆ H ₅	CO ₂ Et	H	NH	S	175–176°	79JHC1563
33	Me	H	H	S	Se	110–115°/2 mm	90ZC18
34	C ₆ H ₅	CO ₂ Et	H	NH	Se	182–184°	79JHC1563
35	4-BrC ₆ H ₄	CO ₂ Et	H	NH	Se	235–237°	79JHC1563
36	4-ClC ₆ H ₄	CO ₂ Et	H	NH	Se	220–222°	79JHC1563
37	3-MeC ₆ H ₄	CO ₂ Et	H	NH	Se	184–186°	79JHC1563
38	4-MeOC ₆ H ₄	CO ₂ Et	H	NH	Se	181–182°	79JHC1563
39	2-thienyl	CO ₂ Et	H	NH	Se	187–190°	79JHC1563
40	C ₆ H ₅ CONH	CO ₂ Et	H	NH	S	> 300° (dec.)	79CS78
41	C ₆ H ₅ CONH	CO ₂ Et	H	NMe	S	231.5–232.5°	79CS78
42	EtO ₂ CNH	CO ₂ Et	H	NMe	S	238–240°	79CS78
43	EtO ₂ CNH	CO ₂ Me	H	NMe	S	> 250°	79CS78
44	CH ₃ CONH	CO ₂ Me	H	NMe	S	> 250°	79CS78
45	NH ₂	CO ₂ Et	H	NMe	S	189–192°	79CS78
46	C ₆ H ₅ CONH	CO ₂ H	H	NH	S	> 250°	79CS78
47	C ₆ H ₅ CONH	CO ₂ H	H	NMe	S	235–240°	79CS78
48	EtO ₂ CNH	CO ₂ H	H	NMe	S	> 250°	79CS78
49	EtO ₂ CNH	H	H	NMe	S	200–201° (dec.)	79CS78
50	EtO ₂ CNH	H	NO ₂	NMe	S	> 240°	79CS78
51	EtO ₂ CNH	Br	NO ₂	NMe	S	> 240°	79CS78

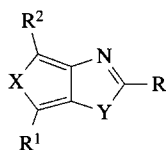
formation of the nitrogen–sulfur bond as shown for the transformation of ketone (**62**) to thieno[3,2-*d*]isothiazole (**8**) with chloramine–sodium hydroxide (Equation (12)) <80JCS(P1)1029>. Hydrogen peroxide–pyridine was employed for the transformation of thioamide (**63**) to the 3-aminothieno[2,3-*c*]isothiazole (**64**) (Equation (13)) <73JPR539, 79LA1271>. The acetal (**65**) and chloroaldehyde (**66**) were

Table 3 1*H*-Thieno[2,3-*d*]imidazoles and 3*H*-thieno[2,3-*d*]imidazoles.

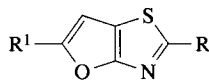
No.	R	R ¹	R ²	R ³	m.p. (°C)	Ref.
1	H	H	CH=CH—CH=CH		193.0–195.0°	86JHC951
2	H	H	N=CH—CH=CH		209.0–210.0°	84JHC587
3	H	H	N=CH—CH=CH		320.0–322.0°	84JHC587
4	H	N(3)–C ₆ H ₅	H	H	102.0–103.0°	77ZOR232
5	H	N(3)–C ₆ H ₅	CHO	H	149°	77ZOR232
6	H	N(3)–C ₆ H ₅	CO ₂ H	H		77ZOR232
7	H	N(3)–Tr	CO ₂ Et	H	yellow oil	87JCS(P1)1457
8	H	N(3)–Tr	CO ₂ Et	NH ₂	203–204°	87JCS(P1)1457
9	H	N(1)–Bn	CO ₂ Et	H	98–100°	87JCS(P1)1457
10	H	N(1)–PMB	CO ₂ Et	H	84–85°	87JCS(P1)1457
11	H	N(1)–DMB	CO ₂ Et	H	unstable	87JCS(P1)1457
12	Me	N(3)–Me	H	H	80.0–81.0°	79JCR(S)96
13	Me	N(1)– <i>c</i> -C ₆ H ₁₁	CO ₂ Me	H		87JCS(P1)1457
14	Me	H	CH=CH—CH=CH		234–235°	70KGS1473
15	Me	H	N=C(Me)—CH=C(Me)		324–326° (HCl)	
16	Me	H	N=C(Me)—CH=C(Me)		244–245°	84JHC587
17	C ₆ H ₅	H	CH=CH—CH=CH		280–281°	84JHC587
18	C ₆ H ₅	N(3)–OH	CH=CH—CH=CH		189–190°	76JCS(P1)80
19	PEB	N(3)–CH ₂ CONEt ₂	H	H	149–151°	76JCS(P1)80
20	PEB	N(3)–CH ₂ CONEt ₂	Et	H	118–119°	79AP(312)845
21	MeO	H	H	H	95–96°	79AP(312)845
22	MeO	N(3)–COCH ₃	H	H	192–195°	79JCR(S)96
23	MeO	N(1)–COCH ₃	H	H	127–129°	79JCR(S)96
24	SMe	N(1)–CH ₂ OEt	CO ₂ Et	H	133–135°	79JCR(S)96
25	SBn	N(1)–CH ₂ OMe	CO ₂ Et	H	70°	87JCS(P1)1457
26	SBn	N(1)–Bn	CO ₂ Et	H	83–84°	87JCS(P1)1457
27	SC ₆ H ₅	N(1)–Bn	CO ₂ Et	H	136–138°	87JCS(P1)1457
					73–75°	87JCS(P1)1457

PMB = 4-MeOC₆H₄CH₂; PEB = 4-EtOC₆H₄CH₂; DMB = 3,4-(MeO)₂C₆H₃.**Table 4** Indolo[3,2-*d*]thiazoles.

No.	R ¹	R ²	R ³	R ⁴	Yield (%)	m.p. (°C)	Ref.
1	H	H	Me	H	52	80–82°	87KGS410
2	H	H	H	Me	41	82–83°	87KGS410
3	H	Me	H	H	40	55–56°	87KGS410
4	Me	H	H	H	45	89–90°	87KGS410
5	H	H	Br	H	52	113–114°	87KGS410
6	Cl	H	Cl	H	45	149–150°	87KGS410
7	Br	H	Br	H	71	161–162°	87KGS410

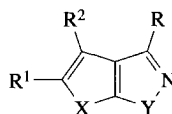
Table 5 Thieno[3,4-*d*]thiazoles ($X = Y = S$), thieno[3,4-*d*]selenazole ($X = S, Y = Se$), selenazolo[3,4-*d*]thiazole ($X = Se, Y = S$), selenazolo[3,4-*d*]selenazole ($X = Y = Se$), thieno[3,4-*d*]imidazoles ($X = S, Y = N$).

No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	Me	Me	H	S	S	79–80°	89JHC709
2	H	C ₆ H ₅	H	S	S	126–128°	78JHC1455
3	H	4-MeOC ₆ H ₄	H	S	S	56–58°	78JHC1455
4	C ₆ H ₅	Me	H	S	S	81–82°	89JHC709
5	C ₆ H ₅	C ₆ H ₅	H	S	S	127–128°	78JHC1455
6	C ₆ H ₅	4-MeOC ₆ H ₄	H	S	S	132–133°	78JHC1455
7	C ₆ H ₅	4-MeSC ₆ H ₄	H	S	S	128–129°	78JHC1455
8	NH ₂	4-NO ₂ C ₆ H ₄	2-benzoxazolyl	S	S	323°	91JHC1449
9	Me	4-NO ₂ C ₆ H ₄	2-benzoxazolyl	S	S	>360°	91JHC1449
10	C ₆ H ₅	Me	H	S	Se	89–90°	89JHC709
11	C ₆ H ₅	Me	H	Se	Se	79–80°	89JHC709
12	H	C ₆ H ₅	H	Se	S	99–100°	78JHC1455
13	H	4-MeOC ₆ H ₄	H	Se	S	82–84°	78JHC1455
14	Me	Me	H	Se	S	83–84°	89JHC709
15	C ₆ H ₅	Me	H	Se	S	86–87°	89JHC709
16	C ₆ H ₅	C ₆ H ₅	H	Se	S	142–143°	78JHC1455
17	C ₆ H ₅	4-MeOC ₆ H ₄	H	Se	S	134–135°	78JHC1455
18	C ₆ H ₅	4-MeSC ₆ H ₄	H	Se	S	141–144°	78JHC1455
19	C ₆ H ₅ CHOH	C ₆ H ₅	CO ₂ CH ₃	S	NH	174–176°	76MC299
20	C ₆ H ₅ CHOH	C ₆ H ₅	CO ₂ H	S	NH	190–192°	76MC299
21	C ₆ H ₅ CO	C ₆ H ₅	CO ₂ CH ₃	S	NH	218–219°	76MC299
22	C ₆ H ₅ CH ₂	C ₆ H ₅	CO ₂ CH ₃	S	NH	163–164°	76MC299
23	C ₆ H ₅	C ₆ H ₅	CO ₂ CH ₃	S	NH	184–186°	76MC299
24	C ₆ H ₅	C ₆ H ₅	CO ₂ CH ₃	S	NHBn	148–150°	76MC299

Table 6 Furo[2,3-*d*]thiazoles.

No.	R	R ¹	m.p. (°C)	Ref.
1	C ₆ H ₅ CONH	CO ₂ CH ₃	273–275°	86CCC1678
2	C ₆ H ₅ CONH	CO ₂ Bu ⁿ	177–178°	86CCC1678
3	CH ₃ CONH	CO ₂ CH ₃	270°(dec.)	86CCC1678
4	CH ₃ CONH	CO ₂ Bu ⁿ	156–157°	86CCC1678
5	2-furoylNH	CO ₂ CH ₃	271–273°	86CCC1678
6	2-furoylNH	CO ₂ Bu ⁿ	189–190°	86CCC1678
7	C ₆ H ₅ CONH	CO ₂ H	250°	86CCC1678
8	CH ₃ CONH	CO ₂ H	230°	86CCC1678
9	2-furoylNH	CO ₂ H	260°	86CCC1678
10	C ₆ H ₅ CONH	CO ₂ Et	264–265°	77CS199
11	EtO ₂ CNH	CO ₂ Et	235–238°	77CS199
12	2-thienylNH	CO ₂ Et	269–270°	77CS199
13	2-furoylNH	CO ₂ Et	230–231°	77CS199
14	C ₆ H ₅ CONH	CO ₂ H	>250°	77CS199
15	EtO ₂ CNH	CO ₂ H	>250°	77CS199

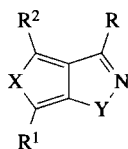
Table 7 Thieno[3,2-*d*]isothiazoles ($X = Y = S$), thieno[3,2-*d*]isoseelenazoles ($X = S$, $Y = Se$), furo[3,2-*d*]isothiazole ($X = O$, $Y = S$), pyrrolo[3,2-*d*]isothiazole ($X = N$, $Y = S$), selenolo[3,2-*d*]isothiazoles ($X = Se$, $Y = S$).



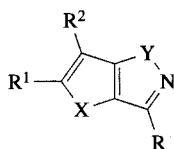
No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	H	H	H	S	S	45°	89AJC1291
2	H	Br	H	S	S	92°	80LA768
3	H	Me	H	S	S	96–98°/5 mm	80JCS(P1)1029
4	H	Me	CO ₂ Et	S	S	70–71°	80JCS(P1)1029
5	H	C ₆ H ₅	H	S	S	160–161°	78KGS561
6	H	CO ₂ Et	H	S	S	97–98°	80JCS(P1)1029
7	H	CO ₂ H	H	S	S	234–235°	80JCS(P1)1029
8	Me	CO ₂ Et	Me	S	S	97–98°	80JCS(P1)1029
9	Me	CO ₂ H	Me	S	S	230° (dec.)	80JCS(P1)1029
10	Me	H	Me	S	S	113–114°	80JCS(P1)1029
11	Me	H	H	S	S	90–92°/1 mm	80JCS(P1)1029
12	SMe	CO ₂ Et	NH ₂	S	S	170–171°	80JCS(P1)1029
13	C ₆ H ₅	CO ₂ Et	NH ₂	S	S	124°	89AJC1291
14	C ₆ H ₅	CO ₂ Et	H	S	S	128–129°	89AJC1291
15	C ₆ H ₅	CO ₂ H	H	S	S	268–270°	89AJC1291
16	C ₆ H ₅	CONH ₂	H	S	S	228°	89AJC1291
17	C ₆ H ₅	COMe	NH ₂	S	S	171°	89AJC1291
18	C ₆ H ₅	COMe	H	S	S	163–164°	89AJC1291
19	C ₆ H ₅	CO ₂ H	NH ₂	S	S	142°	89AJC1291
20	C ₆ H ₅	H	NH ₂	S	S	74°	89AJC1291
21	C ₆ H ₅	H	NHCOCF ₃	S	S	169°	89AJC1291
22	C ₆ H ₅	H	NHCHO	S	S	188–189°	89AJC1291
23	C ₆ H ₅	H	NHCOMe	S	S	171–172°	89AJC1291
24	C ₆ H ₅	Br	NHCOCF ₃	S	S	184–185°	89AJC1291
25	C ₆ H ₅	Br	NH ₂	S	S	116–117°	89AJC1291
26	C ₆ H ₅	Br	NHCOMe	S	S	234–236°	89AJC1291
27	C ₆ H ₅	NO ₂	NHCOCF ₃	S	S	180°	89AJC1291
28	C ₆ H ₅	NO ₂	NH ₂	S	S	212–214°	89AJC1291
29	C ₆ H ₅	NO ₂	OH	S	S	230° (dec.)	89AJC1291
30	C ₆ H ₅	CO ₂ Et	Br	S	S	131°	89AJC1291
31	C ₆ H ₅	CO ₂ H	Br	S	S	272–273°	89AJC1291
32	C ₆ H ₅	H	Br	S	S	80°	89AJC1291
33	C ₆ H ₅	Br	H	S	S	88–89°	89AJC1291
34	C ₆ H ₅	NO ₂	Br	S	S	236–237°	89AJC1291
35	C ₆ H ₅	NO ₂	CN	S	S	221–223°	89AJC1291
36	C ₆ H ₅	NO ₂	CO ₂ H	S	S	220° (dec.)	89AJC1291
37	C ₆ H ₅	NO ₂	H	S	S	178°	89AJC1291
38	C ₆ H ₅	CON ₃	H	S	S	134° (dec.)	89AJC1291
39	C ₆ H ₅	NHCO ₂ Et	H	S	S	144–145°	89AJC1291
40	C ₆ H ₅	NHCO ₂ Pr ¹	H	S	S	168°	89AJC1291
41	SMe	COMe	NH ₂	S	S	189–190°	80G233
42	SMe	COC ₆ H ₅	NH ₂	S	S	159–160°	80G233
43	SMe	CO ₂ Et	NH ₂	S	S	166–169°	80JPR1021
44	SMe	CN	NH ₂	S	S	192–195°	80JPR1021
45	SMe	CONH ₂	NH ₂	S	S	257–259°	80JPR1021
46	SMe	COMe	NH ₂	S	S	191–193°	80JPR1021
47	OMe	CO ₂ Me	NH ₂	S	S	199°	80JPR1021
48	OMe	CN	NH ₂	S	S	210–211°	80JPR1021
49	OMe	COMe	NH ₂	S	S	135–136°	80JPR1021
50	OMe	COC ₆ H ₅	NH ₂	S	S	178°	80JPR1021
51	SCH ₂ COMe	COMe	NH ₂	S	S	178–180°	80G233
52	SCH ₂ COMe	COC ₆ H ₅	NH ₂	S	S	178–180°	80G233
53	SCH ₂ CO ₂ Me	CO ₂ Me	NH ₂	S	S	149–151°	80JPR1021
54	SCH ₂ CN	CN	NH ₂	S	S	203–205° (dec.)	80JPR1021
55	SCH ₂ COMe	COMe	NH ₂	S	S	179–181°	80JPR1021
56	SCH ₂ COPh	COPh	NH ₂	S	S	182–183°	80JPR1021
57	SCH ₂ CO ₂ Et	CN	NH ₂	S	S	145–147°	80JPR1021
58	H	C ₆ H ₅	H	NMe	S	95°	78KGS561
59	H	CH=CH—CH=CH		NH	S	164–167°	90S214

Table 7 Continued.

No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
60	H	C ₆ H ₅	H	O	S	107–108°	78KGS561
61	H	H	H	S	Se	55–57°	80BSB773
62	H	Br	H	S	Se	113–114°	82OMR(19)74
63	H	H	Br	S	Se	100–102°	82OMR(19)74
64	H	H	H	Se	S	63–64°	87BSB407
65	H	H	H	Se	Se	89–91°	80BSB773

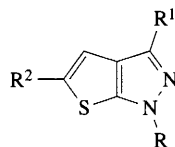
Table 8 Pyrrolo[3,4-*d*]isoxazole (X = N, Y = O) and thieno[3,4-*d*]isoselebazoles (X = S, Y = Se).

No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	H	H	H	S	Se	69–70°	80BSB773
2	Me	C ₆ H ₅	C ₆ H ₅	NMe	O	95–100°	93G633
3	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	NMe	O	137–138°	93G633

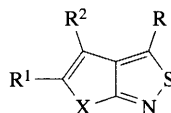
Table 9 Thieno[2,3-*d*]isothiazoles (X = Y = S), thieno[2,3-*d*]isoselebazoles (X = S, Y = Se), selenolo[2,3-*d*]isothiazoles (X = Se, Y = S) and selenolo[2,3-*d*]isoselebazole (X = Y = Se).

No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	H	H	H	S	S	48–49°	80BSB773
2	H	Me	H	S	S	96–98°/5 mm	80JCS(P1)1029
3	H	Me	CO ₂ Et	S	S	70–71°	80JCS(P1)1029
4	Me	H	H	S	S	90–92°/1 mm	80JCS(P1)1029
5	H	H	H	S	Se	80–81°	80BSB773
6	H	H	H	Se	S	77–78°	87BSB407
7	H	H	H	Se	Se	108–110°	87BSB407

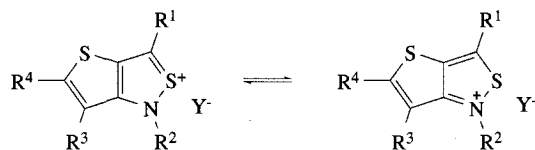
transformed to the thieno[3,2-*d*]isothiazoles (**14**) with sodium–ammonia <81IZV2771> and sulfur–ammonia <80LA768>, respectively (Scheme 14). Further, oxime thioether (**67**) or (**69**) are transformed to the [2,3-*d*] isomers (**68**) <80JCS(P1)1029> or [3,2-*d*] isomers (**70**) (Equations (14) and (15)) <80BSB773, 87BSB407> with either polyphosphoric acid or acetic anhydride. This strategy was used for the synthesis of isothiazolo[5,4-*b*]indole (**71**) (brassicalexin), which is a phytoalexin from *Brassica juncea* (Cruciferae) <90S214>. Formation of the nitrogen–sulfur bond in benzothieno[2,3-*d*]isothiazole (**73**) was achieved by thermal rearrangement of the intermediate (**72**), obtained from 2-aminobenzo-thiophene-3-carboxaldehyde (Equation (16)) <80JCR(M)833>.

Table 10 Thieno[2,3-*c*]pyrazoles.

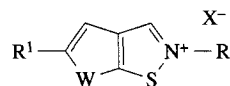
No.	R	R ¹	R ²	m.p. (°C)	Ref.
1	Me	Me	CO ₂ H	316–317°	69KGS760
2	Me	C ₆ H ₅	CO ₂ H	249–250°	69KGS760
3	C ₆ H ₅	C ₆ H ₅	CO ₂ H	282–283°	69KGS760
4	4-NO ₂ C ₆ H ₄	C ₆ H ₅	CO ₂ H	294–295°	69KGS760
5	C ₆ H ₅	Me	H	53°	69KGS760
6	C ₆ H ₅	C ₆ H ₅	H	135–136°	69KGS760
7	4-NO ₂ C ₆ H ₄	Me	H	210–212°	69KGS760
8	C ₆ H ₅	Me	CHO	141.5°	69KGS760
9	C ₆ H ₅	Me	CH ₃ CO	131–133°	69KGS760
10	C ₆ H ₅	H	CO ₂ H	228°	72ZOR1750
11	C ₆ H ₅	Cl	CO ₂ H	266°	72ZOR1750
12	C ₆ H ₅	OH	CO ₂ H	275°	72ZOR1750
13	C ₆ H ₅	EtO ₂ C	CO ₂ H	236°	72ZOR1750
14	C ₆ H ₅	CH ₃	CO ₂ H	235°	72ZOR1750
15	C ₆ H ₅	C ₆ H ₅	CO ₂ H	282°	72ZOR1750

Table 11 Thieno[2,3-*c*]isothiazoles and furo[2,3-*c*]isoxazoles.

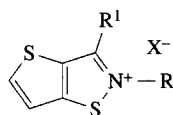
No.	R	R ¹	R ²	X	Y	m.p. (°C)	Ref.
1	H	H	H	S	S	22°	82AJC385
2	Me	CO ₂ Et	H	S	S	57–58°	82AJC385
3	Me	CO ₂ H	H	S	S	255° (dec)	82AJC385
4	Me	CO ₂ Et	NH ₂	S	S	129–131°	82AJC385
5	Me	CO ₂ Et	AcNH	S	S	176–177°	82AJC385
6	Me	CO ₂ Et	OH	S	S	116–117°	82AJC385
7	CH ₂ Br	CO ₂ Et	H	S	S	88–89°	82AJC385
8	CHO	CO ₂ Et	H	S	S	119–120°	82AJC385
9	CH(OEt) ₂	CO ₂ Et	H	S	S	144°	82AJC385
10	CO ₂ H	H	H	S	S	209° (dec)	82AJC385
11	NH ₂	H	H	S	S	138–140°	73JPR539
12	NH ₂	CH ₂ CH ₂ CH ₂		S	S	150–152°	73JPR539
13	NH ₂	CH ₂ CH ₂ CH ₂ CH ₂		S	S	148–149°	73JPR539
14	SMe	CO ₂ Et	NH ₂	S	S	147–148°	80JPR1021
15	SMe	CO ₂ Me	NH ₂	S	S	173–174°	80JPR1021
16	SMe	CN	NH ₂	S	S	205–208°	80JPR1021
17	SMe	CONH ₂	NH ₂	S	S	223–225°	80JPR1021
18	SMe	COMe	NH ₂	S	S	164–166°	80JPR1021
19	SMe	COC ₆ H ₅	NH ₂	S	S	168–169°	80JPR1021
20	SMe	CO ₂ H	NH ₂	S	S	170–173°	80JPR1021
21	4-Me ₂ NC ₆ H ₄ N=N	H	H	S	S	179–180°	73JPR539
22	Me	CH=CH–CH=CH		NMe	O	70–71°	92JOC2127

Table 12 Thieno[3,2-*c*]isothiazolium salts.

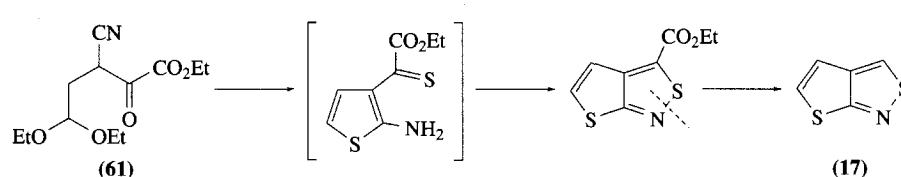
No.	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>Y</i>	<i>m.p.</i> (°C)	Ref.
1	C ₆ H ₅	C ₆ H ₅	H	C ₆ H ₅	ClO ₄ ⁻	241°	76CJC1123
2	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	H	ClO ₄ ⁻	222°	76CJC1123
3	C ₆ H ₅	Me	H	H	ClO ₄ ⁻	204°	76CJC1123
4	Me	C ₆ H ₅	H	C ₆ H ₅	ClO ₄ ⁻	237°	76CJC1123
5	C ₆ H ₅	Me	CH=CH-CH=CH		I ₃ ⁻	169–173°	76CJC1123

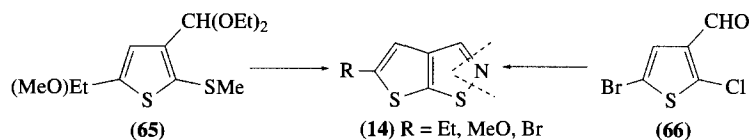
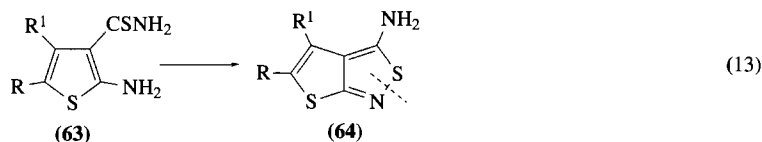
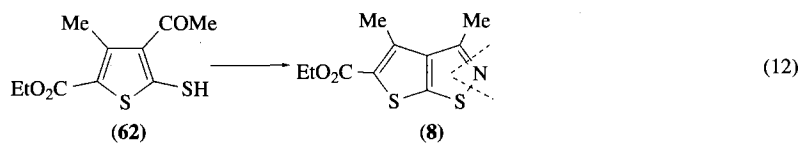
Table 13 Thieno[3,2-*d*]isothiazolium, furo[3,2-*d*]isothiazolium, and pyrrolo[3,2-*d*]isothiazolium salts.

No.	<i>R</i>	<i>R</i> ¹	<i>W</i>	<i>X</i>	<i>m.p.</i> (°C)	Ref.
1	<i>c</i> -C ₆ H ₁₁	Et	S	Br ⁻	167–168°	67KGS1022
2	<i>c</i> -C ₆ H ₁₁	Et	S	Br ₃ ⁻	124–126°	67KGS1022
3	<i>c</i> -C ₆ H ₁₁	Et	S	ZnBr ₃ ⁻	175–176°	67KGS1022
4	Me	C ₆ H ₅	S	MeSO ₄ ⁻	245°	67KGS1022
5	Me	C ₆ H ₅	O	MeSO ₄ ⁻	213°	67KGS1022
6	Me	C ₆ H ₅	NMe	MeSO ₄ ⁻	NA	67KGS1022

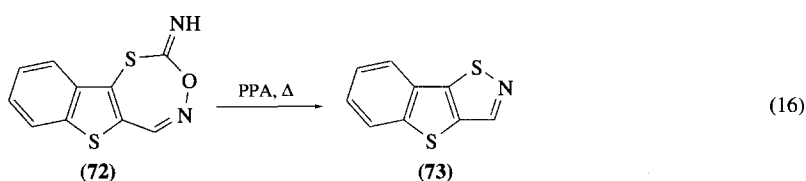
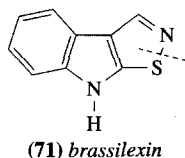
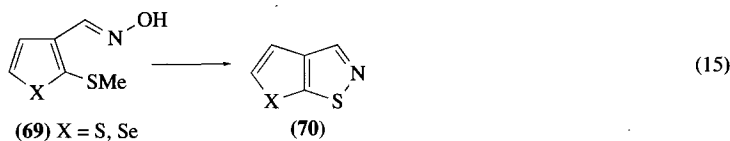
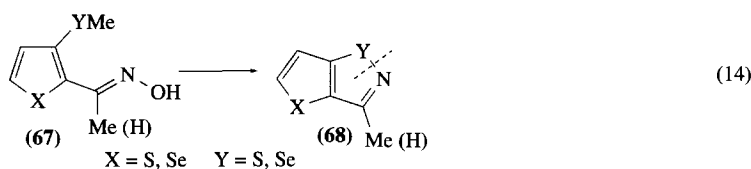
Table 14 Thieno[2,3-*d*]isothiazolium salts.

No.	<i>R</i>	<i>X</i> ⁻	<i>m.p.</i> (°C)	Ref.
1	<i>c</i> -C ₆ H ₁₁	Br ₃ ⁻	126–128°	67KGS1022
2	<i>c</i> -C ₆ H ₁₁	Br ⁻	185–186°	67KGS1022
3	<i>c</i> -C ₆ H ₁₁	I ⁻	154–156°	67KGS1022
4	<i>c</i> -C ₆ H ₁₁	picrate	180–181.5°	67KGS1022
5	<i>c</i> -C ₆ H ₁₁	ZnBr ₃ ⁻	173–174°	67KGS1022

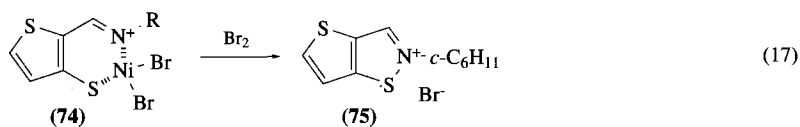
**Scheme 13**

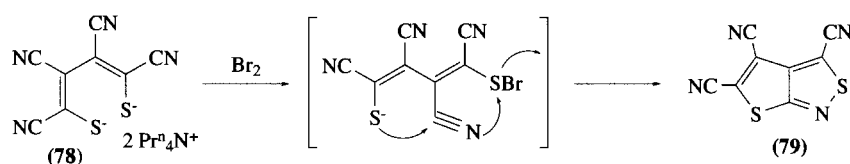
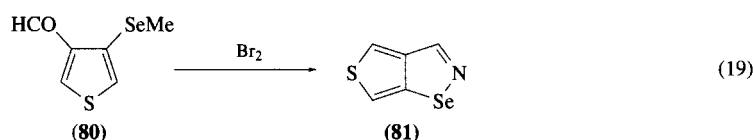
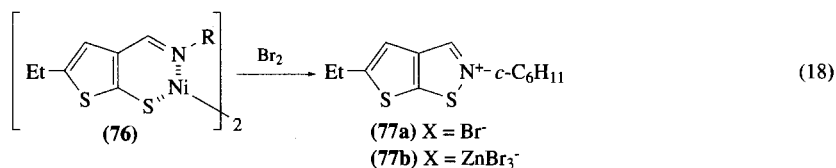


Scheme 14



Bromine-mediated cyclizations have been used to a lesser extent for generation of the nitrogen-sulfur (selenium) bond. The first example was the transformation of nickel chelates of thiolthiophene *N*-cyclohexylaldimines (**74**), (**76**) to the *N*-cyclohexylthieno[2,3-*d*]isothiazolium salts (**75**) and *N*-cyclohexylthieno[3,2-*d*]isothiazolium salts (**77**) (Equations (17) and (18)) <67KGS1022>. If the latter reaction is performed in the presence of zinc bromide, the corresponding *N*-cyclohexylthieno[3,2-*d*]isothiazolium zinc tribromide complex (**77b**) is obtained. A creative example of the cyclization procedure is shown in the conversion of bis(tetrapropylammonium)-1,2,3,4-tetracyanobutadiene-1,4-dithiolate (**78**) to 2,4,5-tricyanothieno[2,3-*c*]isothiazole (**79**) (Scheme 15) <80JOC5113>. The dithiolate (**78**) was obtained from tetracyanothiophene with potassium ethyl xanthate. The conversion of the selenoether aldehyde (**80**) to thieno[3,4-*d*]isoselenazole (**81**) with bromine and ammonia probably occurs via a selenonium bromide intermediate (Equation (19)) <80BSB773>.



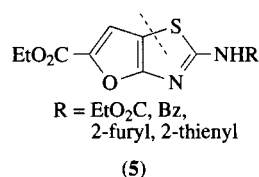
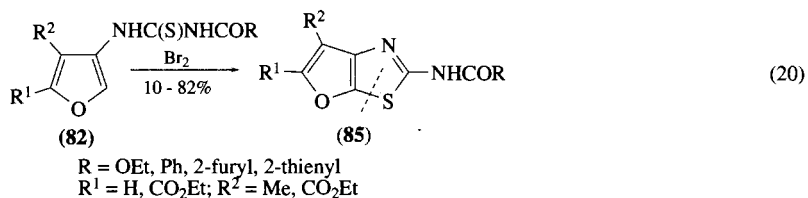


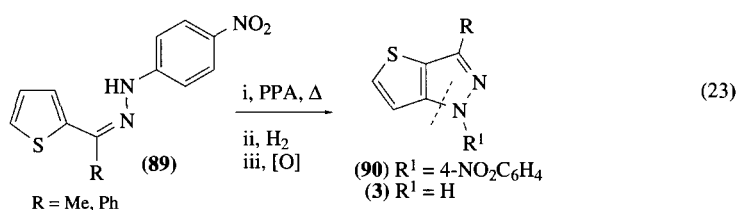
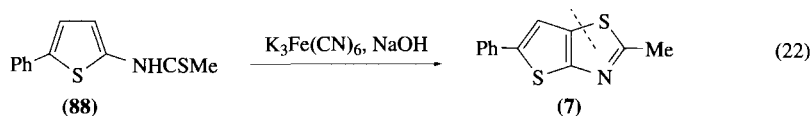
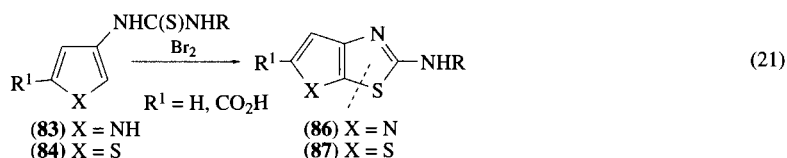
Scheme 15

7.02.7.1.2 [5 + 0] Electrophilic cyclizations

Notable electrophilic cyclization pathways include the bromine-mediated cyclization of 3-(thioureido)furans (pyrroles or thiophenes) (**82**)–(**84**) which afford the corresponding furano (pyrrolo or thieno)[3,2-*d*]thiazoles (**85**)–(**87**) and selenazoles (Equations (20) and (21)). These reactions are proposed to occur by the intermediacy of a sulfinyl (or selenyl) bromide $\langle 77\text{CS199, } 78\text{JHC81, } 79\text{CS78} \rangle$. A similar cyclization of 2-(*N*-acylthioureido)furans to the furo[2,3-*d*]thiazoles (**5**) was also reported $\langle 77\text{CS199, } 86\text{CCCC1678} \rangle$. In contrast, the 2-(thioureido)thiophenes do not undergo cyclization, but afford the 3-bromo-2-thioureidothiophenes $\langle 78\text{JHC81} \rangle$. A complementary cyclization, first reported by Zhiryakov and Levkoev $\langle 58\text{DOK}(120)1035 \rangle$ and reexamined by Pinkin and co-workers $\langle 87\text{KGS410} \rangle$, consists of the potassium ferricyanide-mediated cyclization of 2-(thioacetamido)thiophene (**88**) and 3-(thioacetamido)thiophene to thieno[2,3-*d*]thiazole (**7**) and thieno[3,2-*d*]thiazole, respectively (Equation (22)). However, the general applicability of this cyclization strategy has not been explored.

Another electrophilic cyclization strategy is reported in which polyphosphoric acid cyclization of thienyl 2-hydrazones (**89**) affords 1-(*p*-nitrophenyl)thieno[3,2-*c*]pyrazoles (**90**) (Equation (23)) (<67CJC697>). On initial analysis, the process appears limited to *p*-nitrophenylhydrazones but the *p*-nitrophenyl unit is easily removed in a tandem reduction–oxidation sequence to afford the 1*H*-thieno[3,2-*c*]pyrazoles (**3**).

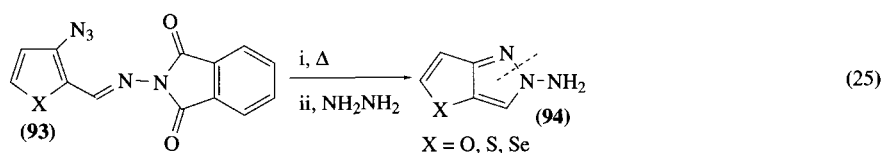
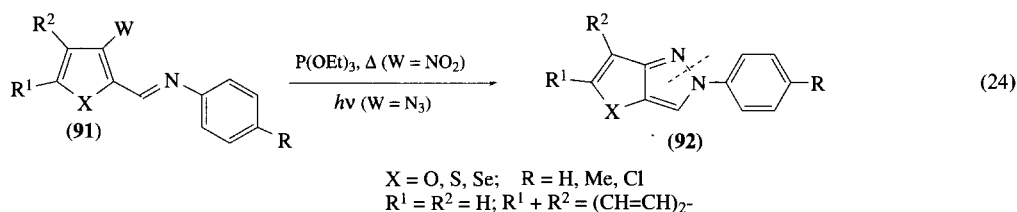


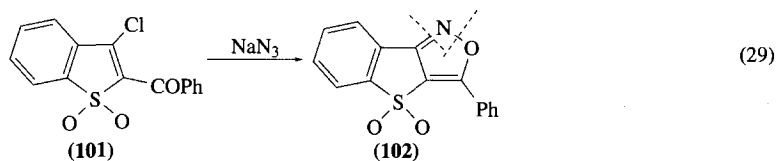
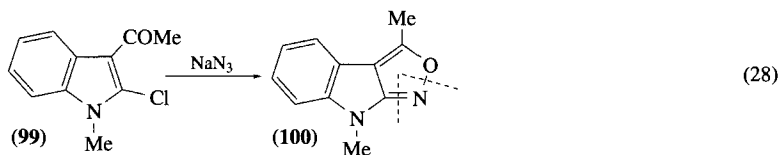
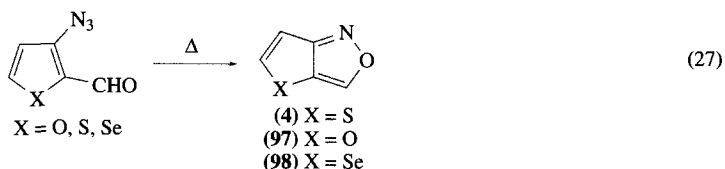
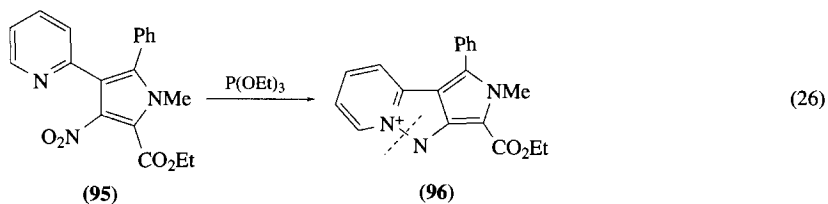


7.02.7.1.3 Nitrene-mediated [5 + 0] cyclizations

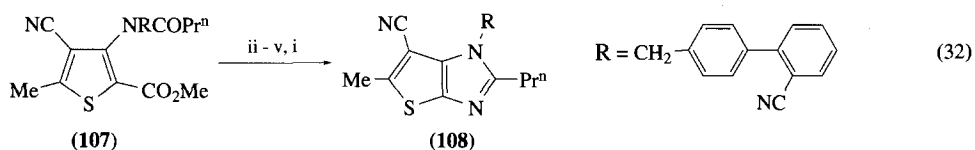
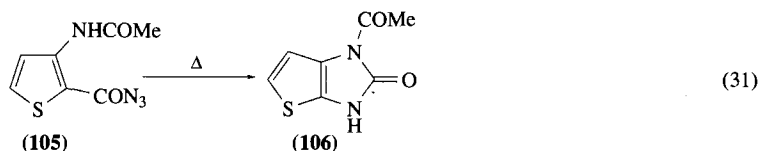
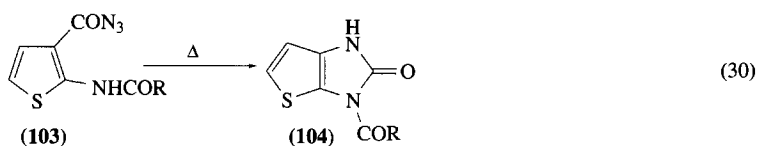
Nitrene-based cyclizations have been the cornerstone for the synthesis of annelated imidazoles, isoxazoles, and pyrazoles. Notably, syntheses of 2-substituted annelated [3,2-*c*]pyrazoles (**92**) either by photolysis of the azido anils (**91**; $\text{W} = \text{N}_3$) or by triethyl phosphite-mediated deoxygenation of the nitro anils (**91**; $\text{W} = \text{NO}_2$) (Equation (24)) have been reported by various laboratories <73JCS(P1)129, 77CS1, 78CC453, 79JCS(P1)1337>. In contrast to the azide photolysis process, the cyclization efficiency in the phosphite deoxygenation process is sensitive to substituent effects on the acceptor phenyl unit. The corresponding annelated 2-aminopyrazoles (**94**) were prepared by thermolysis of the azido *N*-phthalimidohydrazones (**93**) (Equation (25)). Similarly, the pyrrolo[3',4':2,3]pyrazolo-[1,5-*a*]pyridine (**96**) was obtained from the 3-nitro-4-pyridylpyrrole (**95**) (Equation (26)) <79JOC622>.

Thermal decomposition of 3-azido-2-formylfuran, -thiophene, and -selenoles has also been used to prepare furo[3,2-*c*]isoxazole (**97**), thieno[3,2-*c*]isoxazole (**4**), and selenolo[3,2-*c*]isoxazoles (**98**) (Equation (27)) <76CS165>. In contrast, some azido ketones eliminate nitrogen at ambient temperature and cyclize as exemplified in the reactions of 2-chloro-3-acetylindole (**99**) (Equation (28)) and 3-chloro-2-benzoylbenzothiophene dioxide (**101**) (Equation (29)) with sodium azide <78CB1521, 92JOC2127>.





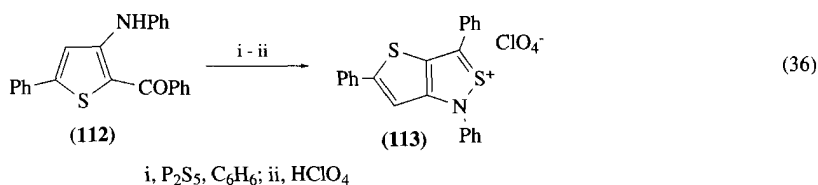
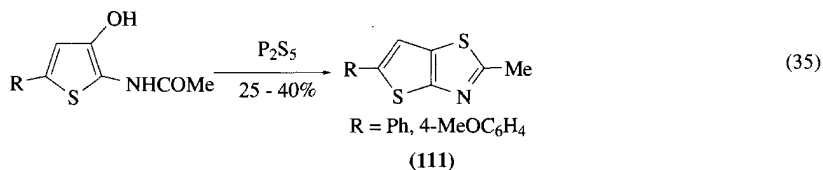
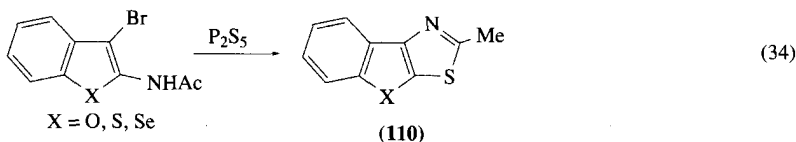
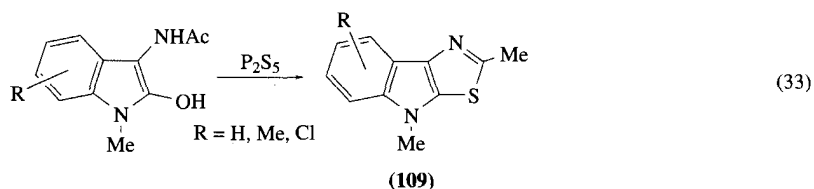
For nonsymmetrical bicyclic imidazoles, direct *N*-alkylation (arylation or acylation) is problematic since site-selectivity is influenced by many subtle electronic effects. Thus, Curtius rearrangement-based syntheses have been used widely for the synthesis of differentiated *N*-substituted thienoimidazoles (**104**), (**106**) from (acylamido)thiophene carbonyl azides (**103**), (**105**) (Equations (30) and (31)) <79JCR(S)96>. These intermediates are useful for the synthesis of angiotensin II antagonists (Equation (32)) <91EUP483683, 92EUP520423>.



i, Δ; ii, NaOH, H₃O⁺; iii, (PhO)₂PON₃; iv, Bu^tOH, Δ; v, deprotection

7.02.7.1.4 Direct [4 + 1] thiation

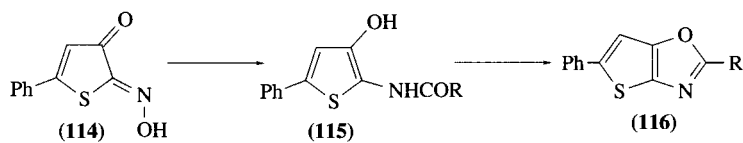
Thiation is used predominantly for the synthesis of annelated thiazoles (e.g., (109)–(111)) from heterocyclic acylamides bearing either adjacent phenol or halogen substituents (Equations (33)–(35)) <70KGS1624, 77KGS1495, 87KGS410>. The thieno[3,2-*c*]isothiazolium perchlorate (113) was obtained from the 2-benzoyl-3-(phenylamino)thiophene (112) by sequential reaction with phosphorus pentasulfide and perchloric acid (Equation (36)) <77CJC1123>.



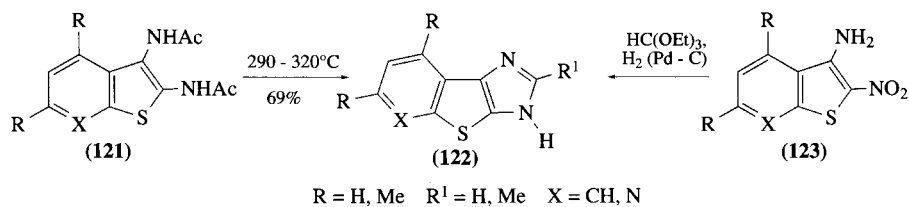
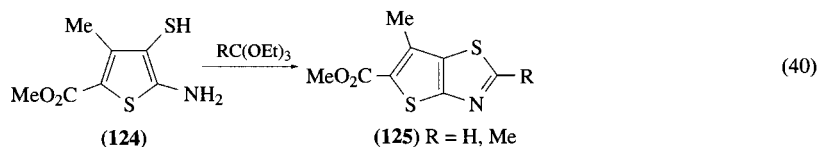
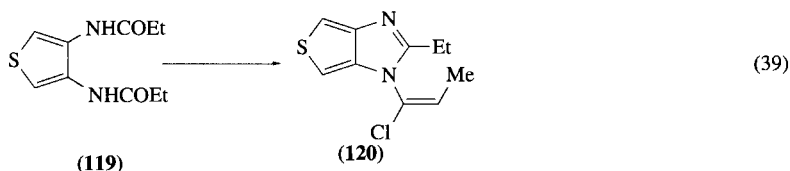
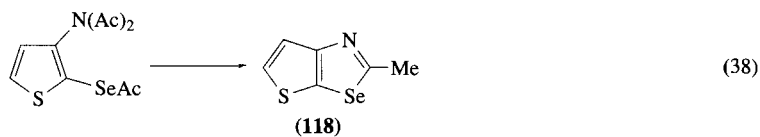
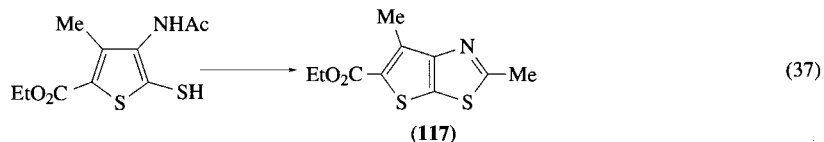
7.02.7.1.5 [5 + 0] and [4 + 1] Carbon closures

This strategy is used for the syntheses of fused heterocycles which have a [1,3]-heteroatom juxtaposition in one of the rings. Thieno[3,2-*d*]oxazole (116) was first obtained in 1915 by dehydrative closure of α -keto oxime (114) with aryl carboxaldehydes via the intermediate acylamino hydroxythiophene (115) (Scheme 16) <55JA5370, 87AP(320)837>. Since then, other variations have afforded syntheses of thieno[3,2-*d*]thiazoles (117) (Equation (37)) and thieno[3,2-*d*]selenazoles (118) (Equation (38)). While a variety of dehydration reagents can be used, surprises can occur as reported by Outurquin and Paulmier. Treatment of the bis(propionamide) (119) with POCl₃–DMF afforded the *N*-(α -chloropropenyl)thienoimidazole (120) in moderate yield (Equation (39)) <83BSF(2)153, 83BSF(2)159>. Similarly, 1*H*-imidazo[3',4':4,5]thieno[2,3-*b*]pyridines (122) have been prepared by either the dehydrative cyclization route (via (121)) or the orthoester approach (via 123) (Scheme 17) <70KGS1473, 84JHC587>.

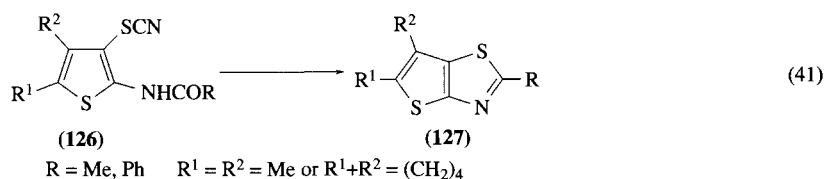
Other one-carbon closures include the synthesis of the thieno[2,3-*d*]thiazoles (125) from the thiolamine (124) and orthoesters (Equation (40)) <88JPR866> and the thermal cyclization of the isothiocyanate (126) to the 2-acylthieno[2,3-*d*]thiazoles (127) (Equation (41)) <74KGS1204>.



Scheme 16



Scheme 17

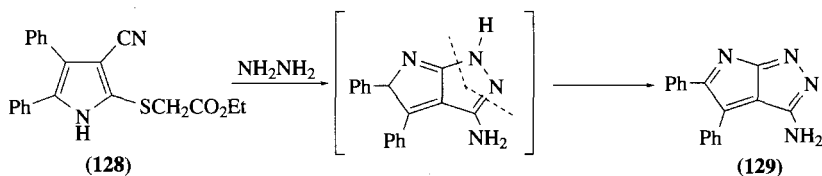


7.02.7.1.6 [2 + 3] Annulations using bisnucleophiles

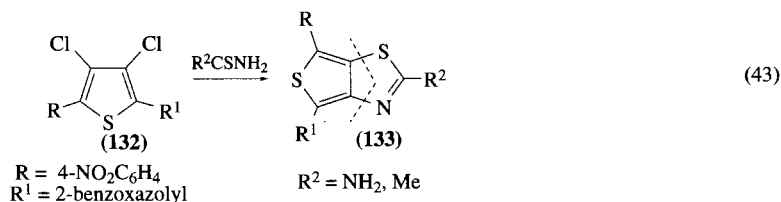
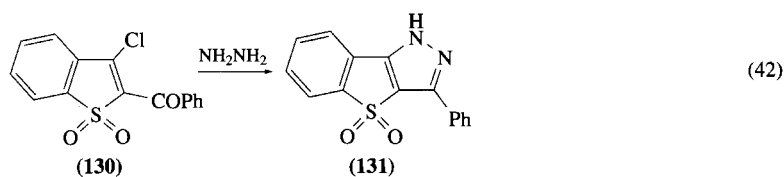
This strategy is used mostly for the synthesis of annelated pyrazoles in which the second reactant has two electrophilic sites in a 1,3-juxtaposition. Under control conditions, the first synthesis of a 3-aminopyrrolo[2,3-*d*]pyrazole (**129**) was realized from ethyl(3-cyano-4,5-diphenylpyrrolylthio)acetate (**128**) (Scheme 18) <91T8243>. The synthesis of the benzothieno[3,2-*c*]pyrazole (**131**) occurred as a two-step process with initial S_NAr addition of hydrazine to the chlorobenzothiophene *S,S*-dioxide (**130**) (Equation (42)) <74LA1248>.

Under special circumstances, three atom synthons can be added to doubly-activated heterocycles. For example, treatment of the unsymmetrical 3,4-dichlorothiophene (**132**) with either thioacetamide

or thiourea afforded the thienothiazoles (**133**) exclusively (Equation (43)). The presence of one regioisomer infers that the chlorine adjacent to the *p*-nitrophenyl group is highly activated and reacts preferentially <91JHC1449>.

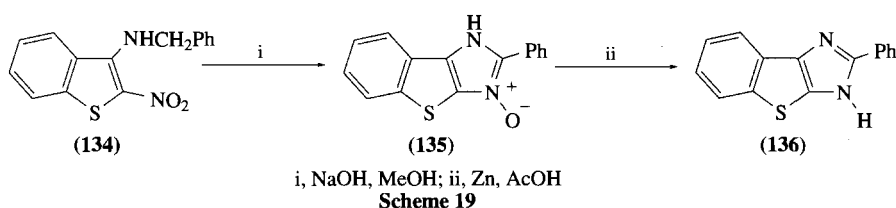


Scheme 18



7.02.7.1.7 Miscellaneous cyclizations

Specialized cyclization sequences should not be forgotten. Preston and Sood have reported that alkaline cyclization of 3-(benzylamino)-2-nitrobenzothiophene (**134**) affords the imidazole *N*-oxide (**135**), which is easily deoxygenated with zinc–acetic acid to the benzothienoimidazole (**136**) (Scheme 19) <76JCS(P1)80>.



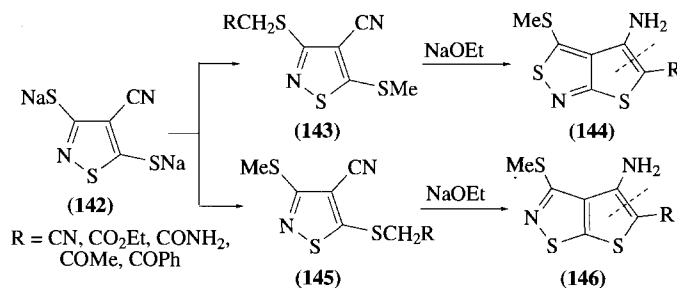
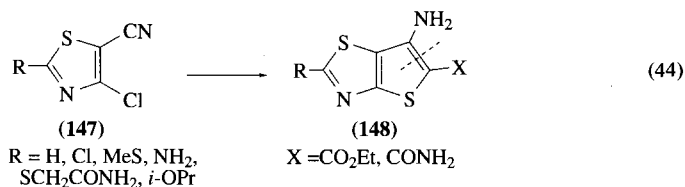
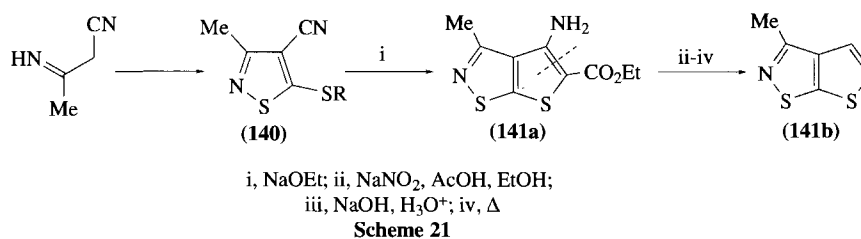
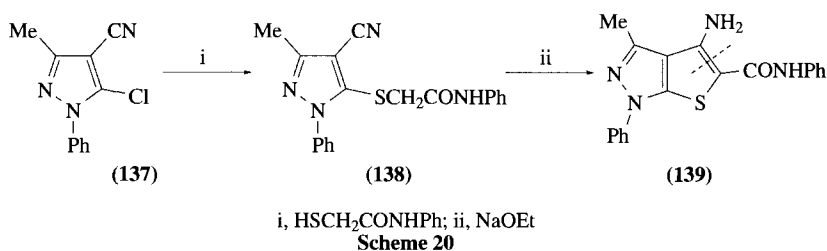
Scheme 19

7.02.7.2 Annulations onto π -Deficient Heterocycles

7.02.7.2.1 Claisen, Thorpe, or aldol cyclizations

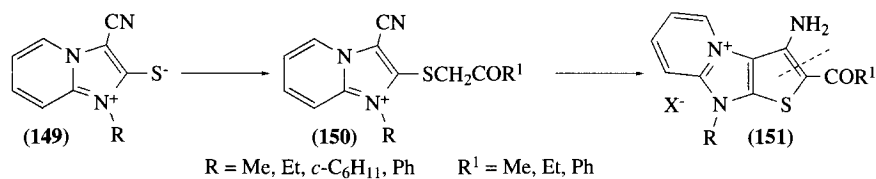
A versatile synthesis of 4-aminothieno[2,3-*c*]pyrazoles (**139**), first described by Kvitko, takes advantage of the ready accessibility of 5-chloro-4-cyanopyrazoles (**137**) and their unique reactivity with thiols. Thorpe cyclization of intermediate (**138**) affords amine (**139**) in good yield (Scheme 20) <69KGS760, 69ZOR1498, 73ZOR2416>. Extension of the method to appropriate precursor isothiazoles and thiazoles provides rapid accessibility to thieno[3,2-*c*]isothiazoles and thieno[2,3-*d*]thiazoles, respectively <92T7689>. 3-Methylthieno[3,2-*d*]isothiazole (**141b**) was obtained sequentially by cyclization of the cyanoisothiazole ester (**140**; $\text{R} = \text{CH}_2\text{CO}_2\text{Et}$) and deamination and decarboxylation of the amino ester (**141a**) (Scheme 21) <89AJC1291>. The creative use of disodium 4-cyanoisothiazolyl-

3,5-dithiolate (**142**), by exploiting the differential reactivity of the two thiols, for the regioselective synthesis of 4-aminothieno[2,3-*c*]isothiazoles (**144**) and 4-aminothieno[3,2-*d*]isothiazoles (**146**) is notable (Scheme 22) <80G233>. The versatility of the method is further exemplified in syntheses of 6-amino-2-substituted-thieno[2,3-*d*]thiazole-5-carboxamides (**148**) from 4-chlorothiazolocarbonitriles (**147**) (Equation (44)) <92T7689>. A similar cyclization strategy was employed in the synthesis of thieno[2',3';4,5]imidazo[1,2-*a*]pyridinium salts (**151**) from the imidazo[1,2-*a*]pyridinium ylides (**149**) (Scheme 23) <80JPR375>. Claisen-type cyclizations have also been realized with the intermediates (**152**) which afford 4-hydroxythieno[2,3-*c*]pyrazoles (**153**) <72USP3649641> and 4-hydroxythieno[3,2-*d*]thiazoles (**154**) respectively (Scheme 24) <90ZC18>.

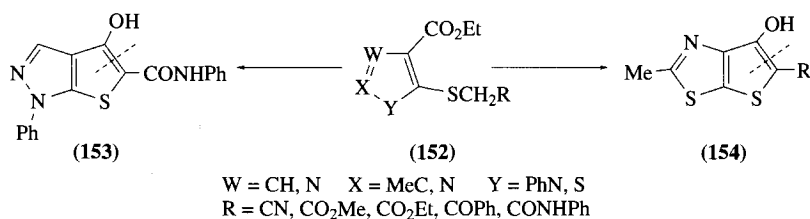


Scheme 22

In variants of the above processes, the bifunctional reactivity of 4-(dialkylamino-methylene)pyrazolin-5-thiones (**155**) (Scheme 25) and oxazolin-5-thiones (**157**) (Equation (45)) with α -halocarboxylic acids (or esters) was exploited for the synthesis of thieno[2,3-*c*]pyrazoles (**156**)

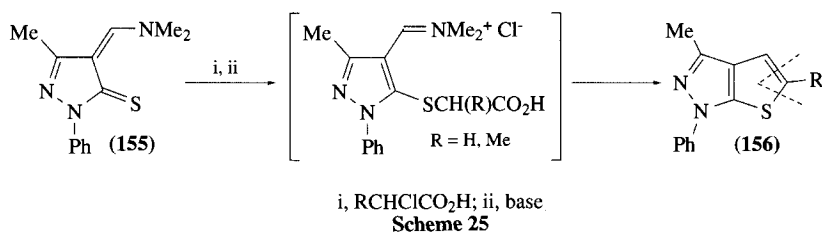


Scheme 23

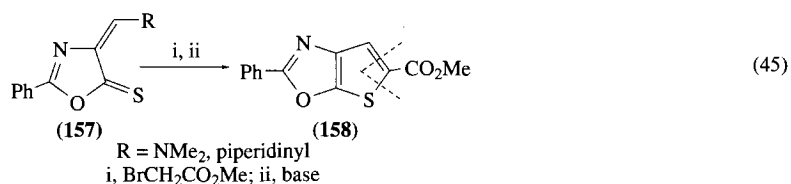


Scheme 24

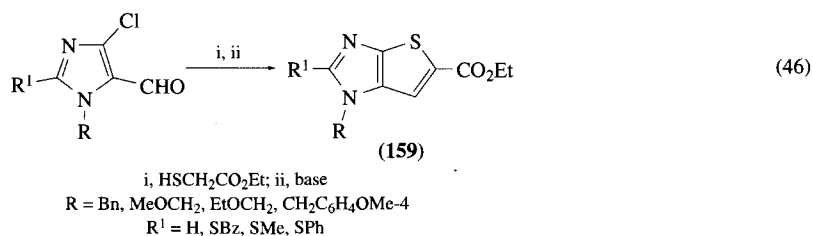
$\langle 71\text{ZOR}1253 \rangle$ and thieno[2,3-*d*]oxazoles (**158**) $\langle 79\text{KGS}474 \rangle$, respectively. Since the intermediate *N,N*-dialkyliminium moiety is functionally equivalent to a carboxaldehyde moiety, the subsequent cyclization is formally a Claisen cyclization. The general synthesis of thieno[2,3-*d*]imidazole-5-carboxylates (**159**) from 1*H*-5(4)-chloroimidazole-4(5)-carboxaldehydes (Equation (46)) illustrates the power of this strategy $\langle 78\text{JHC}81, 87\text{JCS}(\text{PI})1457, 91\text{EUP}461040 \rangle$.



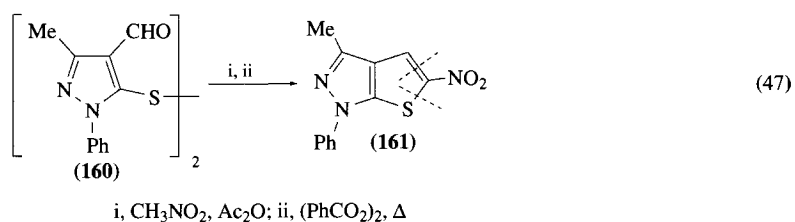
Scheme 25



(45)



(46)

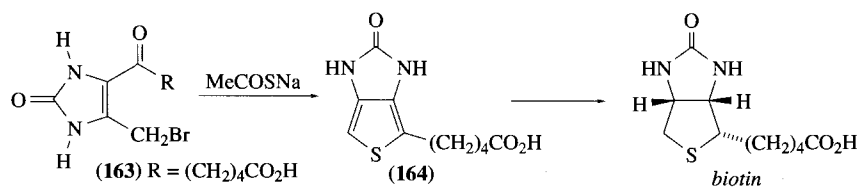
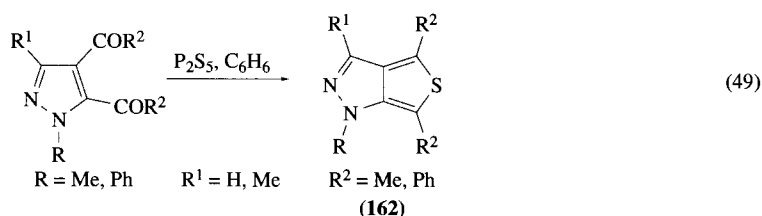
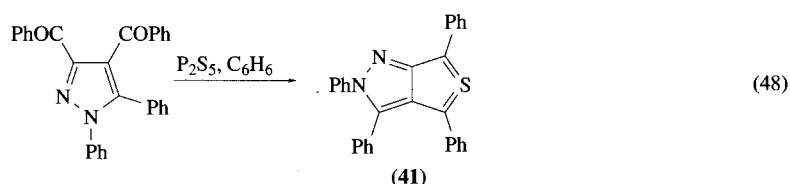


(47)

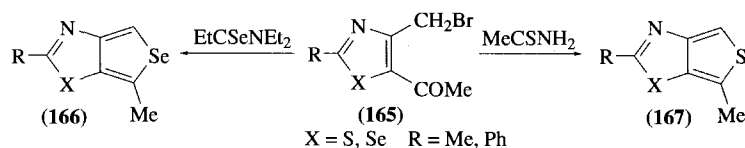
An equivalent two-step strategy in which pyrazolecarboxaldehyde disulfide (**160**) is transformed to a 5-nitrothieno[2,3-*c*]pyrazole (**161**) (Equation (47)) involves: (a) coupling with nitromethane; and (b) cyclization under free radical conditions $\langle 74\text{TL}4069 \rangle$. However, the generality of this latter strategy is not known.

7.02.7.2.2 Amination, thiation, and selenization

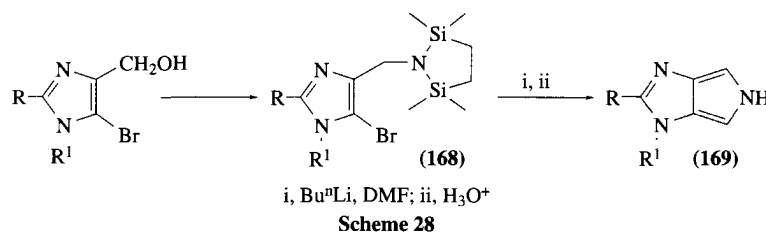
Direct thiation, while limited in scope, has traditionally been used for the transformation of vicinal diketones to [3,4]-annulated thiophenes as exemplified in the synthesis of thieno[3,4-*c*]pyrazoles (**41**) and (**162**) (Equations (48) and (49)) $\langle 73\text{JOC}1769, 74\text{JA}4276, 88\text{CB}95 \rangle$. A variant of the process was used for an early synthesis of ($\pm$)-biotin in which the penultimate intermediate (**164**) was obtained from a bromomethyl ketone (**163**) (Scheme 26) $\langle 74\text{CL}729 \rangle$. Similar cyclizations of 5-acetyl-4-bromo-methylthiazoles (selenazoles) (**165**) to bicyclic selenazoles (**166**) and bicyclic thiophenes (**167**) were accomplished with thioacetamide or *N,N*-diethylselenopropionamide as sulfur and selenium donors, respectively (Scheme 27) $\langle 89\text{JHC}709 \rangle$. In a further extension of the strategy, the synthesis of a pyrrolo[3,4-*d*]imidazole angiotensin II antagonist (**169**) from the 5-bromo-4-(silylamino-methyl)imidazoles (**168**) (Scheme 28) has been reported $\langle 90\text{EUP}407102 \rangle$.



Scheme 26



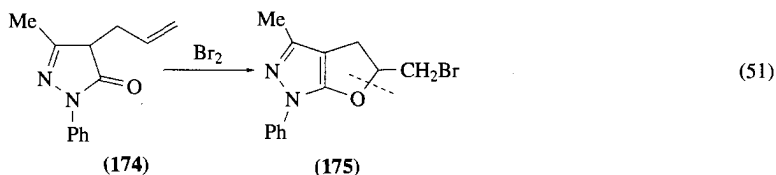
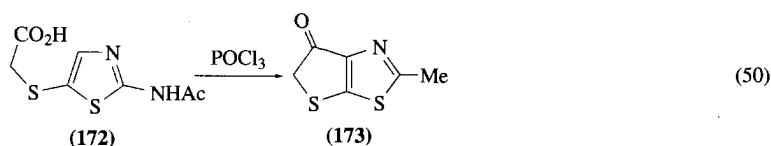
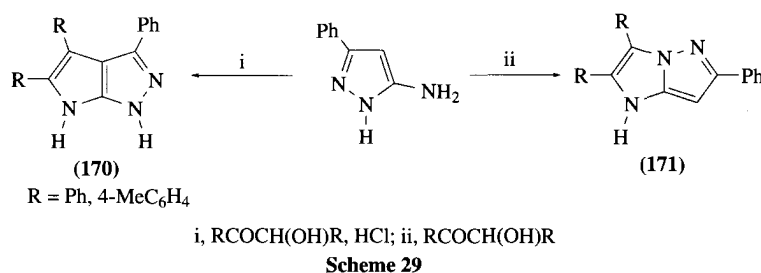
Scheme 27



7.02.7.2.3 Electrophilic cyclizations

While examples of intermolecular electrophilic additions to π -deficient heterocycles are reported less frequently than with π -excessive heterocycles, intramolecular electrophilic cyclization strategies can be used to access some heterocycles of interest. In some cases, different reaction conditions can afford isomeric heterocycles as exemplified in the cyclization of 1,2-diaryl ketols with 2-aminopyrazoles. With hydrogen chloride in the reaction media, pyrrolo[2,3-*c*]pyrazoles (**170**) are obtained, whereas imidazo[1,2-*b*]pyrazoles (**171**) were obtained in the absence of hydrogen chloride (Scheme 29) <84JHC945>. Cycloacylation of the α -(thiazolylthio)acetic acid (**172**) was accomplished with phosphorus oxychloride to give thiazole (**173**) (Equation (50)) <56AC(R)275>.

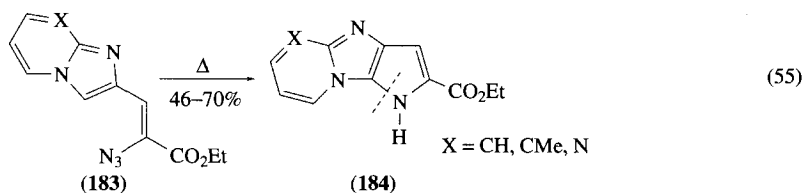
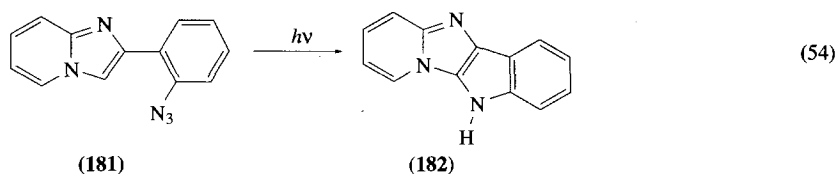
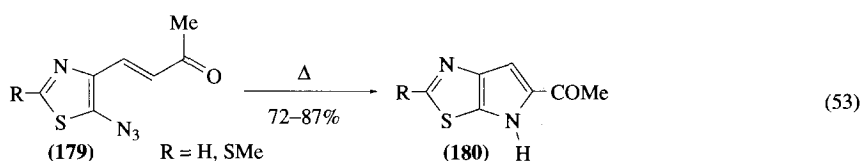
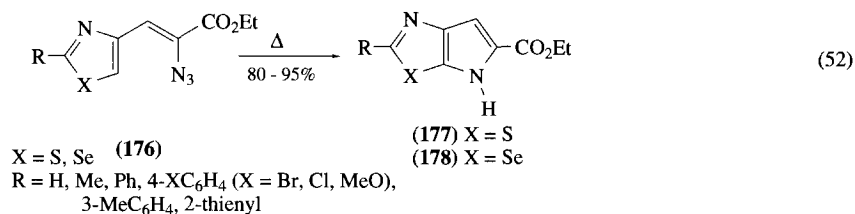
An alternative strategy, reported by Gyul'budagyan and Aleksanyan, is the electrophilic alkene cyclization of 4-allylpyrazol-5-ones (**174**) to 5-(bromomethyl)-4,5-dihydrofuro[2,3-*c*]pyrazoles (**175**) (Equation (51)) <84AKZ112>. Presumably this strategy could also be applied to similar substrates and other electrophiles.



7.02.7.2.4 Nitrene-based cyclizations

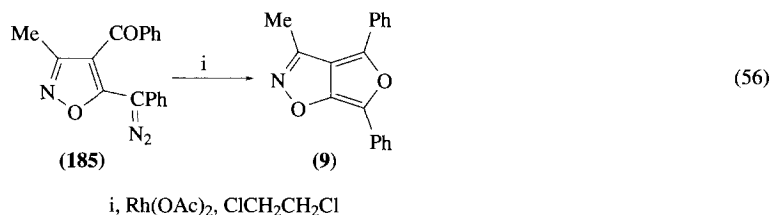
Further applications of nitrene cyclizations have also been reported in which the intermediate nitrene inserts into a π -deficient heterocycle or a nitrene on a π -deficient nucleus inserts into a proximal carbon-hydrogen bond. In general, the preferred source of the nitrene is the photolysis or thermolysis of an azide. The versatility of this approach is shown in two syntheses of pyrrolo[3,2-*d*]thiazoles (selenazoles) (**177**), (**178**), (**180**) (Equations (52) and (53)). Thermolysis of the β -thiazolyl (selenazolyl)- α -azido-esters (**176**) or the β -(4-azido-5-thiazolyl)- α,β -enones (**179**) affords these bicyclic heterocycles in excellent yields <79JHC1563, 92JCS(P1)973>. The same strategy has also been

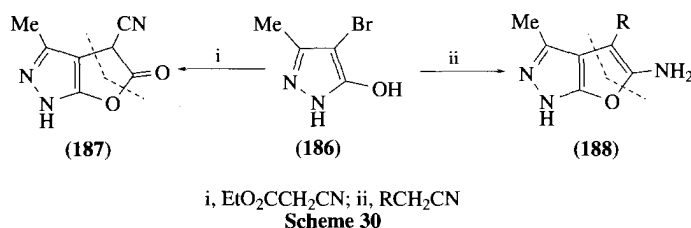
applied to the synthesis of annelated pyrrolo[2,3-*d*]imidazoles (**182**) and (**184**) (Equations (54) and (55)) <89JCS(P1)1895, 92JHC691>.



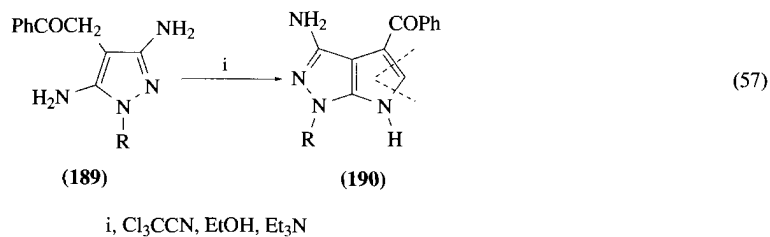
7.02.7.2.5 Miscellaneous cyclizations

Several specialized cyclization strategies should not be dismissed. A novel rhodium acetate-mediated cyclization was employed for the first synthesis of 3-methyl-4,6-diphenylfuro[3,4-*d*]isoxazole (**9**) from the 5-(α -diazobenzyl)isoxazole (**185**) (Equation (56)). The reactive intermediate is believed to be a carbenoid species <91CB2481>. Another strategy exploits the reactivity of 4-halopyrazol-5-ones (e.g., **186**) with stabilized anions (e.g., cyanoacetate esters and nitriles) to afford the 4-cyanofuro[2,3-*c*]pyrazol-5-ones (**187**) and 5-aminofuro[2,3-*c*]pyrazoles (**188**) (Scheme 30) <84H(22)2523>. Also of interest is the trichloroacetonitrile cyclization of aminopyrazole ketones (**189**) to the pyrrolo[2,3-*c*]pyrazoles (**190**) (Equation (57)) <86S74>. The generality of this cyclization is not known.





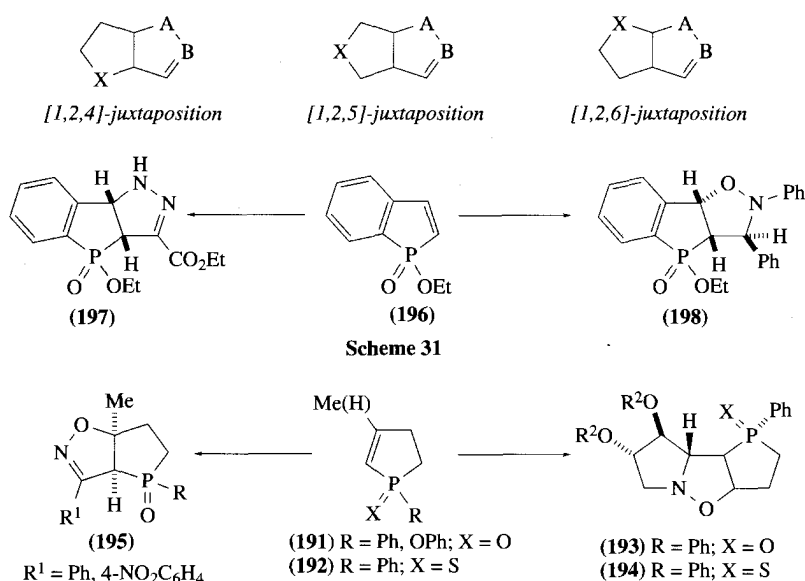
Scheme 30



7.02.8 SYNTHESSES AND REACTIVITY OF NONCONJUGATED SYSTEMS

This section is not intended to be a comprehensive review but highlights the more interesting syntheses and chemistry of the nonconjugated ring systems. While many of the examples are prepared by cycloaddition processes, the stereoelectronic aspects of the various cycloaddition strategies are not reviewed since these issues are discussed in-depth in major reviews <B-84MI 702-01> and papers and in CHEC-I <84CHEC-I(6)1007>. The emphasis is on the breadth of chemistry that the nonconjugated systems display.

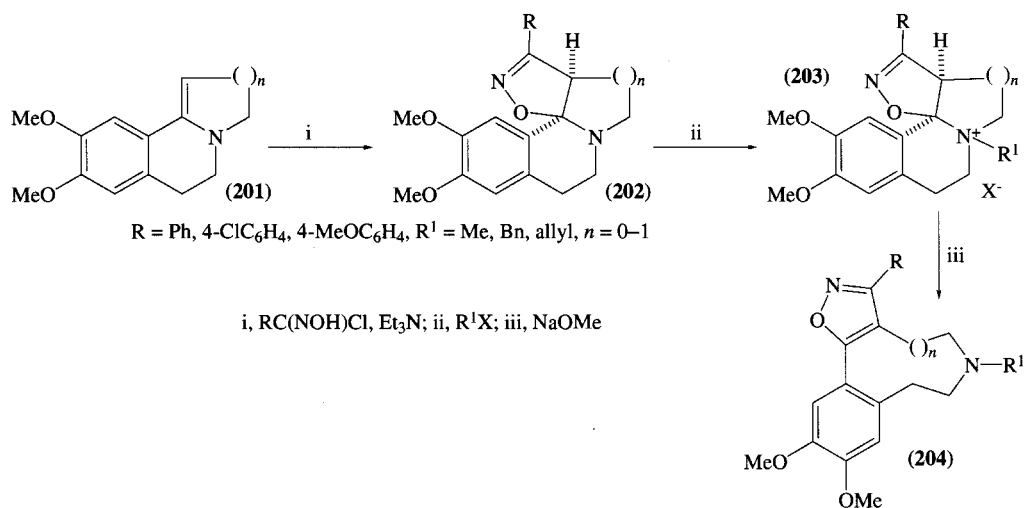
Conceptually those heterocycles with either [1,2,4], [1,2,5], or [1,2,6] heteroatom locants are candidates for synthesis by cycloaddition strategies. Typically dipolar cycloadditions to furans, thiophenes, and phosphindole oxides (196) <89BSB865> afford predominantly the [1,2,4]-orientation adducts (e.g., (197) and (198)) (Scheme 31) <68TL743, 73CR(C)109, 76JOC3349, 77JCS(P2)706, 78JOC3006, 78T3545, 81CZ93>, while 2,3-dihydrofurans and 2,3-dihydropyrroles afford the [1,2,6]-adducts <67BSF4179>. In contrast, the 2,3-dihydro-1-substituted phospholes (191) and (192) afford [1,2,4]-adducts <67DOK(172)1075, 90T7093, 94JOC1315>, except if an additional activating group is present on the phosphole (Scheme 32) <72TL299>.



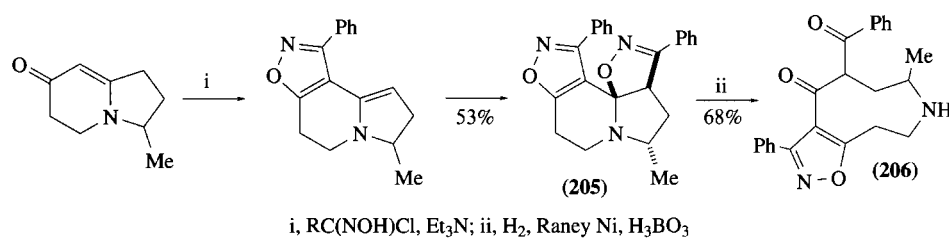
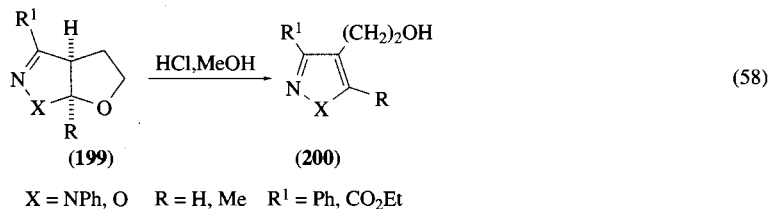
Scheme 32

Those with [1,2,6]-orientation can undergo either (a) aromatization by elimination of the het-

eroatom X, or (b) reductive hydrolysis to a 1,3-diketone species. The simplest example is the acid-catalyzed transformation of tetrahydrofuro[3,2-*d*]isoxazoles (or pyrazoles) (**199**) to the 4-hydroxyethylisoxazoles or 4-hydroxyethylpyrazoles (**200**) (Equation (58)) <68CPB117>. Similarly, the tetrahydropyrrolo[3,2-*d*]isoxazole intermediate (**202**), upon *N*-alkylation and base-catalyzed rearrangement, afforded the azamacrocyclic (**204**) in excellent yields (Scheme 33) <91JOC4701>. An example of the second type of transformation is shown in selective reduction (hydrogen–Raney nickel–boric acid) of the tetracycle (**205**), obtained by double-addition of benzonitrile oxide to 3-methyl-2,3,5,6-tetrahydro-7(1*H*)-indolizinone, to give the azamacrocyclic diketone (**206**) (Scheme 34) <93G425>.

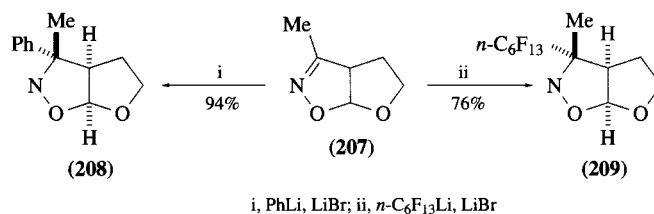


Scheme 33

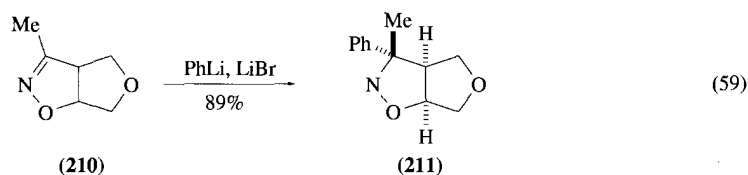


Scheme 34

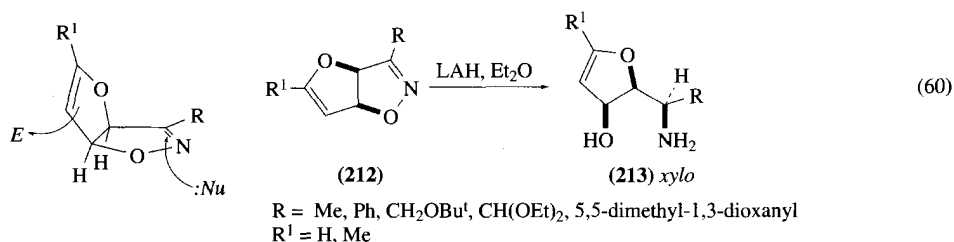
Although the 3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazoles are unstable in the presence of Bronsted acids (e.g., Equation (58)), they are relatively stable to mild Lewis acids. As exemplified in Scheme 35, the combination of an organolithium and lithium bromide facilitates alkylative conversion of the isoxazoline nucleus (**207**) to the bicyclic isoxazolidines (**208**) and (**209**) <89CL1079>. A similar transformation was also reported for the tetrahydrofuro[3,4-*d*]isoxazole (**210**) (Equation (59)).



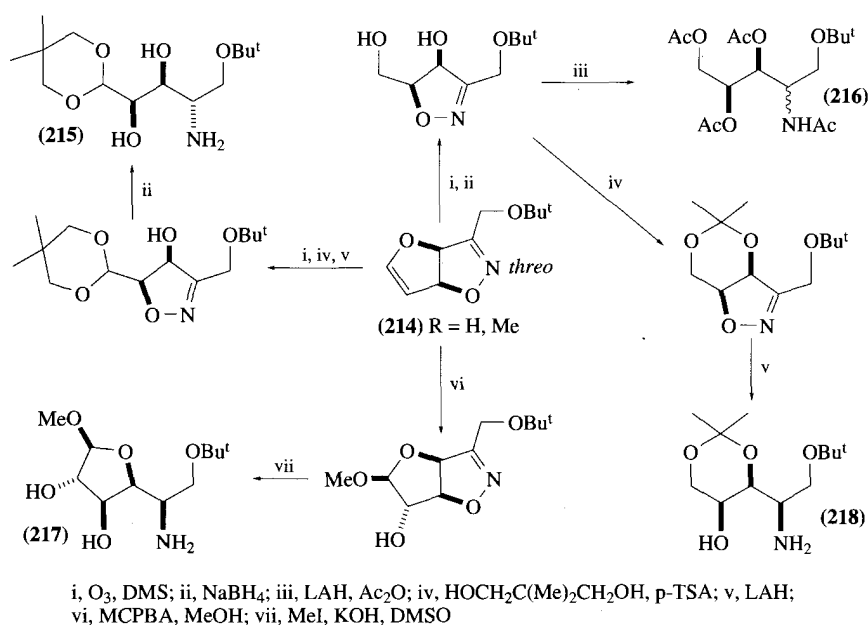
Scheme 35



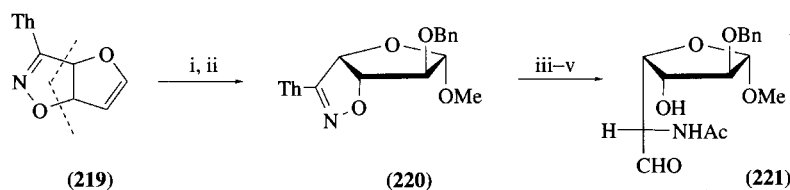
During the last decade numerous developments have been reported on the chemistry of the 3a,6a-dihydrofuro[2,3-*d*]isoxazoles (**212**), which are readily obtained by the addition of nitrile oxides to furans. Reduction of the adducts (**212**) with LAH to give the amines (**213**) (Equation (60)) occurs with high diastereoselectivity, but in some cases ($R = \text{Ph}$) results in a novel [2 + 3] anionic cyclo-reversion. Jäger and Müller have shown that the adducts serve as versatile templates for the regiospecific syntheses of carbohydrates (Scheme 36) <85T3519>. For example, adduct (**214**) is transformed to differentially-protected hexoses and pentoses (**215**)–(**218**). Sequential electrophilic functionalization of the 5,6-double bond and lithium aluminum hydride reduction of the oxime ether moiety afford both diastereoselective reduction of the carbon–nitrogen double bond and cleavage of the nitrogen–oxygen bond to afford the *xylo*-configuration (>95%). The 3-(2-thiazolyl)-3a,6a-dihydrofuro[2,3-*d*]isoxazole (**219**) was similarly transformed to the protected 5-amino-5-deoxydialdoidofuranose derivative (**221**), wherein the thiazolyl unit is a carboxaldehyde synthon (Scheme 37) <88T3215>.



In addition to electrophilic functionalization, the 5,6-double bond of the adducts (see (**222**)) is reported to undergo high-pressure [4 + 2]-cycloaddition with *N*-(2,4-dinitrophenyl)isoquinolinium chloride (**223**) (Bradsher cycloaddition) to afford the naphthol-substituted isoxazoline (**224**) (Equation (61)), which was used for the total synthesis of nogalamycin analogues <92JOC644>.

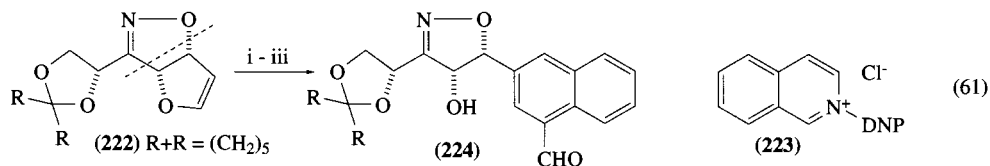


Scheme 36



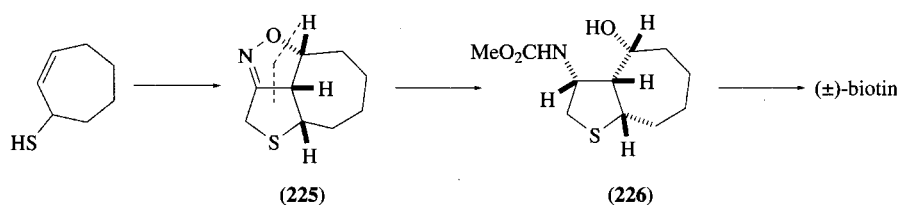
i, MCPBA, MeOH; ii, BnCl, NaH; iii, LAH; iv, Ac₂O; v, MeI, NaBH₄

Scheme 37

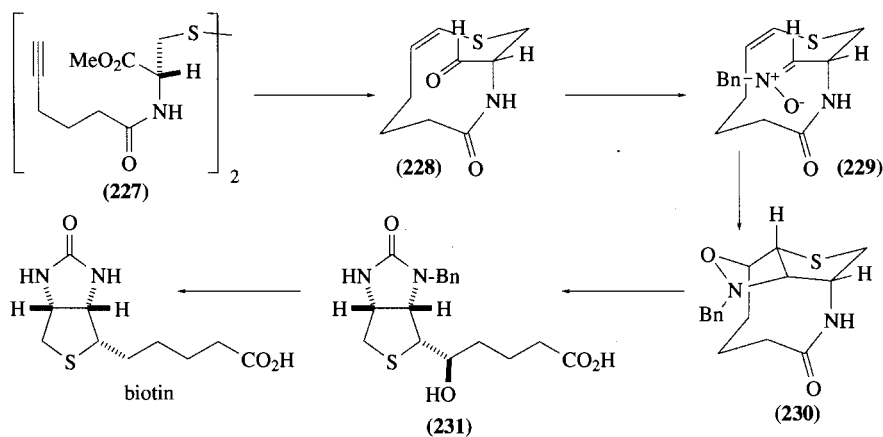


i, (223), 0.6 Kbar, 3 days; ii, Amberlyst - 15 (H⁺); iii, 5% K₂CO₃

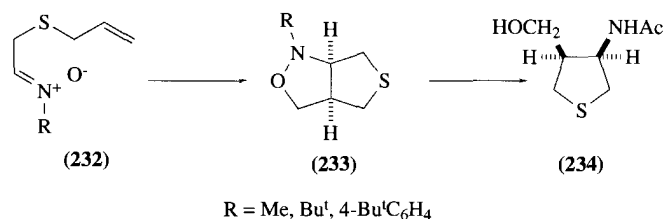
In the last decade, considerable applications of intramolecular dipolar cycloadditions have been reported. These strategies provide a powerful method for the generation of contiguous asymmetric centers with total regiochemical and stereochemical control. Substantial data has been accumulated on the regiochemical aspects of these intramolecular cyclizations. The intramolecular nitrone-alkene cycloadditions, the intramolecular oxime-alkene cycloadditions (IOAC), and the intramolecular nitrile oxide-alkene cycloadditions (INOC) provide synthetic accessibility to various nonconjugated heterocycles that are the subject of this chapter. The majority of the literature shows the syntheses of various [1,2,5]-isomers, with the earliest example of an intramolecular dipole cycloaddition reported by Confalone and co-workers in a synthesis of racemic biotin from cycloheptene via the intermediates (225) and (226) (Scheme 38) <80JA1954>. Few examples of intramolecular dipolar cycloadditions for the synthesis of [1,2,4]-bicyclic systems have been reported. Notable is the second biotin synthesis of Confalone and co-workers (see (227) → (228) → (229) → (230) → (231) → biotin) (Scheme 39) <82JA6460>. In an analogous manner, a synthesis of the racemic tetrahydrothiophene (234) was accomplished from the (allylthio)nitrone (232) (Scheme 40) <88TL5755>



Scheme 38

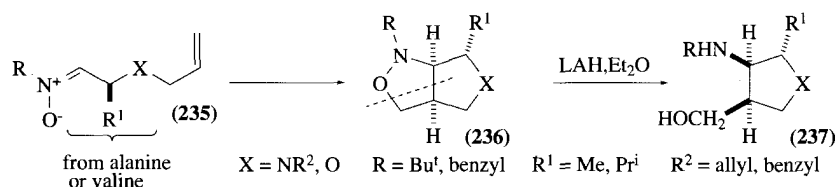


Scheme 39

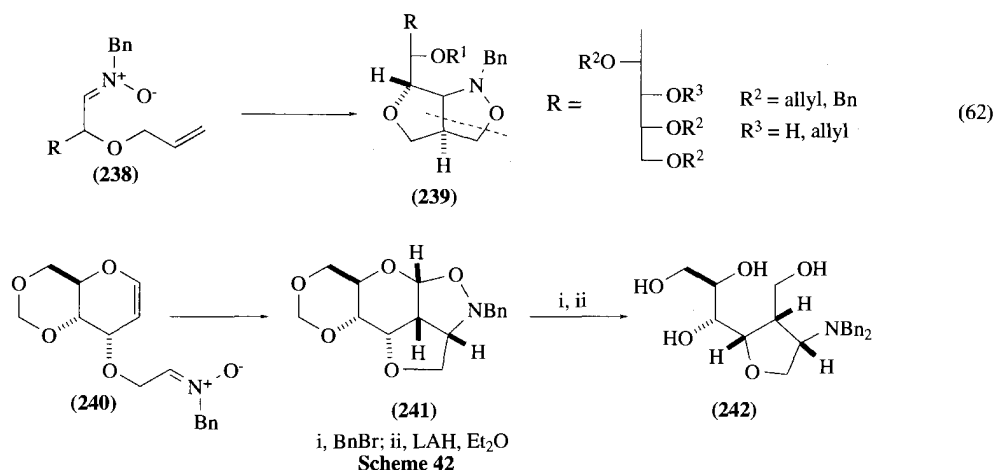


Scheme 40

The power of the intramolecular dipolar cyclizations is further enhanced by the incorporation of chirality into the cyclization precursors. For example, a general synthesis of enantiomerically pure 3,7-dioxa-2-azabicyclo[3.3.0]octanes and 3-oxa-2,7-diazabicyclo[3.3.0]octanes (236) by intramolecular cyclizations of nitrones (235) derived from either alanine or valine (X = NR²) or lactate or malate (X = O) is shown in Scheme 41. These intermediates are further converted to chiral pyrrolidines <93CB787, 95T10497> and carbohydrates (237) <91CB2329> by reductive cleavage of the nitrogen–oxygen bond (236) → (237)). More elaborate carbohydrates (e.g. (239) and (242)) (Equation (62) and Scheme 42) have been obtained from simpler carbohydrates by the intermediacy of 3,7-dioxa-2-azabicyclo[3.3.0]octanes <95TL7729, 95TL7731>.



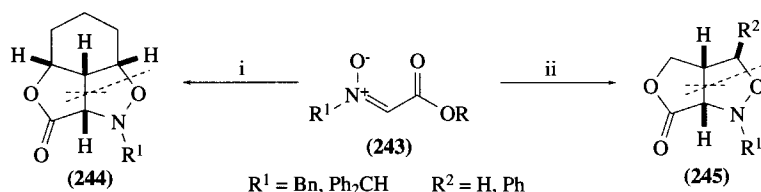
Scheme 41



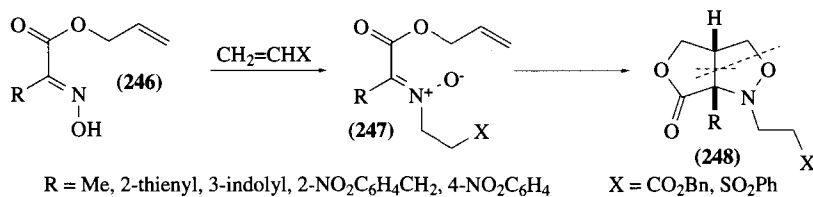
Scheme 42

Further functionality (i.e., 4-oxo) has been introduced by the cyclization of α -allyloxy-carbonylnitrones, which have traditionally been problematic to obtain. Tamura and co-workers have reported that simple alkoxycarbonylnitrones (e.g., (243)) undergo transesterification and cyclization with various allylic alcohols in the presence of titanium isopropoxide (Scheme 43) <95T107, 95T119>. Alternatively, allyl α -oximinocarboxylates (246) are converted *in situ* to nitrones (247) and further cyclized to the bicyclic heterocycles (248) (Scheme 44) <91T4495>. Tetrahydro-1*H*-pyrrolo[3,4-*c*]isoxazoles (250) have been prepared by the condensation of C-acylnitrones with allyl amines <78AJC2013>; further reduction of the bicycles (250) with sodium borohydride affords the 3-oxa-2,7-diazabicyclo[3.3.0]octane (251) (Scheme 45).

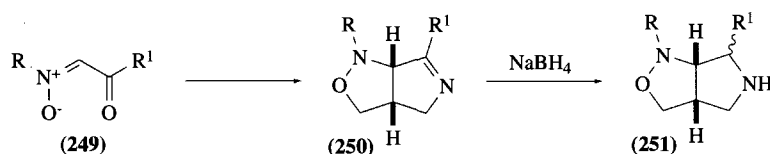
The intramolecular oxime–alkene cyclizations, also known as tandem 1,2-prototropic-cyclo-additions, with nonactivated alkenes was first reported by Oppolzer and Keller in 1970 <70TL1117> but their use for the heterocycles of this chapter was first reported in the 1990s <91T4007>. The methodology is shown in Schemes 46 and 47 in an expedient synthesis of chiral, unfunctionalized

i, cyclohexenol, $\text{Ti}(\text{O-Pr})_4$; ii, $\text{HOCH}_2\text{=CH}_2\text{R}^2$, $\text{Ti}(\text{O-Pr})_4$

Scheme 43

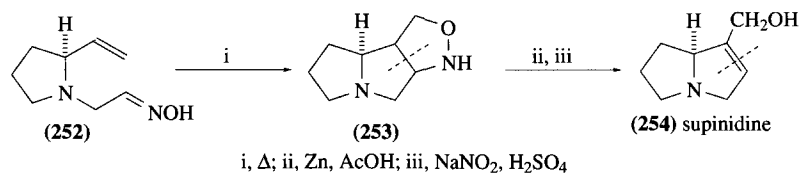


Scheme 44

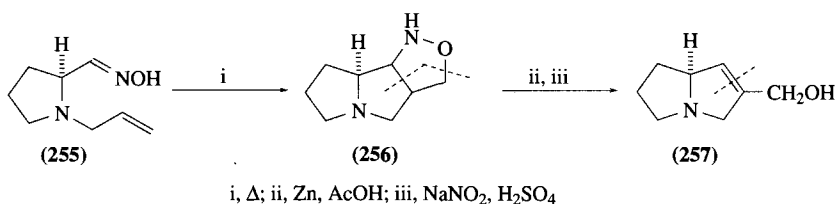


Scheme 45

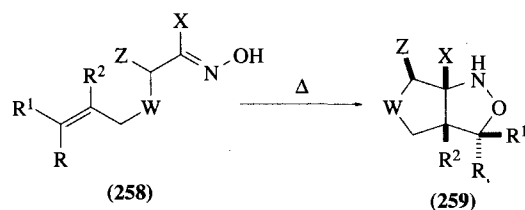
tetrahydropyrrolizindino[3,2-*c*]isoxazoles (**253**) and tetrahydropyrrolizindino[3,2-*c*]isoxazoles (**256**) <91JOC2775>. These intermediates were further transformed to the alkaloid supinidine (**254**) and its isomer (**257**). Both starting oximes were obtained from proline. Hassner and co-workers have extended this strategy to a convenient synthesis of substituted 2-aza-7-hetera-3-oxabicyclo [3.3.0]octanes (**259**) commencing with either α -bromoketones or *O*-silyl α -bromoaloximes (Equation (63)) <93JOC4539>.



Scheme 46



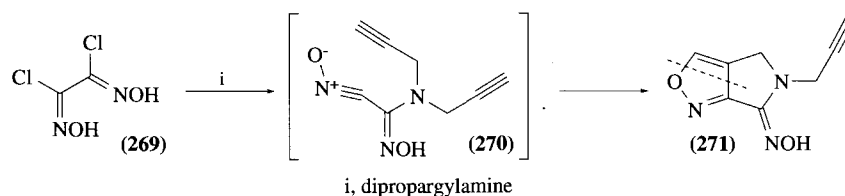
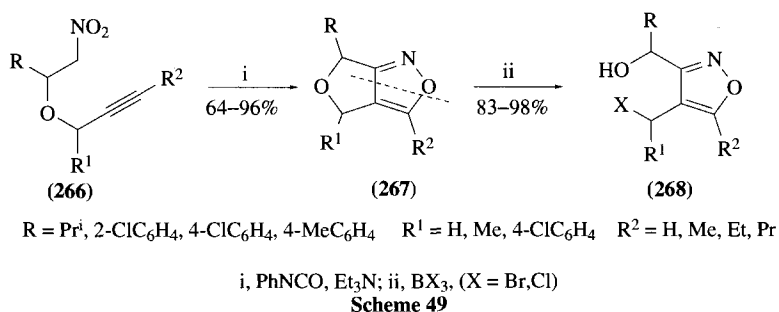
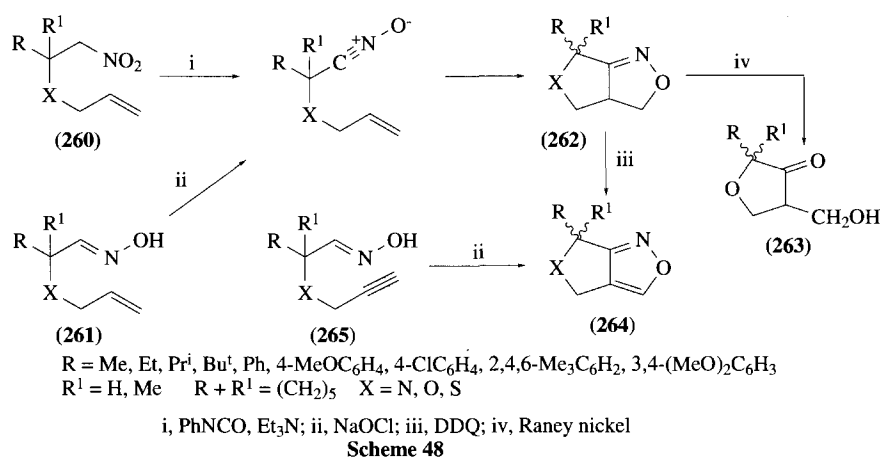
Scheme 47



$\text{W} = \text{O}, \text{S}, \text{NY} \quad \text{X} = \text{H}, \text{Me}, \text{Ph} \quad \text{Y} = \text{allyl}, \text{Me}, \text{Et}, \text{Ph}, \text{c-C}_6\text{H}_{11} \quad \text{Z} = \text{H}, \text{Et}$
 $\text{R} = \text{H}, \text{Me} \quad \text{R}^1 = \text{H}, \text{Me} \quad \text{R}^2 = \text{H}, \text{Me}$

(63)

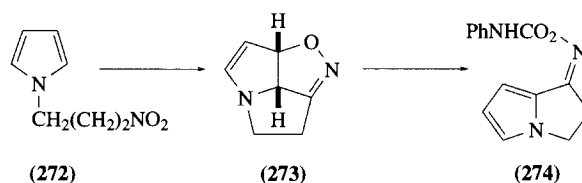
Intramolecular nitrile oxide cyclizations (INOC) are used extensively for the synthesis of tetrahydrofuro[3,4-*c*]-4,4-dihydroisoxazoles (**262**) and tetrahydrofuro[3,4-*c*]isoxazoles (**264**) (Scheme 48). The intermediate nitrile oxide is formed from either aliphatic nitro (e.g., (**260**)) or aldoxime (e.g., (**261**)) precursors. The intermediates (**262**) can be further oxidized to the derivatives (**264**) or selectively reduced to the 4-(hydroxymethyl)tetrahydrofuran-3-ones (**263**) <89JOC5277>. Alkynes are also useful synthons, exemplified by the derivatives (**266**) which give the tetrahydrofuro[3,4-*c*]isoxazoles (**267**) (Scheme 49) <91CB1181>. A useful transformation of these tetrahydrofuro[3,4-*c*]isoxazoles (**267**) is the regioselective Lewis acid fragmentation of the tetrahydrofuran subunit (i.e., (**267**) → (**268**)) <92JOC6513>. The linkage between the alkyne and the nitrile oxide moiety can vary; for example, the reaction of dichloroglyoxime (**269**) with dipropargylamine, which affords the 3,5-dihydropyrrolo[3,4-*c*]isoxazole (**271**), occurs via the unique intermediate (**270**) (Scheme 50) <79KGS991>.



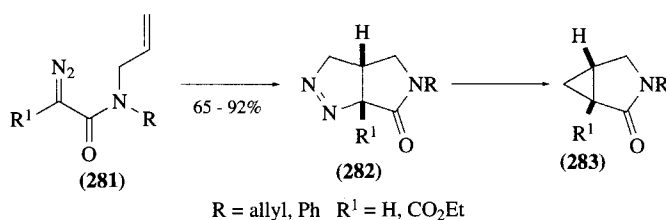
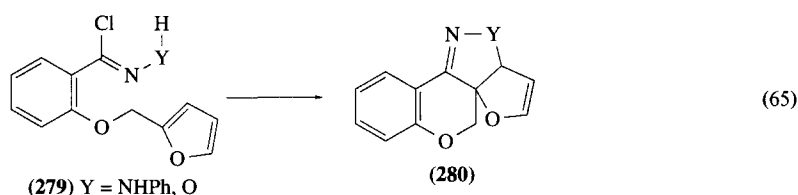
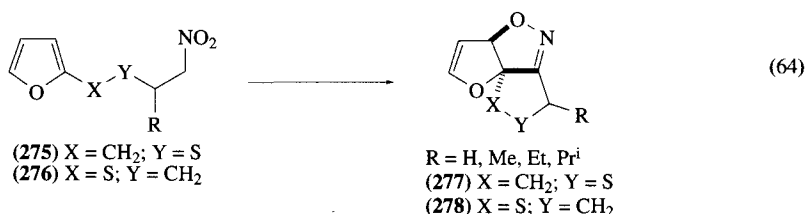
The INOC strategy has been further extended to include a smaller class of cyclizations known as the intramolecular nitrile oxide–heterocycle cyclizations (INHC) in which the alkene component is either a furan or pyrrole (indole) unit. Typically, the furan adducts are more stable whereas the pyrrole adducts fragment (see (**272**) → (**273**) → (**274**)) (Scheme 51) <91JOC896>. While the synthetic

potential of the furan adducts (277), (278), and (280) (Equations (64) and (65)) have yet to be realized, this strategy provides access to novel heterocycles <84CL285, 91T3869>.

Finally, in any discussions on heterocyclic syntheses by dipolar cycloadditions, diazo cycloadditions should not be forgotten. In Scheme 52, the intramolecular cyclization of *N*-allyldiazoacetamides (281) and *N*-allyldiazomalonamides affords *cis*-hexahydropyrrolo[3,4-*c*]-pyrazoles (282) which can be photolyzed to 3-azabicyclo[3.1.0]hexanes (283) <81CB190>.

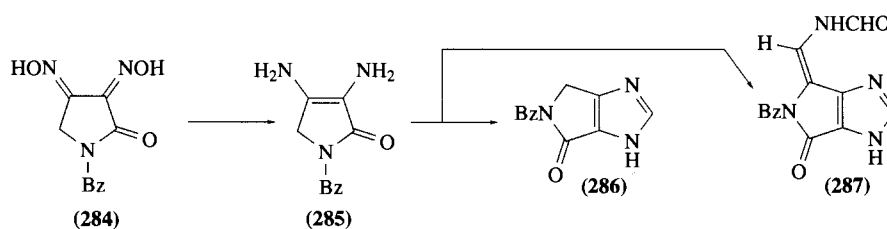


Scheme 51

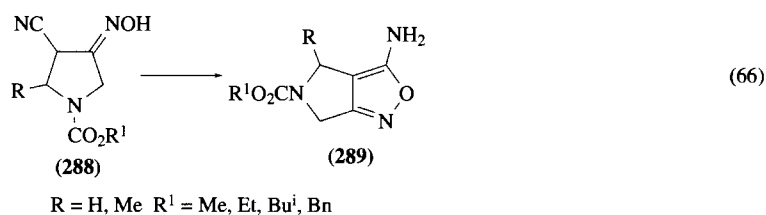


Scheme 52

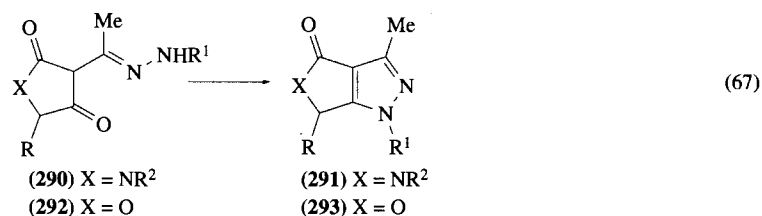
While cycloaddition approaches have been discussed extensively in this chapter, there are certain substitution patterns that are not amenable to such approaches. In these cases, the more traditional annelative approaches are necessary. For example, the 5,6-dihydropyrrolo[3,4-*d*]imidazol-4(3*H*)-one (286) is obtained from the diamine (285) and triethyl orthoformate. If formamide is used in excess, 6-(formamidomethylene)-5,6-dihydropyrrolo[3,4-*d*]imidazol-4(3*H*)-one (287) is obtained (Scheme 53) <70JPS1732>. A variant of the Thorpe cyclization was employed in the preparation of 3-amino-4*H*-pyrrolo[3,4-*c*]isoxazoles (289) from α -cyanooximes (288) (Equation (66)) <68JMC453>. 3-Acyltetramic acid (290; X = NR²) and 3-acyltetronic acid (292; X = O) hydrazones undergo ready cyclization in refluxing xylene with catalytic *p*-toluenesulfonic acid to afford 4-oxo-1,4-dihydro-6*H*-pyrrolo[3,4-*c*]pyrazoles (291) and 4-oxo-1,4-dihydro-6*H*-furo[3,4-*c*]pyrazoles (293), respectively (Equation (67)) <82SC431>. The novel synthesis of 5-amino-6a-hydroxydihydro-6*H*-pyrrolo[2,3-*d*]isoxazole (296) from 3,4-disubstituted 4-(amino)isoxazol-(4*H*)-ones (294) is hypothesized to occur by the cyclization of the ketene aminal intermediates (295) (Scheme 54) <91S127>.



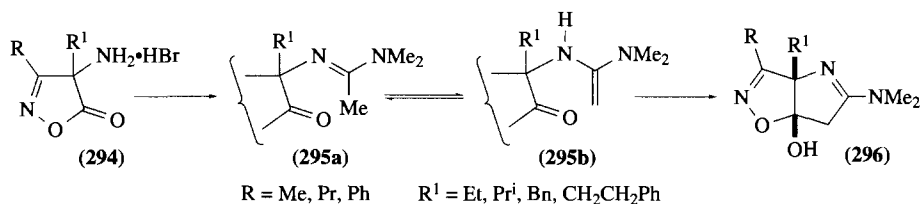
Scheme 53



(66)



(67)

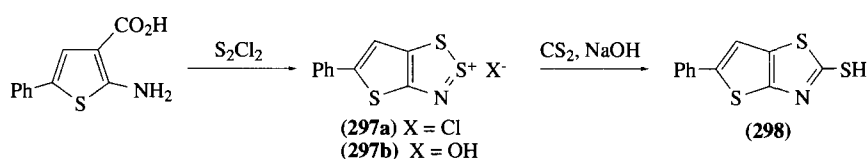


Scheme 54

7.02.9 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROBICYCLIC SYSTEMS

7.02.9.1 Thieno[2,3-*d*]thiazoles

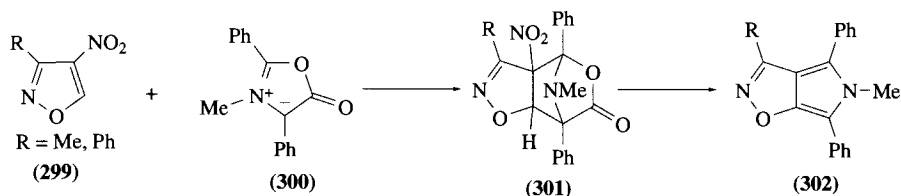
A synthesis of 2-thiethieno[2,3-*d*]thiazoles (**298**) from thieno[2,3-*d*]thioniazolium salts (**297**) has been reported by Abramenko *et al.* (Scheme 55) <79KGS477>. These dithiazolium salts (**297**) are obtained from the reaction of thienylcarboxylic acids with sulfur monochloride. Treatment of the dithiazolium hydroxide (**297b**) with carbon disulfide affords the thiol (**298**) (Scheme 55).



Scheme 55

7.02.9.2 Pyrrolo[3,4-*d*]isoxazoles

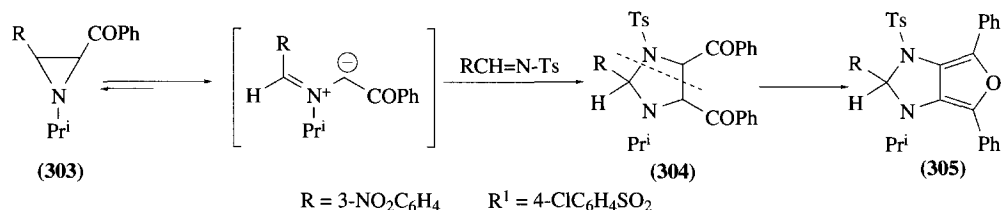
The use of nitro aromatics as dipolarophiles in cycloaddition reactions has shown great utility in heterocyclic synthesis. The reaction of 3-substituted-4-nitroisoxazoles (**299**) with trisubstituted oxazolium 5-oxides (**300**) affords an intermediate adduct (**301**) which eliminates carbon dioxide and nitrous acid to afford 3,4,6-trisubstituted pyrrolo[3,4-*d*]isoxazoles (**302**) (Scheme 56) <93G633>.



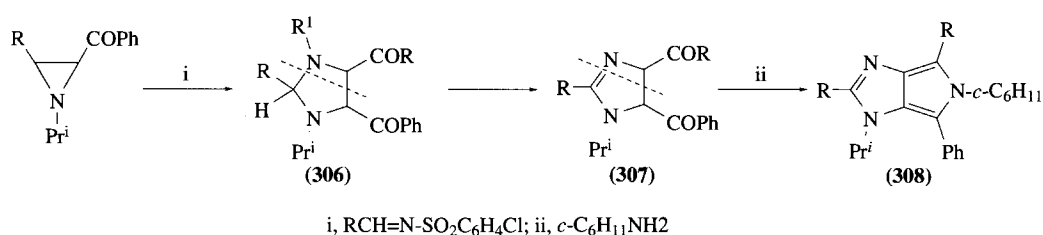
Scheme 56

7.02.9.3 Pyrrolo[3,4-*d*]imidazoles and Furo[3,4-*d*]imidazolines

The 2-arylaziridines (**303**), on thermolysis, provide aroylazomethine ylides which undergo [3 + 2] cycloadditions with various dipolarophiles. Whereas imines are normally inert to dipole synthons, Lown and Landberg reported that the polarized *N*-sulfonyl- α -acylimines afford initially the 1-sulfonyl-4,5-diacylimidazolines (**304**) which undergo cyclodehydration (Paal-Knorr reaction) to the furo[3,4-*d*]imidazolines (**305**) (Scheme 57). A further variant with other substituted *N*-sulfonylimines ($R^1 = 4\text{-ClC}_6\text{H}_4\text{SO}_2$) and sequential amination affords the 1,5-dihydropyrrolo[3,4-*d*]imidazoles (**308**) (Scheme 58) <74CJC798>.



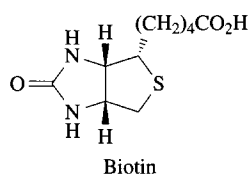
Scheme 57



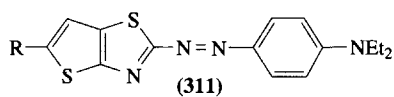
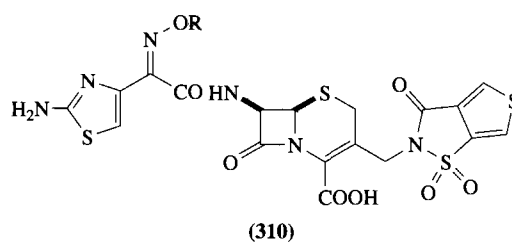
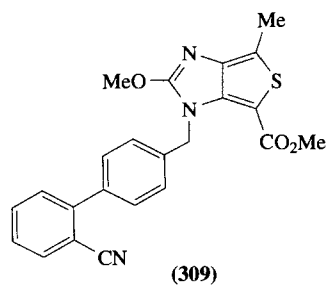
Scheme 58

7.02.10 IMPORTANT COMPOUNDS AND APPLICATIONS

Aside from biotin, whose synthesis and role in biosynthetic processes has been extensively studied <85ANY(447)97, 86MI 702-01, 89MI 702-01>, other representative heterocycles have been evaluated as:



(a) gastric (H^+/K^+)-ATPase inhibitors <88EUP299389, 88EUP301422, 88EUP304732>; (b) angiotensin II antagonists (e.g., **309**) <90EUP407102, 91EUP461040, 91EUP483683, 92EUP520423>; (c) H_2 antagonists <87USP4699906, 88EUP328913, 88JMC1479>; and (d) antibacterials (**310**) <88USP4728732, 88USP4728734>. In addition to biological uses, dichroic dyes (**311**) for liquid crystal displays have been obtained from 2-aminothieno[2,3-*d*]thiazoles <87USP4668050>.



7.03

Bicyclic 5-5 Systems: Four Heteroatoms 1 : 3

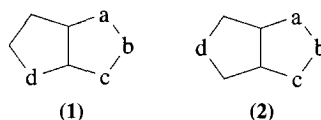
ANTHONY D. M. CURTIS
Keele University, UK

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7.03.1 INTRODUCTION

No single chapter of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) was devoted to 5-5-fused heterocycles containing four heteroatoms arranged 1 : 3 with no heteroatoms occupying the bridgehead position, though the ring index of that edition did contain several examples. Reviews from the 1990s have made scant reference to such heterocycles <90PHC50, 91PHC130, 92PHC123>. This chapter is concerned with such 5-5-fused heterocyclic systems, for example (1) and (2). Both aromatic and nonaromatic examples are examined, with an emphasis on those systems which contain nitrogen, oxygen, and sulfur as heteroatoms. A body of work does exist in which the heterocyclic system contains boron, phosphorus, and selenium, some serving as part of protecting groups for glycosides; these compounds are not surveyed here. This chapter concentrates on work published since the appearance of CHEC-I, although some ring systems from earlier work are included.



7.03.2 THEORETICAL METHODS

There is nothing to report in this area.

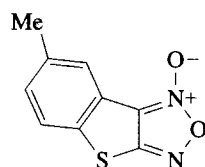
7.03.3 EXPERIMENTAL STRUCTURAL AND SPECTROSCOPIC METHODS

7.03.3.1 X-ray Diffraction

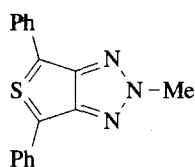
Several compounds of interest have had their crystal and molecular structures elucidated using x-ray analysis. 7-Methylbenzothieno[3,2-c][1,2,5]oxadiazole 1-oxide (3) was found to align itself in the crystal lattice so that the benzene ring of one molecule faces the 1,2,5-oxadiazole oxide moiety of another, thus superposing the least number of atoms <75CSC13>.

The structure of 4,6-diphenyl-2-methylthieno[3,4-d]-1,2,3-triazole (4), an example of a non-classical 10 π -electron heteropentalene, has been solved. The phenyl groups of compound (4) are virtually coplanar with the thienotriazole moiety: the thienotriazole is slightly folded. Compound (4) is of interest as it is unusually inert to reaction with dipolarophiles <77HC(30)317>. In comparison

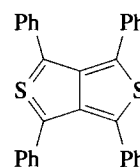
to the known structure of tetraphenylthieno[3,4-*c*]thiophene (**5**), several observations were made which infer that the difference in reactivity is due to electronic factors: the average C—S bond length in (**4**) is 1.732 Å, closely resembling the C—S bond in classical fused thiophenes, yet the C—S—C bond angle of 96.4° does not compare with that of 92° for classical systems. Also, the C—N bond distances in (**4**) are longer than average and the N—N—N bond angle is larger than expected by 2.9° <79AX(B)223>.



(3)

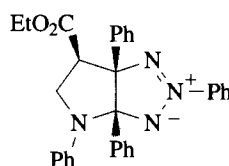


(4)

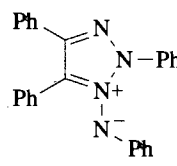


(5)

The structure of 6-*exo*-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo [2,3-*d*]-1,2,3-triazol-2-ium-3-ide (**6**) has been determined; compound (**6**) arises from an initial 1,3-dipolar cycloaddition between ethyl acrylate and the dipole (**7**), followed by sigmatropic rearrangements <90JCS(P1)2537>.



(6)



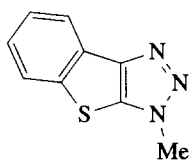
(7)

7.03.3.2 Molecular Spectra

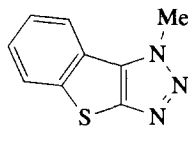
While many of the ring systems described in this chapter give spectral analyses entirely as would be predicted, there are several points of interest worth noting. The original publication should be consulted for data pertaining to an individual molecule.

7.03.3.2.1 NMR Spectroscopy (¹H, ¹³C)

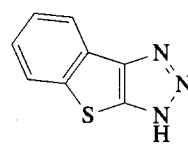
The nuclear Overhauser effect (NOE) was employed in the assignment of structures to the products (**8**) and (**9**) from methylation of 3*H*-[4,5]benzothieno[2,3-*d*]-1,2,3-triazole (**10**), as their ¹H and ¹³C NMR spectra were virtually identical <93JCR(S)128>.



(8)



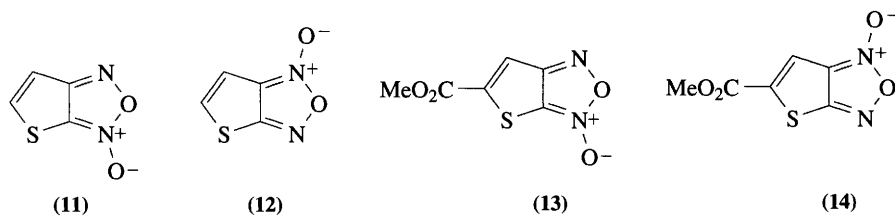
(9)



(10)

Low temperature NMR studies revealed separate signals for the isomeric thieno[2,3-*c*] [1,2,5]oxadiazole *N*-monoxide (**11**) and (**12**) at −45°C. The shielding effect of the *N*-oxide group

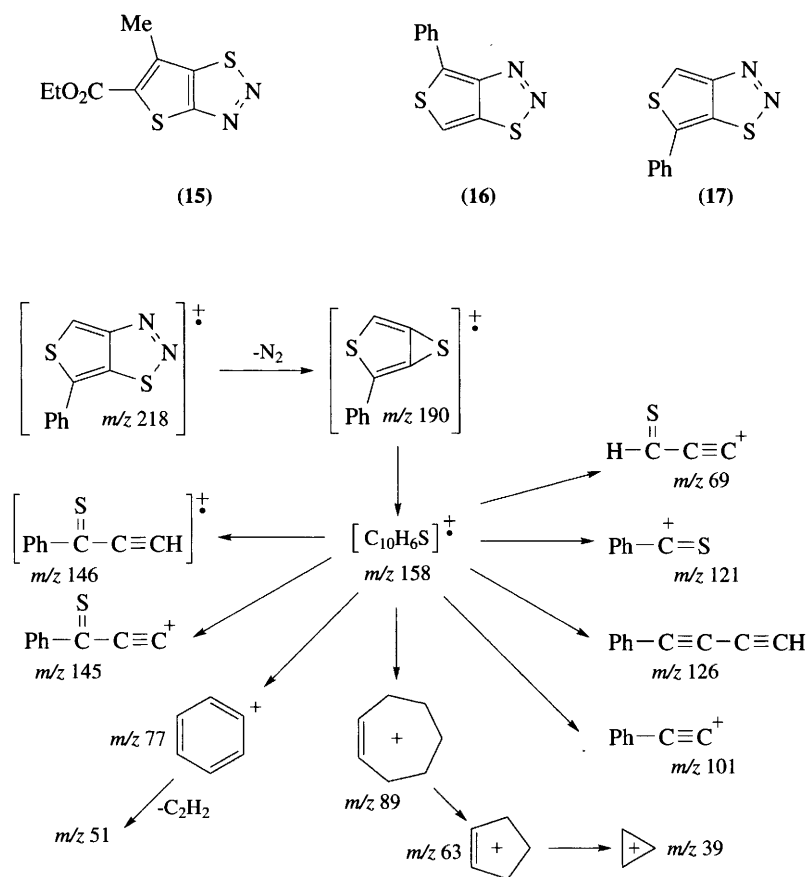
aided in the designation of structure (12) to the predominant isomer <74JOC2956>. In a similar study, the equilibrating 1,2,5-oxadiazole *N*-monoxides (13) and (14) were found to give separate signals at -60°C <89JCS(P2)127>.



7.03.3.2.2 Mass Spectrometry

The mass spectrum of 5-ethoxycarbonyl-6-methylthieno[2,3-*d*]-1,2,3-thiadiazole (15) showed a molecular ion at m/z 228, followed by a characteristic loss of nitrogen to give a $[\text{M}-\text{N}_2]^+$ ion at m/z 200. An alternative fragmentation yielded the $[\text{M}-\text{OEt}]^+$ ion at m/z 183 <88JPR866>.

4-Phenyl- and 6-phenylthieno[3,4-*d*]-1,2,3-thiadiazoles, (16) and (17), both gave similar fragmentation patterns. The initial loss of nitrogen was followed by loss of sulfur and further fragmentation could be assigned as shown in Scheme 1 <78JHC473>.



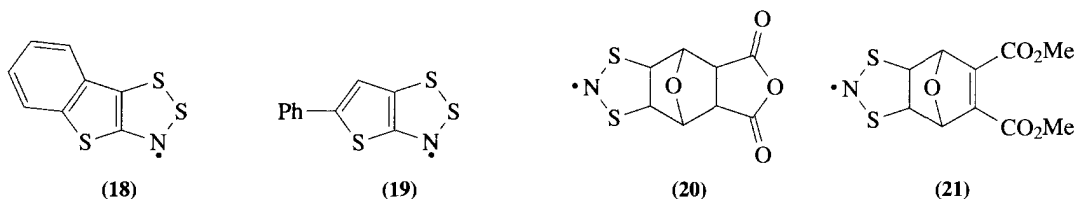
Scheme 1

7.03.3.2.3 IR and UV Spectroscopy

There is nothing to report in this area.

7.03.3.2.4 ESR Spectroscopy

Dithiazolyl radicals, such as [1]benzothieno[2,3-*d*]-1,2,3-dithiazolyl (**18**) and 5-phenylthieno[2,3-*d*]-1,2,3-dithiazolyl (**19**), generated either from the parent thieno[2,3-*d*]-1,2,3-dithiazol-2-ium salt by treatment with various powdered metals or from the parent enamine by treatment with a mixture of sulfur and chlorine in carbon tetrachloride, have been studied using ESR techniques <81ZC146, 82EGP156183>. Delocalization of the unpaired electron over the whole radical was demonstrated for this class of compounds <84CCC684>. Persistent free radicals generated from the reaction of sulfur nitride with alkenes have also been investigated by electron spin resonance, and these include the heterocyclic compounds (**20**) and (**21**) <80JCS(F1)1490>.



7.03.4 THERMODYNAMICS AND AROMATICITY

7.03.4.1 Thieno[2,3-*c*][1,2,5]oxadiazoles

The energetics of the equilibrium between the isomeric thieno[2,3-*c*][1,2,5]oxadiazole *N*-monoxides (**11**) and (**12**) has been studied using low temperature NMR techniques, together with a comparison with other 1,2,5-oxadiazole 2-oxide systems <74JOC2956>. A similar study commented that the rate of isomerization between (**13**) and (**14**) is fast on the NMR timescale at room temperature. The equilibrium constant K_c for the isomerization between (**13**) and (**14**) is 65 whilst the free energy of activation for the isomerization is 51.3 kJ mol⁻¹ <89JCS(P2)127>.

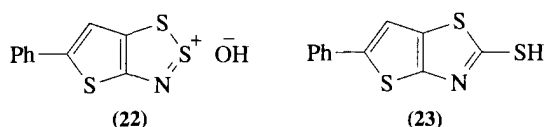
7.03.5 REACTIVITY OF FULLY-CONJUGATED RING SYSTEMS

Usually, investigations into the chemistry of the fully conjugated ring system are reported more frequently than corresponding investigations into the nonconjugated ring system. For 5-5-fused heterocycles containing four heteroatoms arranged 1 : 3 with no heteroatoms occupying the bridge-head position, however, more examples exist of studies into the reactivity of nonconjugated ring systems, this fact being reflected in the following sections.

7.03.5.1 Thieno[2,3-*d*]-1,2,3-dithiazoles

Treatment of 5-phenylthieno[2,3-*d*]-1,2,3-dithiazol-2-ium hydrate (**22**) with CS₂ and base yielded the thienothiazole (**23**) in 15% yield <79KGS477>.

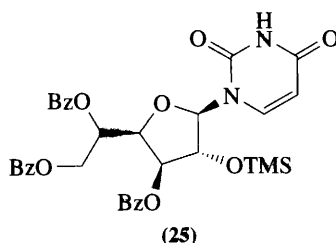
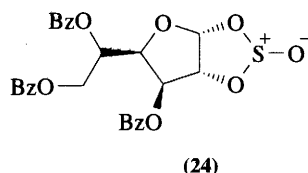
Various substituted furo-, pyrrolo- and thieno-[3,4-*d*]-1,2,3-thiadiazoles were reacted with sulfur to yield pentathiepin derivatives in moderate yields <85EUP13862>.



7.03.6 REACTIVITY OF NONCONJUGATED RING SYSTEMS

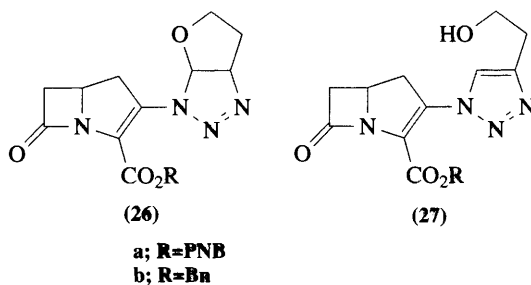
7.03.6.1 Furo[2,3-*d*]-1,3,2-dioxathioles

The furo[2,3-*d*]-1,3,2-dioxathiole system may be used to good effect in the synthesis of glycosides. For example, reaction of the sulfite (**24**) with excess bis(trimethylsilyl)uracil in a fusion process without a catalyst gave the glycoside (**25**) in 93% yield. Addition of water to the reaction mixture yields glycosides which are unprotected at the C-2' hydroxyl group <88CAR(180)233>.



7.03.6.2 Furo[2,3-*d*]-1,2,3-triazoles

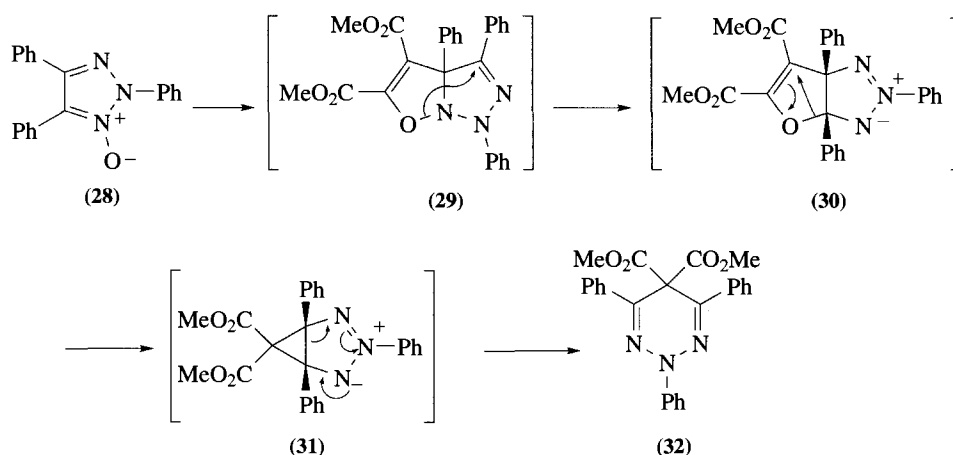
Under the reaction conditions used for their generation, the carbapenem-substituted 3a,5,6,6a-tetrahydro-3*H*-furo[2,3-*d*]-1,2,3-triazoles (**26**) isomerized to yield the triazoles (**27**) <85TL5407>.



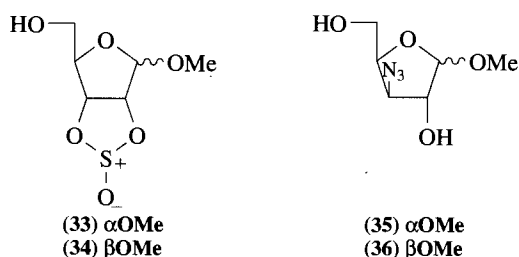
Unstable furo[2,3-*d*]-1,2,3-triazoles are intermediates in the cycloaddition reaction of 1,2,3-triazolium 1-oxides to yield 1,2,3-triazines. For example, compound (**28**) reacted with DMAD to give initially the 1,3-dipolar cycloadduct (**29**). Rearrangement of this adduct (**29**) gives the unstable furo[2,3-*d*]-1,2,3-triazole derivative (**30**) which rearranges further to yield 1,2,3-triazine (**32**) via the intermediate (**31**) (Scheme 2) <90JCS(P1)3321>.

7.03.6.3 Furo[3,4-*d*]-1,3,2-dioxathioles

This particular system finds most use as a reactive protective group in carbohydrate syntheses. For example, the cyclic sulfite moiety may be attacked by nucleophiles, opening the ring regio- and stereoselectively. The methyl furanosides (**33**) and (**34**) when treated with NaN₃ yield the glycosides (**35**) and (**36**), respectively. This is in contrast to the opening of carbohydrate C(2)–C(3) epoxides which produce a mixture of isomers <85TL6343>. The sulfite moiety may be conveniently removed using a mild hydrolysis <93JMC3424>.

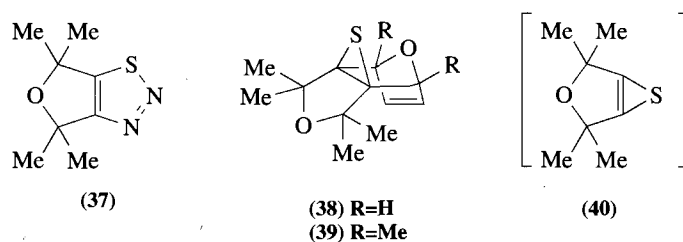


Scheme 2

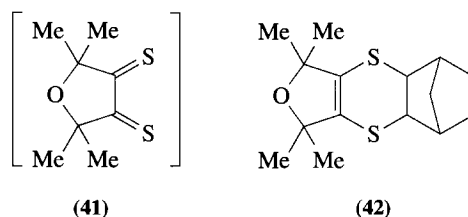


7.03.6.4 Furo[3,4-*d*]-1,2,3-thiadiazoles

4,6-Dihydro-4,4,6,6-tetramethylfuro[3,4-*d*]-1,2,3-thiadiazole (37) has been used to prepare some highly reactive intermediates. Photolysis of compound (37) in the presence of furan gave the adduct (38) in 11% yield; a similar reaction in the presence of 2,5-dimethylfuran gave the adduct (39) in 12% yield. The authors claim that formation of adducts (38) and (39) unequivocally proves the intermediacy of the antiaromatic thiirene (40) <87TL2867>.

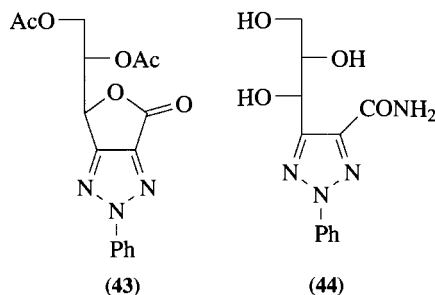


In an attempt to prepare the 1,2-dithione (41), 4,6-dihydro-4,4,6,6-tetramethylfuro[3,4-*d*]-1,2,3-thiadiazole (37) was treated with molten sulfur, yielding a mixture of cyclopolythiophenes. Subsequent photolysis of this mixture in the presence of an alkene (e.g., norbornene) gave adducts such as compound (42), indicating the intermediacy of the dithione (41) <87TL4833>.

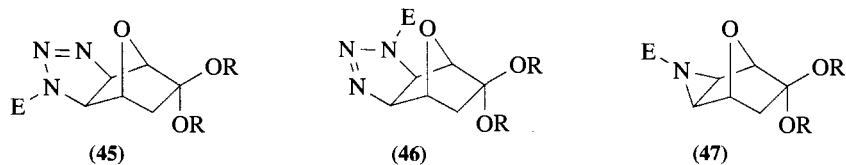


7.03.6.5 Furo[3,4-*d*]-1,2,3-triazoles

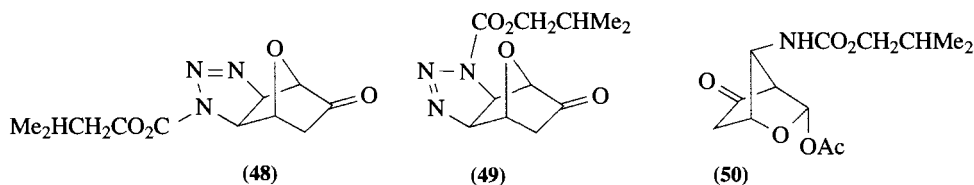
Triazole lactones derived from dehydroascorbic acid can be reacted with a variety of nitrogen nucleophiles to yield monocyclic triazoles. For example, the lactone (43) reacts with NH_3 to yield the triazole (44) <77CAR(59)141, 83CAR(124)97>.



The triazoles (45) and (46) are converted smoothly to aziridines (47) using a mercury light source <89HCA882>. Allied to this research is the observation that the triazoles (48) and (49) rearrange under acid catalysis to yield the carbamate derivative (50) via cationic intermediates <90C342>.



a; R=Me, E=CO₂Et
 b; R=Bn, E=CO₂Et
 c; R=Me, E=CO₂Bu^t
 d; R=Bn, E=CO₂Bu^t

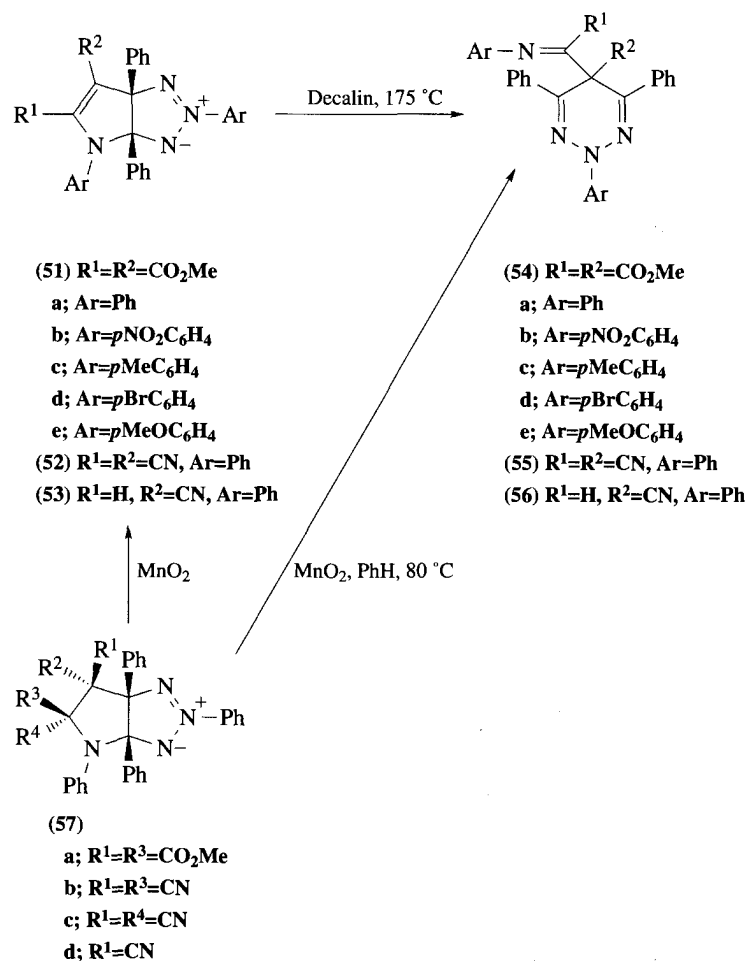
7.03.6.6 Pyrrolo[2,3-*d*]-1,2,3-triazoles

The triazol-2-ium-3-ide derivatives (51a-e), (52), and (53) undergo a thermolytic rearrangement and ring expansion to yield 2,5-dihydro-1,2,3-triazines (54a-e), (55), and (56) in high yields. The double bond at C(5)-C(6) is essential for this rearrangement to take place: compounds (57a-d) do not yield triazines without prior oxidation. Manganese dioxide was also found to catalyze the rearrangements such that they may be carried out directly from compounds (57a-d) in refluxing benzene without isolation of the intermediate C(5)-C(6) unsaturated species (Scheme 3) <93JCR(S)78>.

The triazol-2-ium-3-ide derivatives described above may also undergo a photolytic rearrangement to yield imidazo[4,5-*c*]pyrazoles. Thus, compounds (51) and (58) yield the corresponding imidazo[4,5-*c*]pyrazoles (59) via the mechanism shown in Scheme 4 <93JCS(P1)2757>.

7.03.6.7 Pyrrolo[3,4-*d*]-1,2,3-triazoles

The thermal decomposition of adducts of *N*-phenylmaleimide and *N*-phenylcitraconimide with benzyl azides to yield aziridines via the loss of N_2 has been studied by thermogravimetric and differential scanning calorimetric methods. It was found that the decomposition of the triazolines (60a-d) depends upon the nature of the *para*-substituent on the benzyl moiety. Also, the methyl



Scheme 3

group present in the triazolines (**61a-d**) destabilizes the adducts such that aziridine formation is extremely rapid <84MI 703-01>.

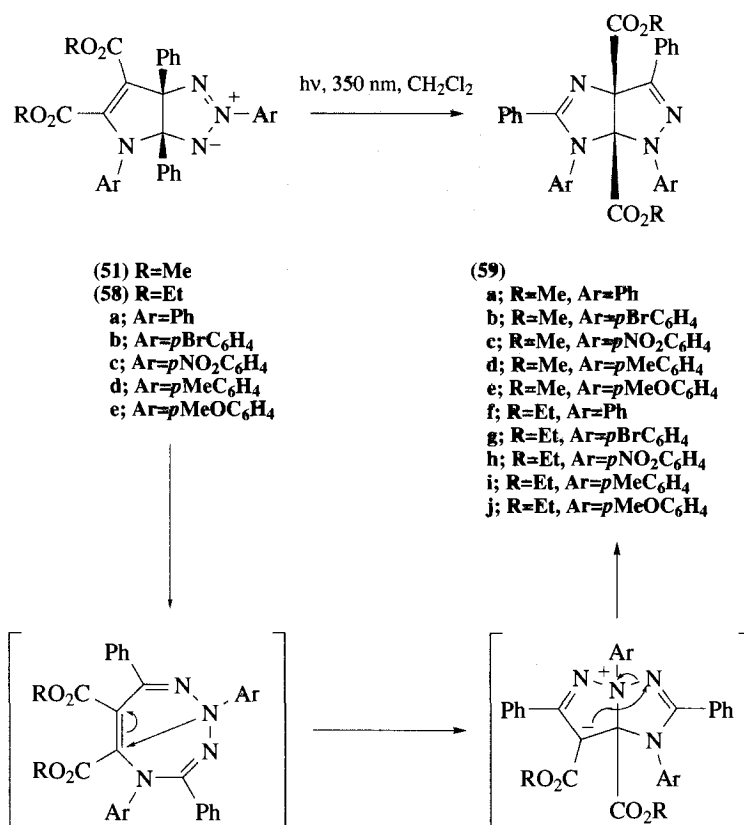
The synthetic utility of the photolytic decomposition pathway of pyrrolo[3,4-*d*]-1,2,3-triazole derivatives has been realised in the asymmetric synthesis of (–)-quinocarcin. Thus, the triazine (**62**) was irradiated using a mercury light source to give aziridine (**63**) in 90% yield via loss of nitrogen <93JA10742>.

3a,8b-Dihydro-5-methyl-1-phenyl-1*H*-1,2,3-triazolo[4,5':4,5]thieno[2,3-*c*]pyridine 4-dioxide (**64**) when heated above 100°C decomposes to yield aziridine (**65**) <80HCA1719>.

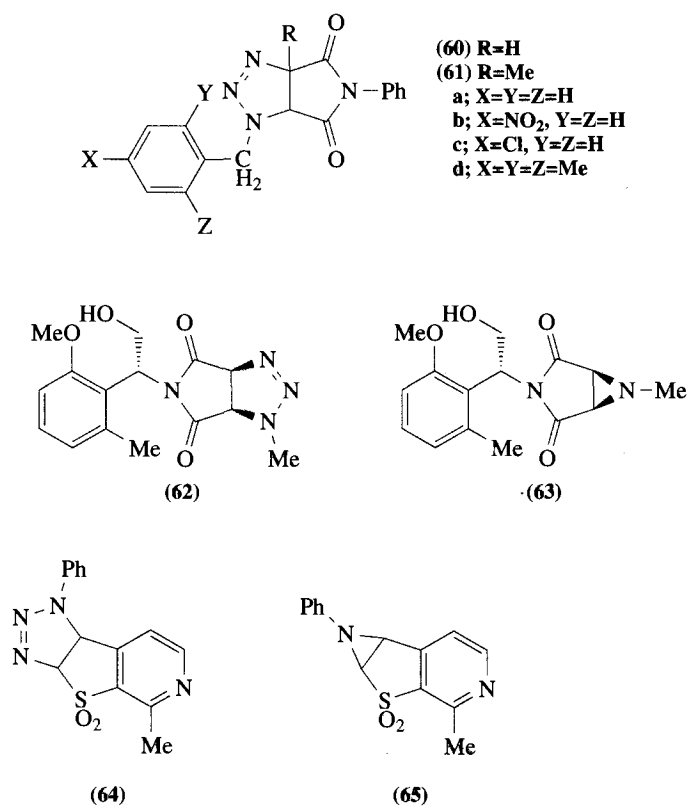
Reaction of the quaternary salts (**66a-c**) under basic conditions led to a mixture of products. For example, treatment of compounds (**66**) with Et_3N/KOH led predominantly to *exo*-methylene triazolines (**67**). Alternatively, treatment of compounds (**66**) with a mixture of 1% NaOH in MeOH favored the isomeric triazoles (**68**) as the major products <80JHC267>.

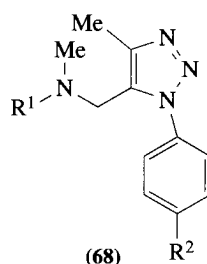
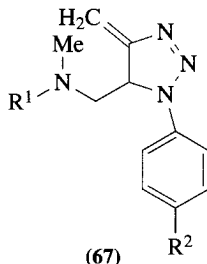
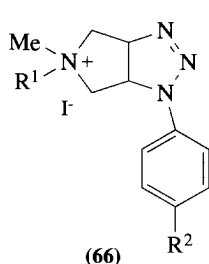
7.03.6.8 Thieno[2,3-*d*]-1,2,3-triazoles

An investigation into the methylation of 3*H*-[1]benzothieno[2,3-*d*]-1,2,3-triazole (**10**) demonstrated that the combination of Me_2SO_4 and the silver salt of (**10**) gives reasonable yields of 3-methyl-[1]benzothieno[2,3-*d*]-1,2,3-triazole (**8**). The reagent of choice for preparation of 2-methyl-[1]benzothieno[2,3-*d*]-1,2,3-triazole (**69**) was MeI, and MeOTf gives good yields of 1-methyl-[1]benzothieno[2,3-*d*]-1,2,3-triazole (**9**) <93JCR(S)128>.

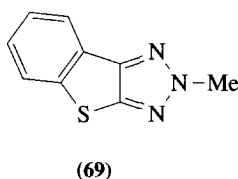


Scheme 4



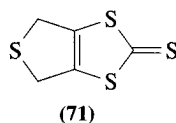
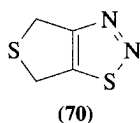


a; R¹=Me, R²=NO₂
 b; R¹=Bn, R²=NO₂
 c; R¹=Bn, R²=CN



7.03.6.9 Thieno[3,4-*d*]-1,2,3-thiadiazoles

Upon treatment with CS₂ at 170 °C, 4,6-dihydrothieno[3,4-*d*]-1,2,3-thiadiazole (70) yielded 4,6-dihydrothieno[3,4-*d*]-1,3-dithiole-2-thione (71), which was a useful intermediate for the synthesis of a novel organic conductor <89TL7249>.



7.03.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

There is nothing to report in this area.

7.03.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

There is nothing to report in this area.

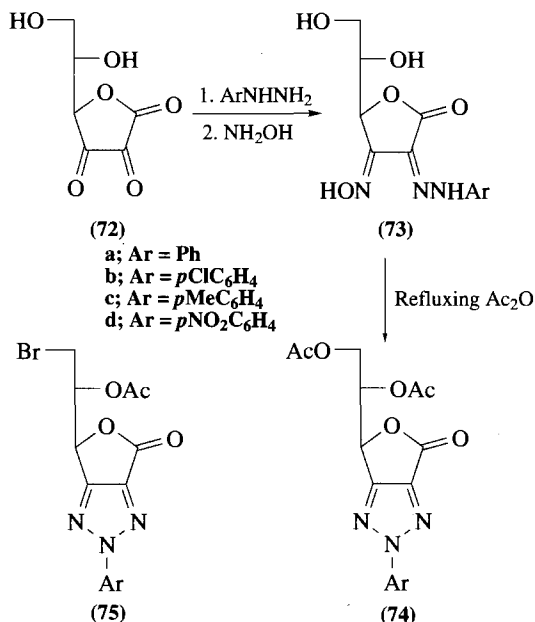
7.03.9 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

7.03.9.1 Synthesis of the Second Heterocyclic Ring from [5 + 0] Atom Fragments

7.03.9.1.1 Furo[3,4-*d*]-1,2,3-triazoles

Treatment of dehydro-L-ascorbic acid (72) with phenyl hydrazine followed by hydroxylamine yielded the hydrazone oxime (73a), cyclization of which in refluxing acetic anhydride gave 4-[L-threo-2,3-diacetoxy-(1-hydroxypropyl)]-2-phenyl-1,2,3-triazole-5-carboxylic acid lactone (74a) <77CAR(59)141>. Analogous reactions of the derivatives (72) with substituted aryl hydrazines yielded the triazoles (74b-d). Alternatively, the hydrazone oximes (73a-d) may be treated with HBr in

AcOH prior to refluxing in Ac₂O, yielding the bromo derivatives (**75a-d**) (Scheme 5) <82CAR(110)229>. Identical studies were also carried out using dehydro-D-arabinoascorbic acid-2-arylhydrazone-3-oximes <83CAR(124)97>.



Scheme 5

7.03.9.1.2 Pyrrolo[3,4-*c*][1,2,5]oxadiazoles

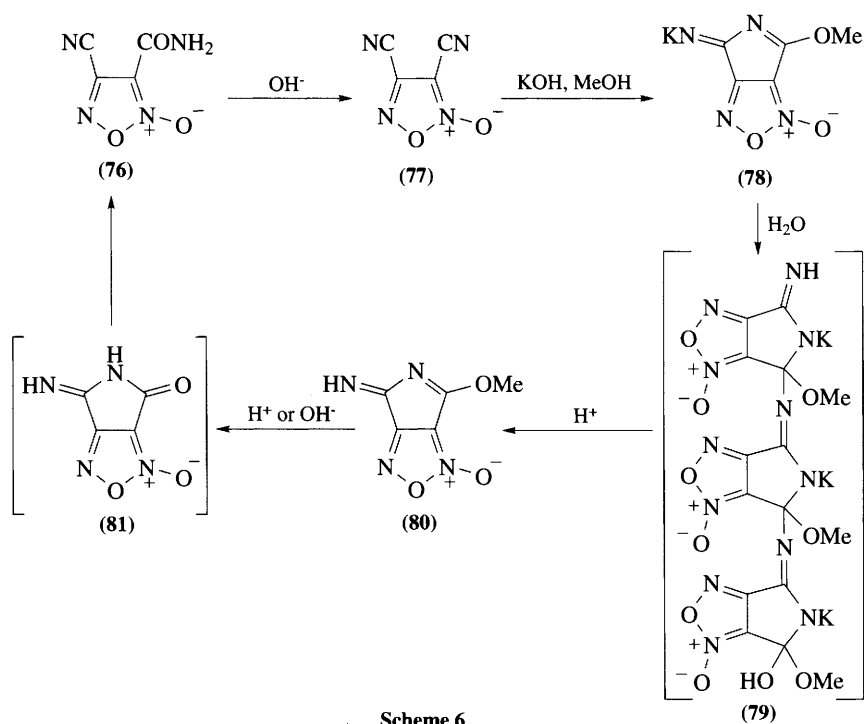
A method for preparing 6-alkoxy-4-imino-4*H*-pyrrolo[3,4-*c*][1,2,5]oxadiazole 1-oxides from 3-carbamoyl-4-cyano-1,2,5-oxadiazole 2-oxide (**76**) has been described. For example, reaction of compound (**76**) with base yields the dinitrile (**77**), subsequent reaction of which with KOH in MeOH gives the potentially explosive compound (**78**) (93% yield). Treatment of this salt (**78**) with water yields the polymeric hydrate (**79**), from which 6-methoxy-4-imino-4*H*-pyrrolo[3,4-*c*][1,2,5]oxadiazole 1-oxide (**80**) may be obtained in 84% yield. Either acid or base will convert (**80**) back to the original oxadiazole (**76**) via the oxide (**81**) (Scheme 6) <75LA1029>.

7.03.9.1.3 Pyrrolo[3,4-*d*]-1,2,3-thiadiazoles

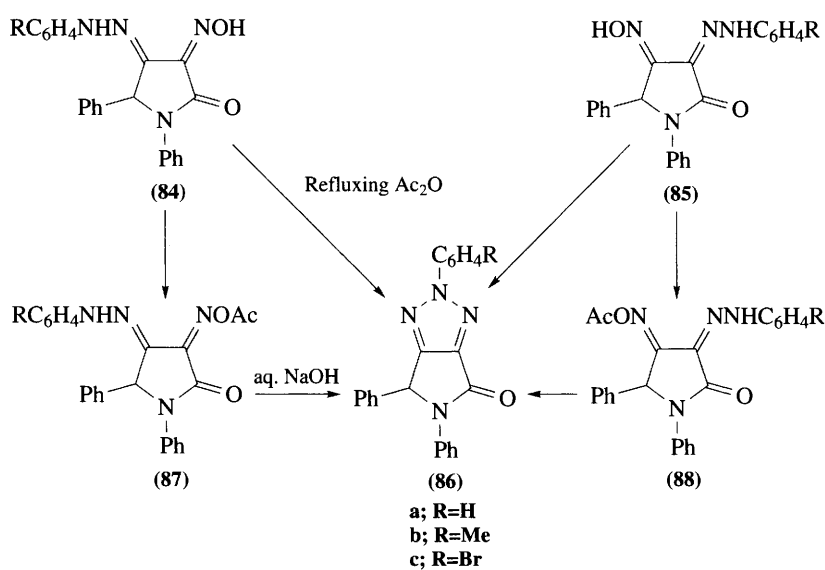
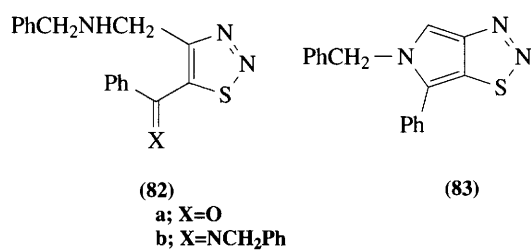
Both of the thiadiazoles (**82a**) and (**82b**) can be converted to 5-benzyl-6-phenylpyrrolo[3,4-*d*]-1,2,3-thiadiazole (**83**) by treatment with acid <78JHC473>.

7.03.9.1.4 Pyrrolo[3,4-*d*]-1,2,3-triazoles

The cyclization of compounds containing both hydrazone and oxime moieties is a popular method for the preparation of 1,2,3-triazoles and is exploited in the preparation of 2-substituted 5,6-dihydro-5,6-diphenylpyrrolo[3,4-*d*]-1,2,3-triazol-4(2*H*,4*H*)ones. The isomeric hydrazone oximes (**84**) and (**85**) may be cyclized in refluxing Ac₂O to yield the corresponding pyrrolo[3,4-*d*]-1,2,3-triazolones (**86**). Alternatively, the pyrrolo[3,4-*d*]-1,2,3-triazolones (**86**) may be attained by alkylation of the hydrazone oximes (**84**) and (**85**), followed by treatment with aqueous NaOH. The routes described are high yielding with only one exception: pyrrolo[3,4-*d*]-1,2,3-triazolone (**86c**) is unavailable from either compound (**87c**) or compound (**88c**) (Scheme 7) <90M671>.



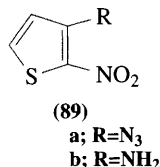
Scheme 6



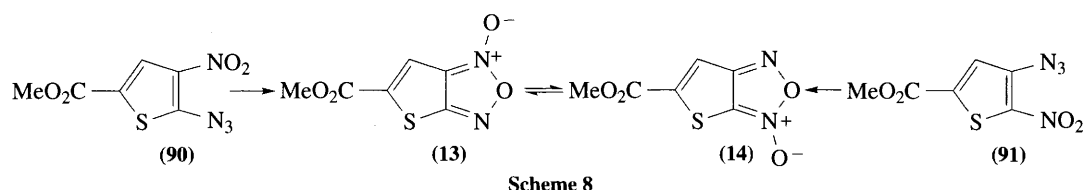
Scheme 7

7.03.9.1.5 Thieno[2,3-*c*][1,2,5]oxadiazoles

Thieno[2,3-*c*][1,2,5]oxadiazole 1-oxide (**12**) was prepared in 45% yield by thermal decomposition of the azide (**89a**). This oxadiazole oxide (**12**) was also prepared, albeit in lower yield, from the amine (**89b**) <74JOC2956>.

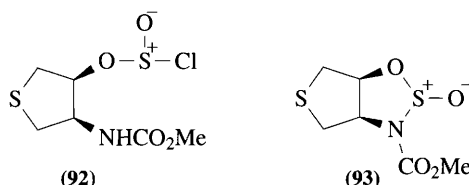


The azide (**90**) decomposes to yield *N*-monoxide (**13**), whilst the isomeric azide (**91**) decomposes to yield *N*-monoxide (**14**). The products (**13**) and (**14**) are in rapid equilibrium (Scheme 8) (see also Sections 7.03.3.2.1 and 7.03.4.1) <89JCS(P2)127>.



7.03.9.1.6 Thieno[3,4-*d*]-1,2,3-oxathiazoles

The *cis*-carbamate (**92**) can be cyclized by either basic or thermal catalysis to give 3-methoxycarbonyl-3a,4,6,6a-tetrahydro-3*H*-thieno[3,4-*d*]-1,2,3-oxathiazole monoxide (**93**) in reasonable yield <75KGS334>.



7.03.9.2 Synthesis of the Second Heterocyclic Ring from [4 + 1] Atom Fragments

7.03.9.2.1 Furo[2,3-*d*]-1,3,2-dioxathioles

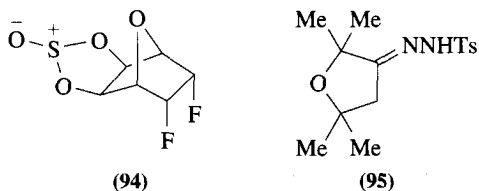
The furo-1,3,2-dioxathiole ring system has found particular use in the area of carbohydrate synthesis, and much of the literature concerning this heterocyclic system focuses on this research front. The furo[2,3-*d*]-1,3,2-dioxathiole system is of most importance when the cyclic sulfite is a substrate in glycosidation reactions and methodology has been developed for the synthesis of sulfites from tetrahydrofuran-1,2-diols <86MI 703-01>. For example, compound (**24**) was prepared from the corresponding diol by treatment with SOCl₂ <88CAR(180)233>.

7.03.9.2.2 Furo[3,4-*d*]-1,3,2-dioxathioles

A wealth of literature has been amassed concerning the synthesis and utility of the furo-1,3,2-dioxathiole ring system, particularly in the area of carbohydrate synthesis. The furo[3,4-*d*]-1,3,2-dioxathiole system may be conveniently prepared by treatment of a tetrahydrofuran-3,4-diol species with SOCl₂ in the presence of pyridine: *cis*-diols favor the formation of the desired cyclic sulfite

whereas *trans*-diols lead to elimination products <85ACS(B)375>. The regioselective synthesis of cyclic sulfites may be achieved by utilizing Bu_2SnO prior to SOCl_2 treatment <85TL6067>.

Myo-Inositol was treated with a mixture of SF_4 and anhydrous HF yielding the novel cyclic sulfite (94) <92JFC(58)87>.

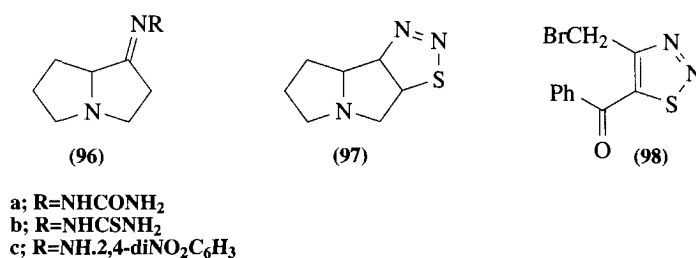


7.03.9.2.3 Furo[3,4-d]-1,2,3-thiadiazoles

Treatment of the hydrazone (95) with SOCl_2 gave 4,6-dihydro-4,4,6,6-tetramethylfuro[3,4-d]-1,2,3-thiadiazole (37) in 60% yield <87TL2867>.

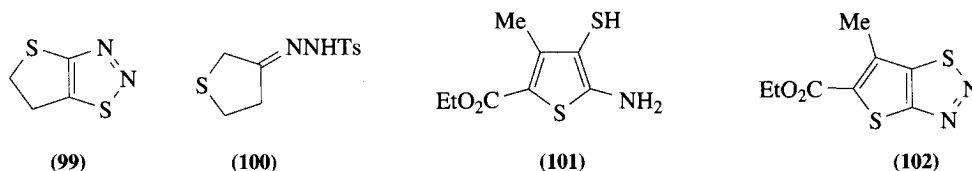
7.03.9.2.4 Pyrrolo[3,4-d]-1,2,3-thiadiazoles

The semicarbazone (96a), thiosemicarbazone (96b) and 2,4-dinitrophenyl hydrazone (96c) were all reacted with SOCl_2 to yield 9*H*-1,2,3-thiadiazolo[4,5-*a*]-4,5,6,7-tetrahydropyrrolizine (97) <83JJC(B)822>. The reaction of varying amounts of benzylamine with 4-bromomethyl-5-benzoyl-1,2,3-thiadiazole (98) gave 5-benzyl-6-phenylpyrrolo[3,4-*d*]-1,2,3-thiadiazole (83) in low yields <78JHC473>.



7.03.9.2.5 Thieno[2,3-d]-1,2,3-thiadiazoles

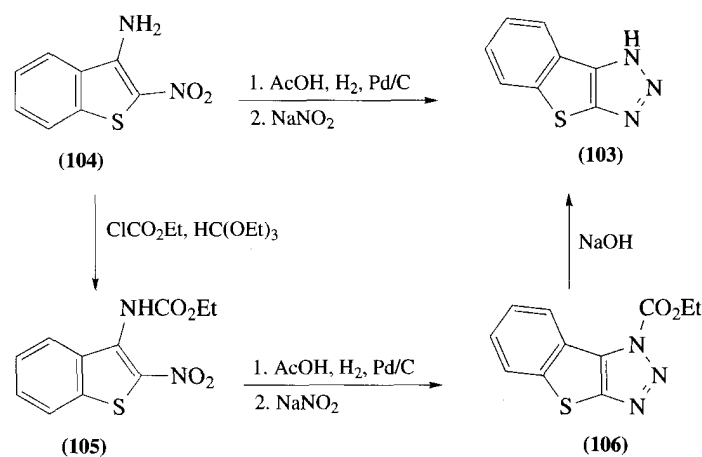
4,5-Dihydrothieno[2,3-*d*]-1,2,3-thiadiazole (99) was obtained by treatment of the hydrazone (100) with SOCl_2 <89TL7249>. The polysubstituted thiophene (101) upon treatment with NaNO_2 in concentrated HCl yielded 5-ethoxycarbonyl-6-methylthieno[2,3-*d*]-1,2,3-thiadiazole (102) in 70% yield <88JPR866>.



7.03.9.2.6 Thieno[2,3-d]-1,2,3-triazoles

Two routes to the 1*H*-[1]benzothieno[2,3-*d*]-1,2,3-triazole system (103) have been described in a comparative study. Reduction of 3-amino-2-nitrobenzothiophene (104) followed by reaction with

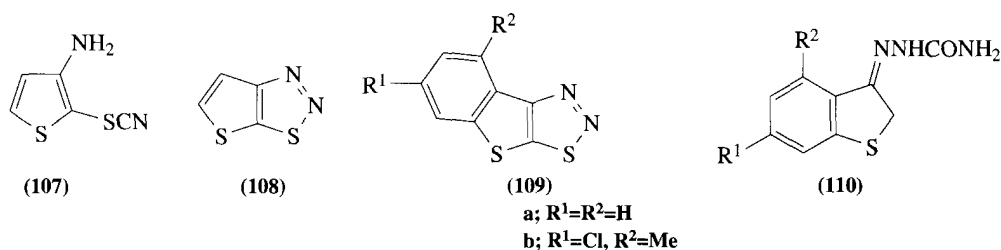
NaNO₂ gave compound (103) in 25% yield. Alternatively, the thiophene (104) may be elaborated to yield the carbamate (105), which is subsequently reduced and cyclized to give the thienotriazole (106) in 80% overall yield. 1*H*-[1]Benzo[thieno[2,3-*d*]-1,2,3-triazole (103) is ultimately prepared in 80% yield by hydrolytic decarboxylation of compound (106) (Scheme 9) <86JHC951>.



Scheme 9

7.03.9.2.7 Thieno[3,2-*d*]-1,2,3-thiadiazoles

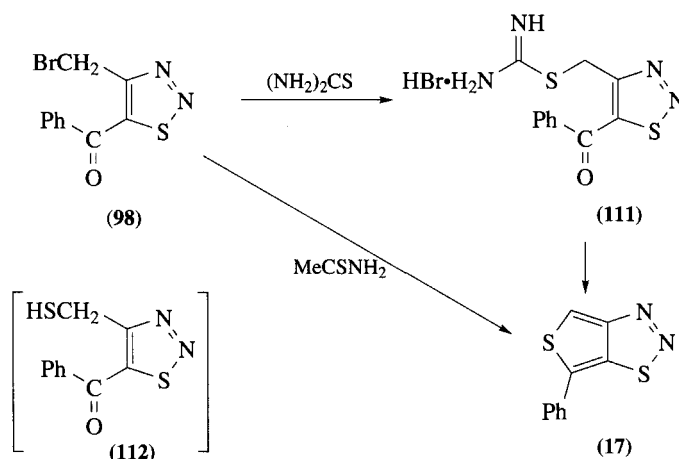
Reaction of the unstable 3-aminothiophene (107) with NaNO₂ in concentrated H₂SO₄ gave thieno[3,2-*d*]-1,2,3-thiadiazole (108) in 36% yield <78TL1797>. [1]Benzo[thieno[3,2-*d*]-1,2,3-thiadiazole (109a) was prepared in 51% yield by reacting the semicarbazone (110a) with SOCl₂. Similarly, 6-chloro-8-methyl[1]benzo[thieno[3,2-*d*]-1,2,3-thiadiazole (109b) was prepared in 84% yield <80CB183>.



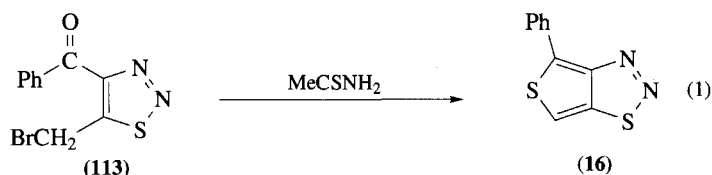
7.03.9.2.8 Thieno[3,4-*d*]-1,2,3-thiadiazoles

The synthesis of 6-phenylthieno[3,4-*d*]-1,2,3-thiadiazole (17) from 4-bromomethyl-5-benzoyl-1,2,3-thiadiazole (98) was achieved using two routes. The thiadiazole (98) reacted with thiourea to give the intermediate (111) in 90% yield and subsequent cyclization gave (17) in 60% yield (Scheme 10). Alternatively, compound (98) reacted with thioacetamide to give (17) directly in 92% yield. Presumably, the cyclizations proceed via the intermediacy of the thiol (112) but reaction of (98) with H₂S failed to produce any of the desired product. 4-Phenylthieno[3,4-*d*]-1,2,3-thiadiazole (16) was also prepared in an analogous process from the thiadiazole (113) in a yield of 90% (Equation (1)) <78JHC473>.

As part of an effort to synthesize novel organic conductors based upon tetrathiafulvalene, 4,6-dihydrothieno[3,4-*d*]-1,2,3-thiadiazole (70) was prepared from the hydrazone (100), together with an appreciable amount of 4,5-dihydrothieno[2,3-*d*]-1,2,3-thiadiazole (99) <89TL7249>.



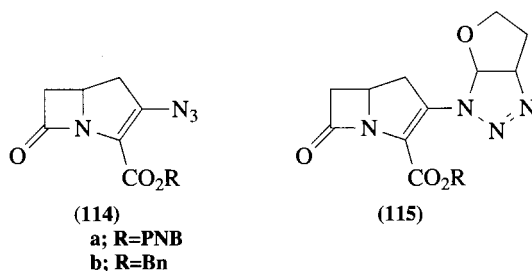
Scheme 10



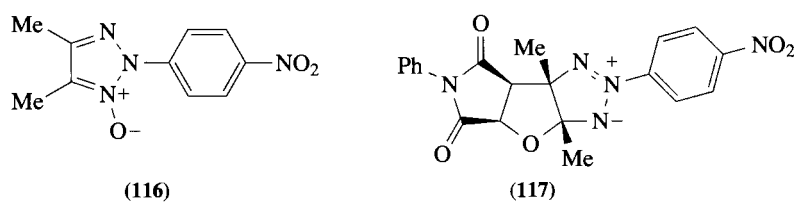
7.03.9.3 Synthesis of the Second Heterocyclic Ring from [3 + 2] Atom Fragments

7.03.9.3.1 Furo[2,3-d]-1,2,3-triazoles

The reactions of azido-substituted carbapenems have been surveyed: reaction of the carbapenems (114) with dihydrofuran yielded the respective 3a,5,6,6a-tetrahydro-3*H*-furo[2,3-*d*]-1,2,3-triazoles (115) in very high yield. This is in contrast to the reaction of azidocephems which form iminoethers when treated with dihydrofuran <85TL5407>.



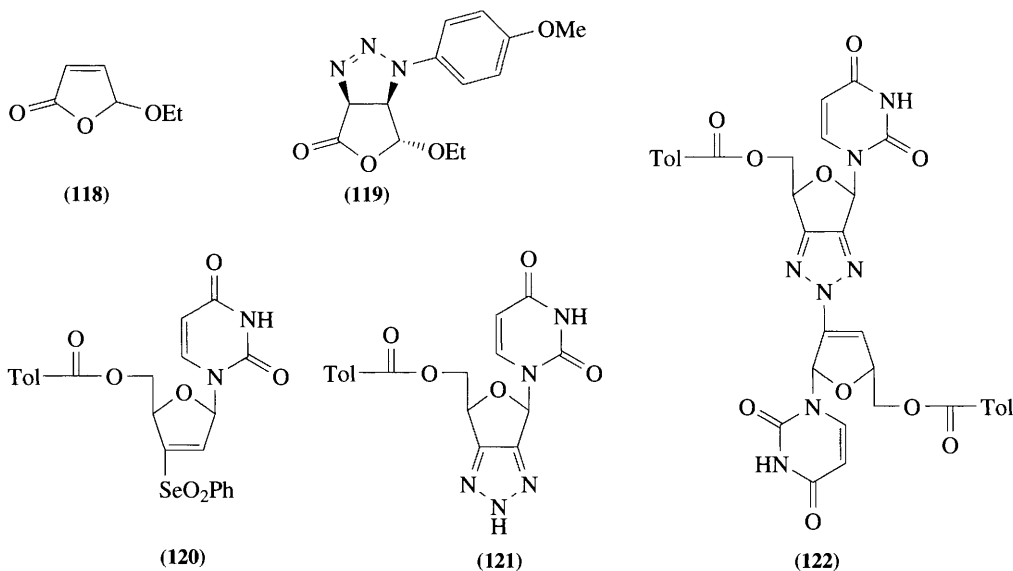
Butler and co-workers prepared an example of the furo[2,3-*d*]-1,2,3-triazole ring system by reaction of the 1,2,3-triazolium 1-oxide (116) with *N*-phenylmaleimide, yielding 75% of the stable triazol-2-ium-3-ide (117) which is the result of a 1,3-dipolar cycloaddition followed by sigmatropic rearrangements <90JCS(P1)3321>.



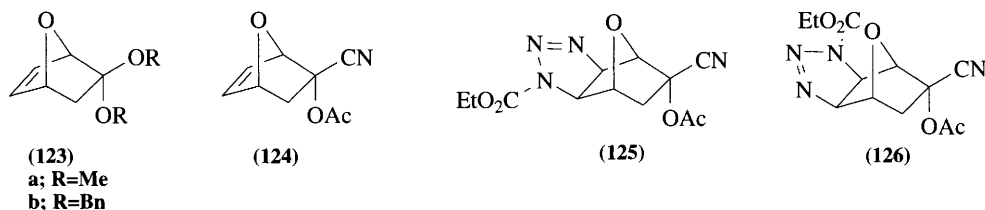
7.03.9.3.2 Furo[3,4-*d*]-1,2,3-triazoles

Reaction of the lactone (**118**) with *para*-methoxyphenyl azide gave the furo [3,4-*d*]-1,2,3-triazol-4-one (**119**) in 40% yield as a single diastereomer <84H(22)2363>.

During a study of the reactivity of 2',3'-ene-3'-phenylselenones derived from uracil furanosides, the selenone (**120**) was treated with NaN₃ in DMSO yielding 64% of the 4,6-dihydro-2*H*-furo[3,4-*d*]-1,2,3-triazole (**121**), together with a 33% yield of the coupled product (**122**) <90T3037>.

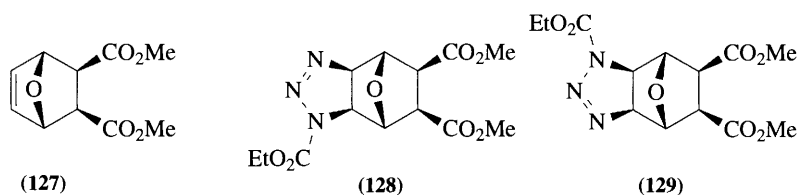


The furo[3,4-*d*]-1,2,3-triazole system has been prepared by Vogel and co-workers using a familiar 1,3-dipolar cycloaddition strategy. Reaction of the ketals (**123a**) or (**123b**) with ethyl azidoformate gave 9 : 8 mixtures of the diastereomeric triazolines (**45a**) : (**46a**) and (**45b**) : (**46b**) respectively in 80% yield. Similarly, treatment of ketals (**123a**) and (**123b**) with *t*-butylazidoformate yielded 1 : 1 mixtures of the triazolines (**45c**) : (**46c**) and (**45d**) : (**46d**) respectively which are separable by crystallization. Reaction of the alkene (**124**) with ethyl azidoformate led to a 2 : 1 mixture of the diastereomers (**125**) and (**126**) <88TL3695>.

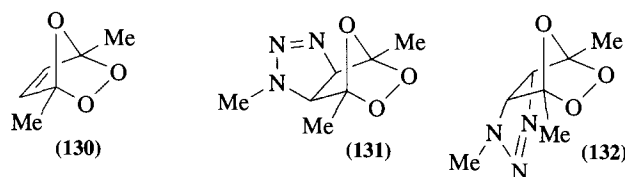


The diester (**127**) reacts with ethyl azidoformate (or with *t*-butyl azidoformate) yielding the triazole (**128**), which could be isomerized to give a 3 : 2 mixture of the triazoles (**128**) and (**129**) <90HCA674>.

Singlet oxygen reacts with π -electron rich compounds leading to interesting new compounds such

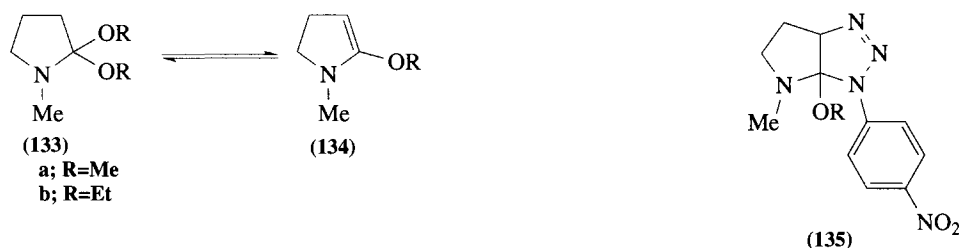


as the furan derivative (130). The reaction of the adduct (130) with *p*-nitrophenyl azide proceeded stereoselectively to yield a single cycloadduct (83%) (determined by ^{13}C NMR), which has the structure (131) or (132) <85T2057>.

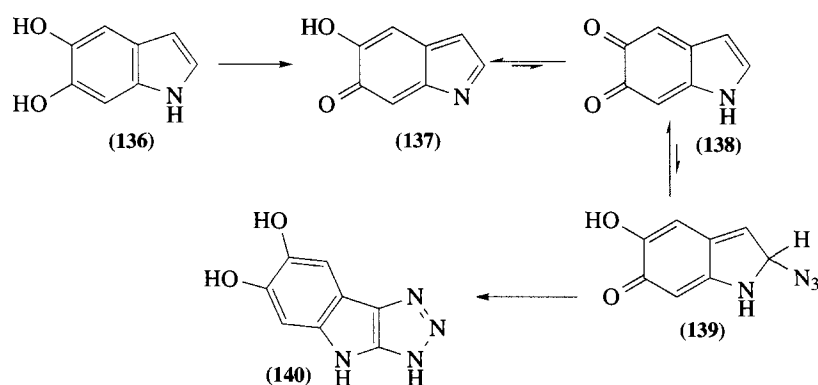


7.03.9.3.3 Pyrrolo[2,3-*d*]-1,2,3-triazoles

A study of ketene *N,O*-acetals has shown that such compounds derived from lactam acetals may be used in the preparation of larger heterocyclic systems via reaction with a 1,3-dipolar species, the initial cycloadducts stabilizing their structures by aromatization. Pyrrolo[2,3-*d*]-1,2,3-triazole derivatives, however, do not undergo such elimination reactions and stable cycloadducts may be obtained. Thus, the lactam acetals (133) give the ketene *N,O*-acetals (134), which on reaction with *p*-nitrophenyl azide yield substituted pyrrolo[2,3-*d*]-1,2,3-triazole derivatives (135) <86CB3591>.



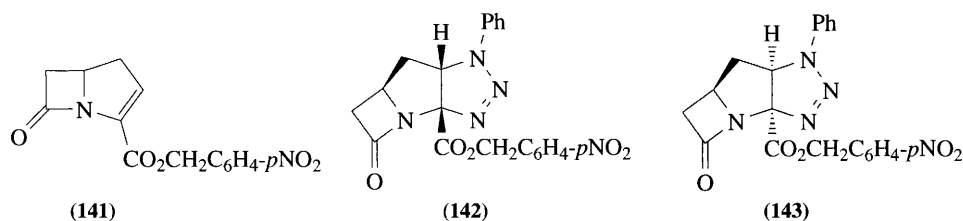
High-energy irradiation of aqueous solutions of 5,6-dihydroxyindole (136) in the presence of azide ions yields the oxidized product (137) in equilibrium with the quinone (138). Reaction of the quinone (138) with azide leads to the trapped product (139) and subsequently to 6,7-dihydroxy-1,2,3-triazolo[4,5-*b*]indole (140). It appears that the driving force for this reaction (138) $\rightarrow$ (140) is the electrocyclic ring closure as the quinone (138) is unreactive towards other nucleophiles (Scheme 11) <92TL3045>.



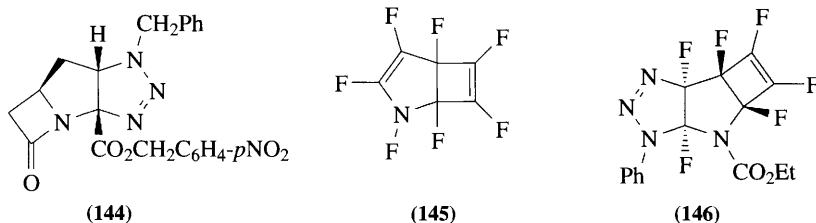
Scheme 11

In a study of olivanic acid analogues, the β -lactam (141) was reacted with phenyl azide to give the *p*-nitrophenylmethyl 3a,5,6,6a,7,7a-hexahydro-5-oxo-1-phenyl-1*H*-azeto[1',2':1,5]pyrrolo[2,3-*d*]-1,2,3-triazole-3a-carboxylate (142) as the major cycloadduct (47% yield) together with the minor regioisomer (143) (18% yield). The regioselectivity of addition to yield the major cycloadduct (142) is favored by the frontier molecular orbital interactions, whilst any alternative regioisomers are disfavored for steric reasons. Additionally, compound (141) gave *p*-nitrophenylmethyl 1-benzyl-

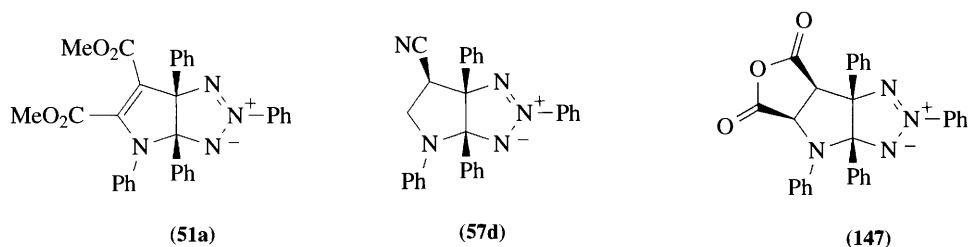
3a,5,6,6a,7,7a-hexahydro-5-oxo-1*H*-azeto[1',2':1,5]pyrrolo[2,3-*d*]-1,2,3-triazole-3a-carboxylate (**144**) in 57% yield from reaction with benzyl azide <86JCS(P1)973>.



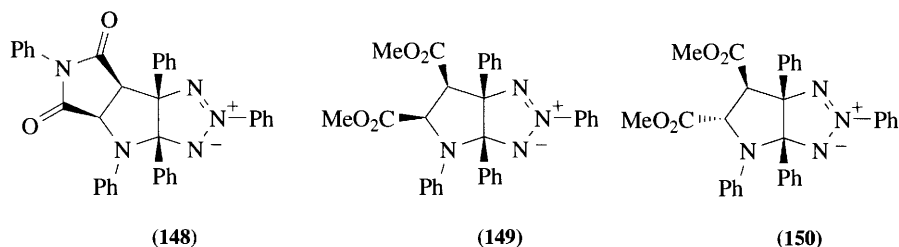
The perfluorinated compound (**145**) was treated with phenyl azide at 70°C for a total of 27 days to yield 75% of a compound assigned the 3a,5,6,6a-tetrahydro-3*H*,4*H*-pyrrolo[2,3-*d*]-1,2,3-triazole structure (**146**), although the regiochemistry of cycloaddition was not determined unambiguously <82JCS(P1)2105>.



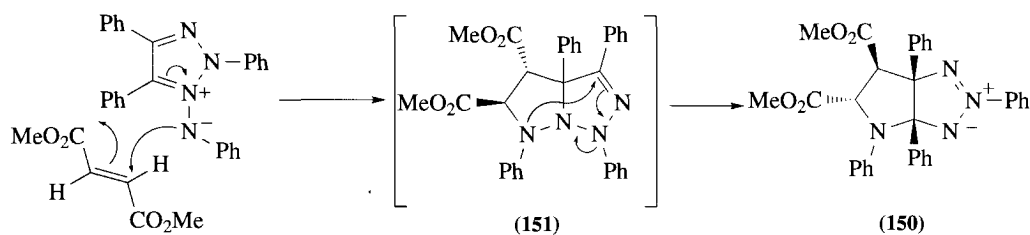
After a reevaluation of prior results obtained from investigations into the reactivity of *cis*-bis(areneazo)ethylenes with dienophiles, Butler and co-workers reacted the 1,3-dipole (**7**) with a variety of dipolarophiles to yield the triazol-2-ium-3-ide derivatives (**6**), (**51a**), (**57d**), and (**147**), all of which had previously been assigned incorrect structures <83CC762>.



N-Phenylmaleimide yielded compound (**148**) from reaction with the ylide (**7**) and other *cis*-bis(areneazo)ethylenes were also investigated. The stereospecificity of the reaction was probed using dimethylmaleate and dimethylfumarate as dipolarophiles, yielding compounds (**149**) and (**150**), respectively.



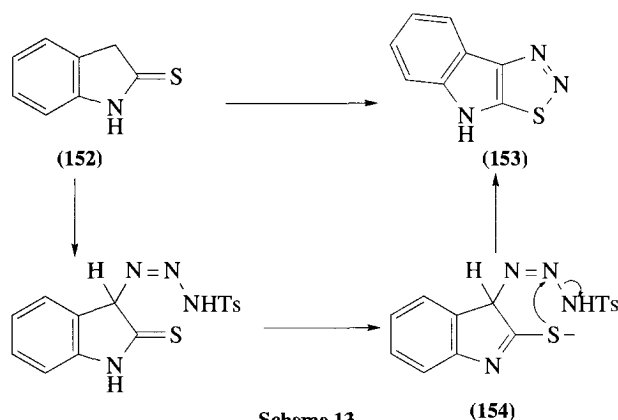
All of the product triazol-2-ium-3-ides were obtained via an unusual mechanism, involving an initial 1,3-dipolar cycloaddition to yield intermediates with structure (**151**), followed by a sigmatropic rearrangement, as exemplified by the reaction of compound (**7**) with dimethyl fumarate (Scheme 12) <90JCS(P1)2537>.



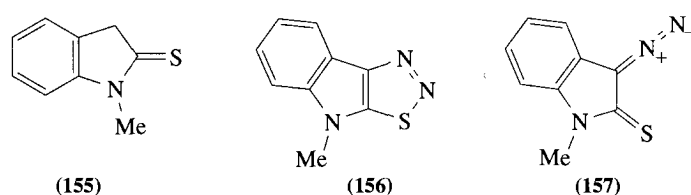
Scheme 12

7.03.9.3.4 Pyrrolo[3,4-d]-1,2,3-thiadiazoles

Indoline-2-thione (**152**) reacted “vigorously” with both tosyl azide and *p*-chlorophenylsulfonyl azide in pyridine to give 4*H*-[1,2,3]-thiadiazolo[5,4-*b*]indole (**153**) in 60–62% yield. Analogous reaction of 1-methylindoline-2-thione (**155**), however, yielded the indole (**156**) in only milligram quantities. This difference of reactivity was ascribed to the presence of an acidic proton in the reaction intermediate leading to the indole (**153**) (Scheme 13). This proton can be abstracted in pyridine solution to give the anionic intermediate (**154**), which leads to the product (**153**). 1-Methylindoline-2-thione (**155**) can initially react by losing *p*-toluenesulfonamide to form the diazo derivative (**157**) which may then preferentially lose N₂ and subsequently dimerize <74JCS(P1)2384>.

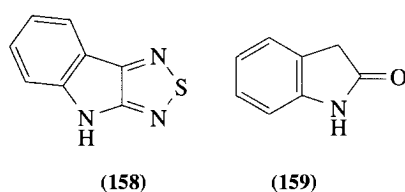


Scheme 13



7.03.9.3.5 Pyrrolo[3,4-c]/[1,2,5]thiadiazoles

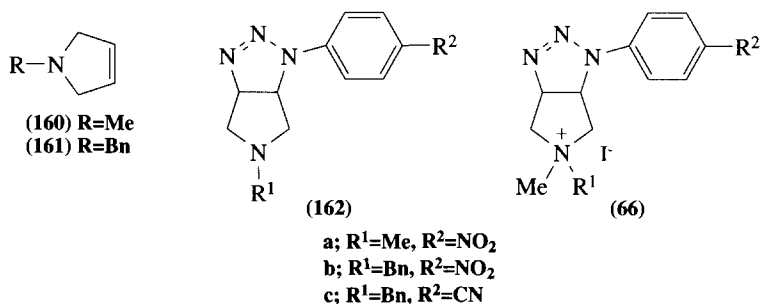
Sulfur nitride has been shown to be a useful reagent in heterocyclic chemistry and has been used to prepare a number of interesting compounds. Among the novel ring systems attained using this compound, 1,2,5-thiadiazolo[3,4-*c*]indole (**158**) was prepared from oxindole (**159**), though only in poor yield <80JHC1681>.



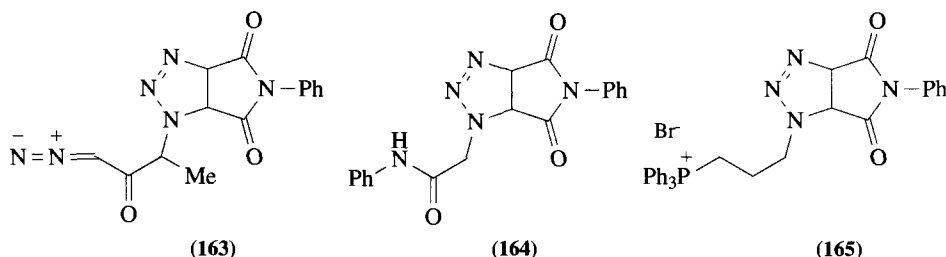
7.03.9.3.6 Pyrrolo[3,4-*d*]-1,2,3-triazoles

Reaction with a dipolarophile is the proving ground for azide reactivity. As such, many azide-containing molecules are reacted in a 1,3-dipolar fashion to yield triazine derivatives. Of interest here is the reaction of azides with a heterocyclic dipolarophile, such as an *N*-substituted maleimide.

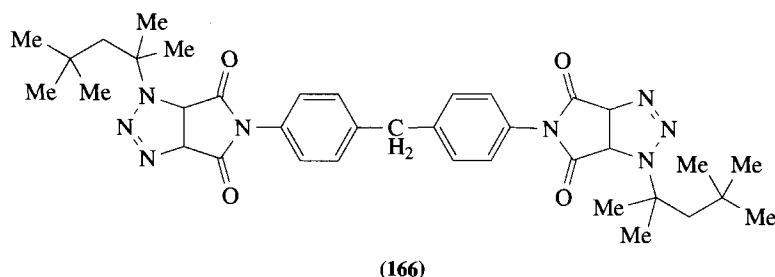
Reaction of 1-methyl- and 1-benzyl-2,5-dihydropyrrole, (**160**) and (**161**) respectively, with either 4-nitro- or 4-cyanophenylazide led to the triazolines (**162a-c**) in moderate yields. These compounds were subsequently treated with methyl iodide to yield the quaternary ammonium iodides (**66a-c**) (<80JHC267>).



Azidoalkyl α -diazoketones have been reacted with *N*-phenylmaleimide, yielding, for example, the 4,6-dioxo-3a,4,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*d*]-1,2,3-triazole (**163**) (<84KGS514>). Similarly, 2-azido-*N*-arylacetamides have been reacted with *N*-phenylmaleimide to yield, for example, 4,6-dioxo-3a,4,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*d*]-1,2,3-triazole (**164**) (<92MI 703-01>). Various ω -azidoalkyltriphenylphosphonium bromides have also been reacted with *N*-phenylmaleimide giving, for example, 4,6-dioxo-3a,4,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*d*]-1,2,3-triazole (**165**) (<92BSF308>).

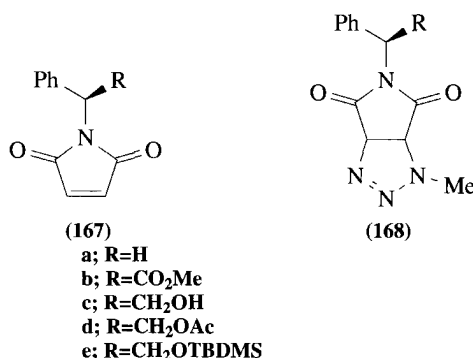


An interesting development of the reaction of *N*-phenylmaleimide with azides is the synthesis of a polymer-bound pyrrolo[3,4-*d*]-1,2,3-triazole system, potentially useful as a linkage in block- and graft-copolymers. First, 2-azido-2,4,4-trimethylpentane was successfully reacted with bis(4-maleimidophenyl)methane to yield the bis-adduct (**166**). This subsequently led to azide-bearing poly(2-methylpropene) being reacted with bis(4-maleimidophenyl)methane to yield a mixture of mono- and bis-adducts (<92MAC2495>).

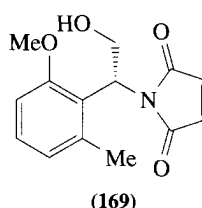


As part of an interesting synthetic route to the natural products naphtharidinomycin and quino-carcin, Garner *et al.* prepared a number of 3a,4,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*d*]-1,2,3-triazole derivatives. For example, *N*-benzylmaleimide (**167a**) reacted with methyl azide to give the triazoline (**168a**) in 73% yield. Analogous reactions of *N*-substituted maleimides (**167b-e**) with methyl azide led to diastereomeric mixtures of triazolines (**168b-e**) via nondiastereoselective cyclo-

addition <88TL3525, 89JOC2041>. The foundations of an asymmetric approach to quinocarcin, based upon a 1,3-dipolar cycloaddition strategy, were thus described <91JOC5893>.



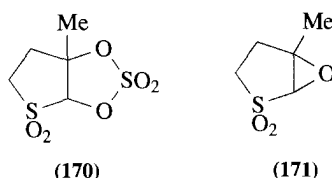
However, the synthesis of (–)-quinocarcin required a suitably substituted maleimide precursor which incorporated a chiral auxiliary moiety that could subsequently form part of the target molecule. Consequently, the maleimide (169) was reacted with methyl azide to give the triazoline (62) in 99% yield <93JA10742>.



The regioselectivity of the 1,3-dipolar cycloadditions of azides to alkenes is usually difficult to predict due to the similar energies for the transition states which involve either the HOMO (dipole) or the LUMO (dipole). The results of a study which utilized 5-alkoxy-3-pyrrolin-2-ones as dipolarophiles in reactions with a variety of aryl azides seemed to reflect this problem; the results suggested that the low regioselectivity observed was due to the frontier molecular orbital interactions between dipole and dipolarophile, and not any steric hindrance offered by the 5-alkoxy function <84H(22)2363>.

7.03.9.3.7 Thieno[2,3-d]-1,3,2-dioxathioles

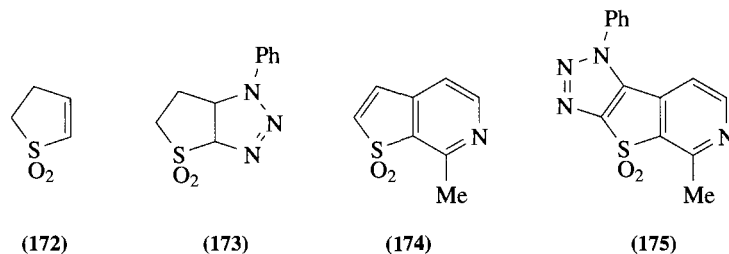
6a-Methyl-3a,5,6,6a-tetrahydrothieno[2,3-d]-1,3,2-dioxathiole tetraoxide (170) was obtained by treatment of the epoxide (171) with NaSCN in dilute H₂SO₄ <85KGS331>.



7.03.9.3.8 Thieno[2,3-d]-1,2,3-triazoles

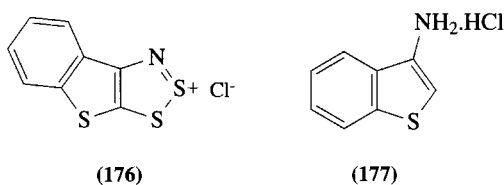
2-Sulfolene (172) on treatment with phenyl azide yielded 3a,5,6,6a-tetrahydro-1H-thieno[2,3-d]-1,2,3-triazole 4-dioxide (173) together with an aziridine, presumably resulting from the thermal decomposition of triazoline (173) <74UKZ433>.

Reaction of the sulfoxide (174) with phenyl azide gave 3a,8b-dihydro-5-methyl-1-phenyl-1*H*-1,2,3-triazolo[4,5':4,5]thieno[2,3-*c*]pyridine 4-dioxide (64) which, on aerial oxidation, gave 5-methyl-1-phenyl-1*H*-1,2,3-triazolo[4,5':4,5]thieno[2,3-*c*]pyridine 4-dioxide (175) <80HCA1719>.



7.03.9.3.9 Thieno[3,2-*d*]-1,2,3-dithiazoles

[4,5]Benzothieno[3,2-*d*]-1,2,3-dithiazol-2-ium chloride (176) was obtained in 95% yield from 3-aminobenzothiophene (177) <76KGS1355>.



7.03.9.4 Synthesis from Acyclic Precursors

There is nothing to report in this area.

7.03.10 RING SYNTHESSES BY TRANSFORMATION OF ANOTHER BICYCLIC RING SYSTEM

There is nothing to report in this area.

7.03.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND COMPARISON OF THE ROUTES AVAILABLE

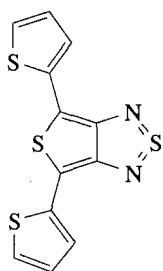
Many of the compounds described have been prepared by common strategies. Two methods stand out for the synthesis of 1,2,3-triazole derivatives. First, the cyclization of hydrazone oximes yields 1,2,3 triazoles in high yields <77CAR(59)141, 82CAR(110)229, 83CAR(124)97, 90M671>. Secondly, there is a plethora of examples demonstrating the utility of azides in the synthesis of 1,2,3-triazoline derivatives via a 1,3-dipolar cycloaddition; these range from the simple <74JCS(P1)2384, 74UKZ433, 80HCA1719, 80JHC267, 82JCS(P1)2105, 84H(22)2363, 84KGS514, 85T2057, 85TL5407, 86CB3591, 86JCS(P1)973, 88TL3695, 89JOC2041, 90HCA674, 91JOC5893, 92BSF308, 92MI 703-01> to the sophisticated <83CC762, 84H(22)2363, 90JCS(P1)2537, 90JCS(P1)3321, 92MAC2495, 92TL3045, 93JA10742>.

The insertion of one atom into a bifunctional moiety to form a five-membered ring is another popular route to heterocycles of interest. One sulfur atom may be inserted using SOCl_2 , or NaNO_2 may be used to insert one nitrogen atom.

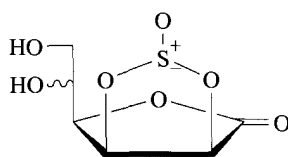
7.03.12 IMPORTANT COMPOUNDS AND APPLICATIONS

4,6-Di(2-thienyl)thieno[3,4-*c*][1,2,5]thiadiazole (**178**) has been polymerized to give a narrow band gap heterocyclic polymer with interesting optical and electrochemical properties <93SM1251>. Stable dithiazolyl radicals, such as (**18**) and (**19**), are useful as inhibitors and stabilizers for radical reactions <82EGP156366>.

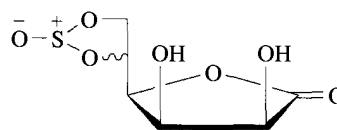
Various γ -lactones derived from carbohydrates have found use as antioxidants. For example, the 2,3- and 5,6-sulfinyl-L-gulono- γ -lactones (**179**) and (**180**) may be used as preservatives in lubricating oils, foodstuffs, and a variety of other substances <93EUP552651>.



(178)



(179)



(180)

The furo[2,3-*d*]-1,3,2-dioxathiole and furo[3,4-*d*]-1,3,2-dioxathiole systems, by virtue of the utility of cyclic sulfites and sulfates as protecting/activating groups in carbohydrate chemistry, have been mentioned in a variety of papers and patents concerning the synthesis of biologically-active nucleosides. Saliently, the sulfite group was used in the synthesis of zidovudine (AZT) <88EUP295090, 90USP4916218>. Many other examples of the utility of these heterocyclic systems can be found <82CZP199949, 82CZP204212, 84JAP(K)5959698, 84JAP(K)5959699, 89CCC1358, 90KFZ154, 90TL2337, B-91MI 703-01, 91MI 703-02, 92MI 703-02, 93T901>.

7.04

Bicyclic 5-5 Systems: Four Heteroatoms 2 : 2

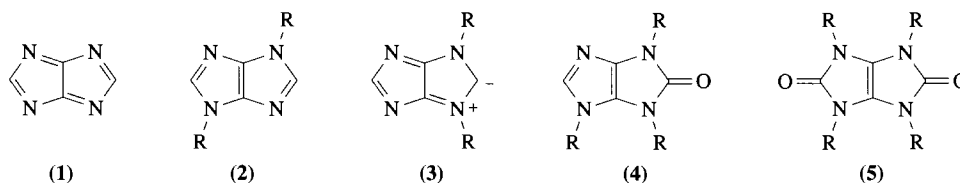
STEPHEN P. STANFORTH

University of Northumbria at Newcastle, UK

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7.04.1 INTRODUCTION

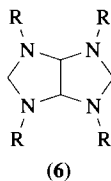
The structural variety of fully conjugated bicyclic 5:5 systems which are associated with two heteroatoms in each ring can be appreciated by considering these heterocycles according to the number of π -electrons, the number of groups with exocyclic conjugation and the substitution pattern. Thus, imidazo[4,5-*d*]imidazole (1) is associated with eight π -electrons, has no groups with exocyclic conjugation and has a 1,3,4,6 substitution pattern. The 1*H*,4*H*-imidazo[4,5-*d*]imidazoles (2) similarly have no groups with exocyclic conjugation and have a 1,3,4,6 substitution pattern but are associated with ten π -electrons. In this heterocyclic system (2), the nitrogen atoms located at the 1 and 4 positions formally contribute two electrons each to the π system, whereas the nitrogen atoms located at the 3 and 6 positions formally contribute one electron each to the π system. However, covalent structures such as (2) cannot always be drawn and one example of a molecule which can only be represented as a dipolar structure is heterocycle (3) where the 1,3 nitrogen atoms formally contribute two electrons each to the π system and the 4,6 nitrogen atoms formally contribute one electron each to the π system. Heterocycles such as those depicted in structure (3) are termed heteropentalene mesomeric betaines because of their isoelectronic relationship to the pentalenyl dianion and have been discussed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)1027>. There are no reported examples of heteropentalene mesomeric betaines relevant to this chapter. Heteropentalenes which can be represented by hypervalent structures have been discussed in CHEC-I <84CHEC-I(6)973>. Heterocycles (4) and (5) represent two further examples of the 1,3,4,6 substitution pattern; heterocycle (4) is associated with twelve π -electrons and has one carbonyl group with exocyclic conjugation, and heterocycle (5) is associated with fourteen π -electrons and has two carbonyl groups with exocyclic conjugation.



Another chapter of CHEC-I includes 5:5 fused-ring systems with two or more heteroatoms <84CHEC-I(5)111>, although heterocycles with two nonbridgehead heteroatoms in each ring, which are the subject of this chapter, are only briefly considered there.

Heterocycles (1)–(5) represent examples of the 5:5 fused-ring system with the 1,3,4,6 substitution pattern. It can readily be appreciated that the three other possible substitution patterns (1,2,4,5; 1,2,4,6; and 1,2,5,6), all of which can be associated with varying numbers of π -electrons and groups with exocyclic conjugation, will incorporate an extremely diverse range of heterocyclic molecules, especially when systems which are not fully conjugated such as dihydro and tetrahydro derivatives are considered. It will be apparent that some types of heterocycle have received considerable attention whereas others are as yet unknown, and this is hardly suprising given the enormous structural diversity possible.

The nomenclature for fused 5:5 systems is generally related to the two fused component heterocyclic rings as indicated above for imidazo[4,5-*d*]imidazole (1), although compounds are sometimes named as hetero derivatives of pentalene. Heterocycles which are not fully conjugated can be named as dihydro, tetrahydro, etc., derivatives of the fully conjugated parent system or as hetero derivatives of the saturated parent hydrocarbon. For example heterocycle (6) can be named as a tetraaza bicyclo[3.3.0]octane.

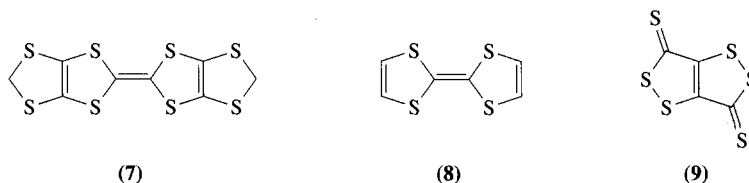


To provide coherence in this chapter, the material has been organized so that fully conjugated systems are considered before their partially conjugated and nonconjugated derivatives. For the fully conjugated systems, heterocycles with the lowest number of π -electrons are considered first; should the number of π -electrons be the same in two heterocycles, then the compound with the

lowest number of groups with exocyclic conjugation will have precedence. The substitution pattern of the heterocycles will then be taken into account if either the π -electron count or the number of groups with exocyclic conjugation cannot assign precedence. For partially conjugated and nonconjugated systems heteroatom lone pairs will be counted with π -electrons.

7.04.2 THEORETICAL METHODS

MNDO calculations have been reported for the heterocycle (7) in order to predict its HOMO energy and ionization potential <89SM179>. Compound (7) is a derivative of tetrathiafulvalene (8) and sulfur-containing compounds related to heterocycle (8) are of intense current interest as organic metals. CNDO calculations on 3,6-dithioxo-1,2,4,5-tetrathiapentalene (9) have been reported and there is agreement between experimental and calculated ^{13}C NMR data <84ZC418>.



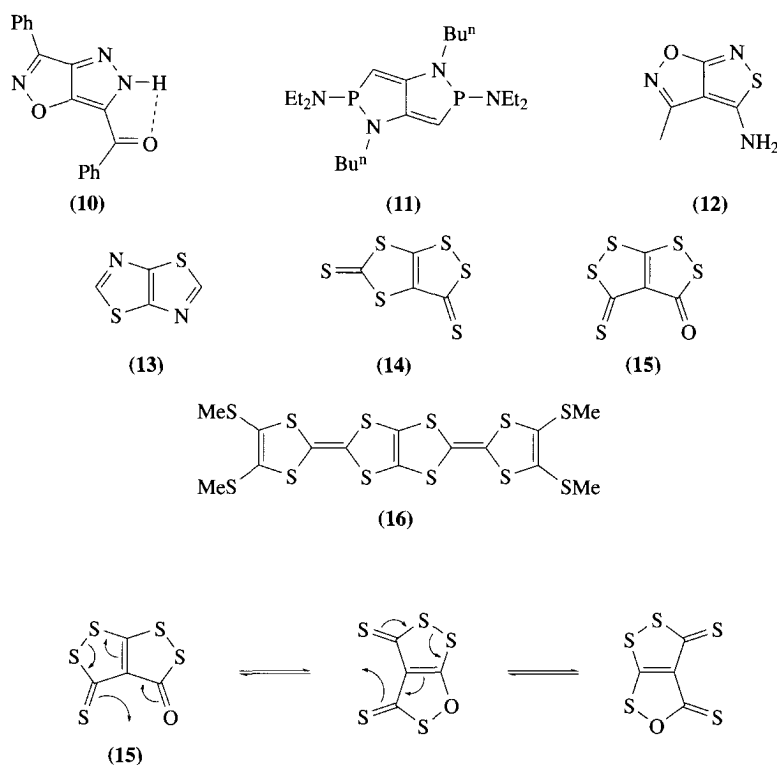
7.04.3 EXPERIMENTAL STRUCTURAL METHODS

7.04.3.1 Fully Conjugated Systems

X-ray crystallographic investigations have been carried out on numerous fully conjugated heterocycles. In the 2*H*-pyrazolo[3,4-*d*]isoxazole derivative (10), hydrogen bonding is apparent between the benzoyl group and pyrazole hydrogen atom <88S884>. The structure of the diazadiphosphabicyclooctadiene derivative (11) has been determined <87DOK(297)376>. The isothiazolo[3,4-*c*]isoxazole derivative (12) shows intermolecular hydrogen bonding and the two planar rings are tilted 1.7° relative to each other <90JHC1481>. The interatomic distances in thiazolo[5,4-*d*]thiazole (13) have been compared to those of thiazole <87AX(C)2106>. In the iodine complex of heterocycle (14) both rings are planar and tilted 1° relative to each other and short intermolecular S—S distances and thiocarbonyl-iodine distances are apparent <89JOC2165>. The mass spectrum of compound (14) shows loss of carbon disulfide and carbon subsulfide (C₃S₂). 3-Oxo-4-thioxo-1,2,5,6-tetrathiapentalene (15) is also planar but shows an unusually short transannular S—O distance (3.16 Å) as well as short intermolecular S—S and S—O distances <89CC1716>. The ^{13}C NMR spectrum of compound (15) showed two unusually broad signals (ca 1 ppm at 20°C) for the thiocarbonyl carbon atom and one of the bridgehead carbon atoms which has been used as evidence for fluxional behavior (Scheme 1). Compound (16) is planar except for the methyl groups and shows short (3.45 Å) intermolecular S—S distances <92CL2321>. The UV absorption spectrum of thiazolo[5,4-*d*]thiazole (13) has been determined in both solution and the solid state <83MCLC263>.

7.04.3.2 Nonconjugated Systems

Heterocycles (17) and (18) are products of cycloaddition reactions and their structures have been determined by x-ray crystallography in order to establish the regioselectivity of the cycloaddition <90T1145>. The 1*H*,3*H*-[1,2]oxasilolo[4,3-*c*][1,2]oxasilole derivative (19) showed the ring C—C and C=C bond lengths to be 1.49 Å and 1.33 Å respectively <90JOM(398)229>. Heterocycle (20) does not show conjugation in the butadiene fragment as evident from the ring C—C and C=C bond lengths (1.40 Å and 1.36 Å respectively) <91POL1203>. The fully saturated heterocycles (21) <92AX(C)1532> and (22; R = COMe or COEt) <92AX(C)1528> have an envelope conformation. Intermolecular hydrogen bonding is apparent in heterocycle (23) and severe intramolecular interactions between the trifluoromethyl and nitro groups in the dinitro derivative (24) were observed <87JOC1113>. Selected bond lengths and angles for compounds (23) and (24) and the corresponding trinitro and tetranitro derivatives are given in Table 1. The N—NO₂ bond gradually lengthens along the series and the



Scheme 1

N—C—N angle gradually sharpens, indicating increasing steric crowding. In the tetranitro derivative the bridgeheads are twisted 30° from the eclipsed conformation. Spectroscopic discrimination between the isomers (25) and (26) was difficult and consequently their structures were established by x-ray crystallography <89TL4825>. The diastereoisomers (27) and (28) ($R = 2,5$ -dibenzoyloxyphenyl) were the products of a 1,3-dipolar cycloaddition reaction and their structures were determined by x-ray crystallography <91JOC1364>. The dihedral angle between the protons H_a and H_b in diastereoisomers (27) and (28) is approximately 90° and no coupling is therefore observed in their ^1H NMR spectra. The dihedral angle between the ring planes in structures (29) <88AX(C)696> and (30) <85AX(C)1680> are 118° and 115° , respectively. Electrochemical oxidation of BMDT-TTF [bis(methylenedithio)tetrathiofulvalene] (7) in dichloroethane solution in the presence of tetrabutylammonium perchlorate gave an adduct $(BMDT-TTF)_3ClO_4(1,2\text{-dichloroethane})$ which showed short intermolecular S—S distances (3.42–3.69 Å) <84CL1693>. $(BMDT-TTF)_3PF_6(1,2\text{-dichloroethane})$ has similarly been prepared <84CL993>.

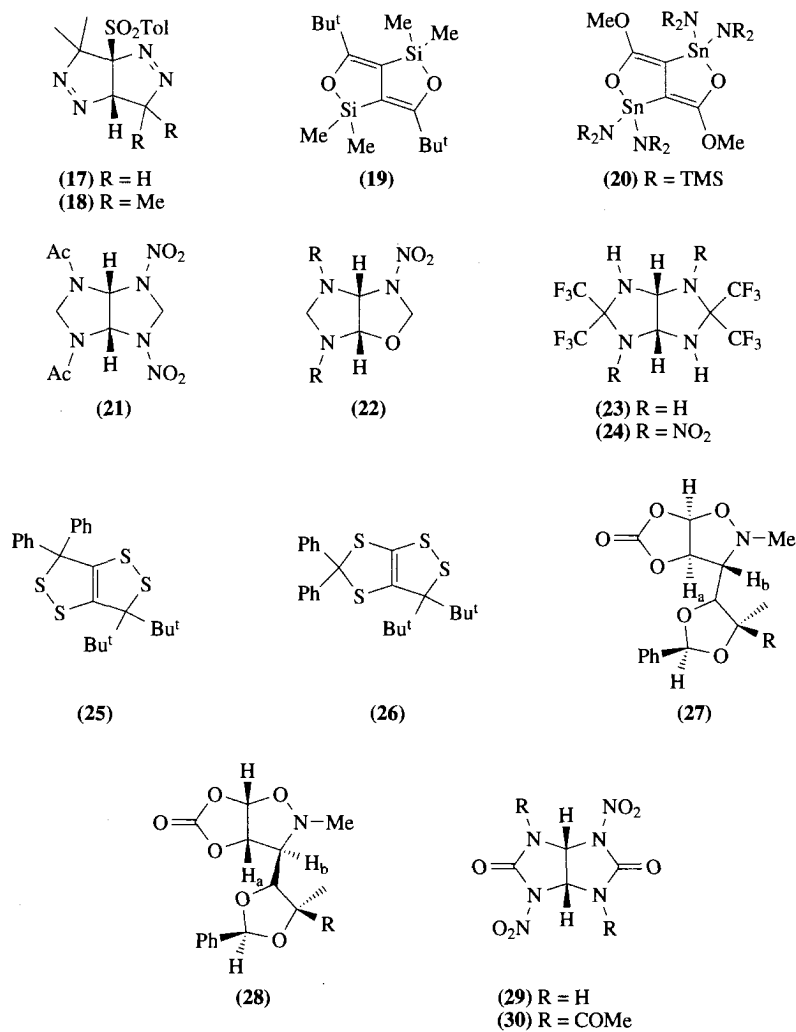
7.04.4 THERMODYNAMIC ASPECTS

Current interest in sulfur-containing heterocycles as potential organic metals <86T1209, 87SR155> has led to the investigation of charge transfer complexes of molecules such as heterocycle (7) <85MCLC341>. The liquid crystalline behavior of thiazolo[5,4-*d*]thiazole derivatives (31; $R = \text{alkyl chain with 3–8 carbons}$) has been reported and both the nematic and smetic phases were observed <90MCLC297>.

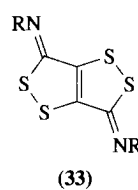
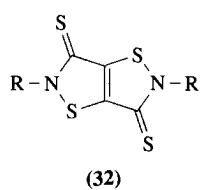
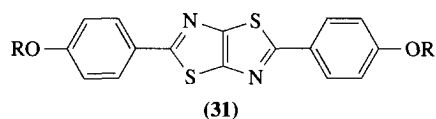
7.04.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.04.5.1 Thermal and Photochemical Reactions

Heterocycle (32; $R = Me_2NC_6H_4$) is converted into isomer (33; $R = Me_2NC_6H_4$) in good yield either photochemically or by treatment with a Lewis acid <90JPR387>.

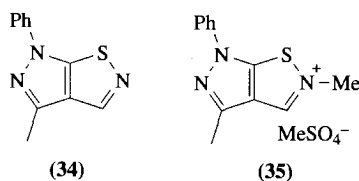
**Table 1** Selected bond lengths and angles for compounds (23), (24), (78), and (79).

Geometrical parameter	(23)	Dinitro (24)	Trinitro (78)	Tetranitro (79)	Ref.
C—CF ₃ (pm)	152.9	154.4	157.5	158.2	87JOC1113
N—NO ₂ (pm)		138.6	140.5	141.3	87JOC1113
N—C—N (deg)	105.6	99.5	99.7	98.5	87JOC1113



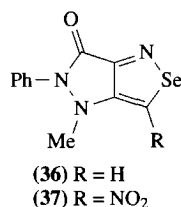
7.04.5.2 Electrophilic Attack at Nitrogen

Treatment of the 1*H*-pyrazolo[4,3-*d*]isothiazole derivative (34) with dimethyl sulfate yielded the corresponding salt (35) in good yield <85KGS223>.



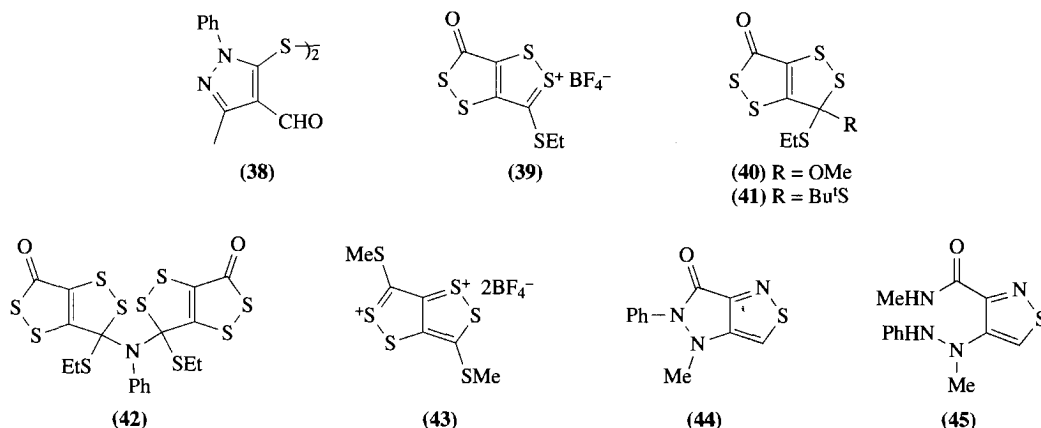
7.04.5.3 Electrophilic Attack at Carbon

Nitration ($\text{HNO}_3\text{--H}_2\text{SO}_4$) of compound (36) gave the nitro derivative (37) (37%) <87TL4579>.



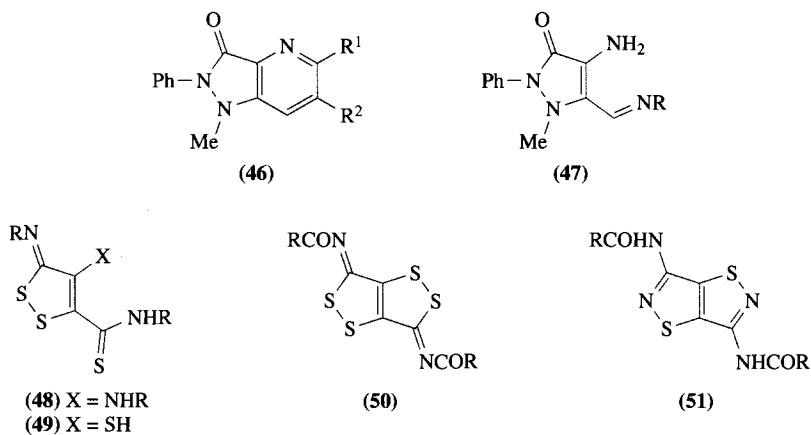
7.04.5.4 Nucleophilic Attack at Carbon

Salt (35) was hydrolyzed in good yield to the disulfide derivative (38) <85KGS223>. Salt (39) reacted with methanol and *t*-butylthiol, respectively, giving the corresponding adducts (40) and (41) in quantitative yield. With aniline as the nucleophile the salt (39) gave the 2:1 adduct (42) <91M71>. Salt (43) gave heterocycles (32; R = aryl) as the major products when treated with aromatic amines in propanol and heterocycles (33; R = aryl) as the major products in acetic acid <89T125>. Compound (44) is cleaved by aqueous methylamine, giving the isothiazole derivative (45) and other amines effect a similar reaction <86JHC1773>.

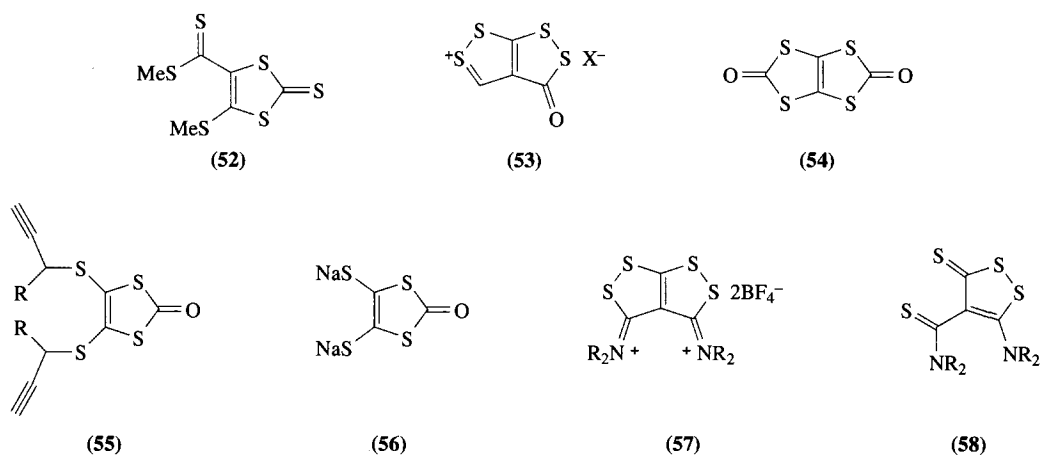


The seleno analogue (36) has been reacted with a variety of activated methylene compounds, giving pyrazolo[4,3-*b*]pyridine derivatives with the general structure (46) <85CPB3065>, and also with amines, yielding the imines (47) <87CPB398>. Heterocycle (9) reacted with aromatic amines giving a mixture of products (32; R = aryl) and (33; R = aryl), with the former product predominating <89T125>. With aliphatic amines, heterocycle (9) gave the products (33; R = alkyl) together with the

products (48) and (49), formed by ring cleavage <91JPR19>. Heterocycles (50) are transformed into isothiazolo[5,4-*d*]isothiazole derivatives (51) when treated with hydroxylamine <89ZC17>.

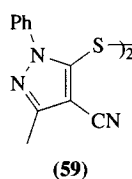


Reaction of heterocycle (14) with Et_3BHLi followed by treatment with methyl iodide afforded the monocyclic sulfur-containing compound (52) <89JOC2165>. Salt (53) gave heterocycle (15) when treated with sulfur and pyridine <89CC1716>. Treatment of 1,3,4,6-tetrathiapentalene-2,5-dione (54) with propargyl bromide derivatives under basic conditions yielded monocyclic products (55) (e.g., 85% yield when $\text{R} = \text{H}$) <84JOC564>. With sodium carbonate under phase-transfer conditions <91SM2381> or with sodium methoxide <84NJC653>, heterocycle (54) gave the disodium salt (56). Salts (57) formed the thioamide derivatives (58) when treated either with aqueous hydrogen sulfide or with the sodium salt of malononitrile <89SM537>.



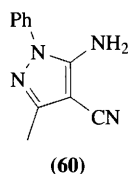
7.04.5.5 Nucleophilic Attack at Hydrogen

1-Phenyl-3-methylpyrazolo[4,3-*d*]isothiazole (34) was transformed under aqueous conditions (pH 5–6) into the nitrile derivative (59) in good yield <85KGS223>.



7.04.5.6 Reduction

Reduction of compound (37) with zinc in acetic acid gave the pyrazole derivative (60) (22%) <87TL4579>.



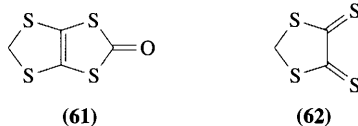
7.04.5.7 Oxidation

Electrochemical oxidations of sulfur-containing heterocycles, for example compounds (7) <84CL993, 84CL1693> and (15) <89CC1716>, have been reported.

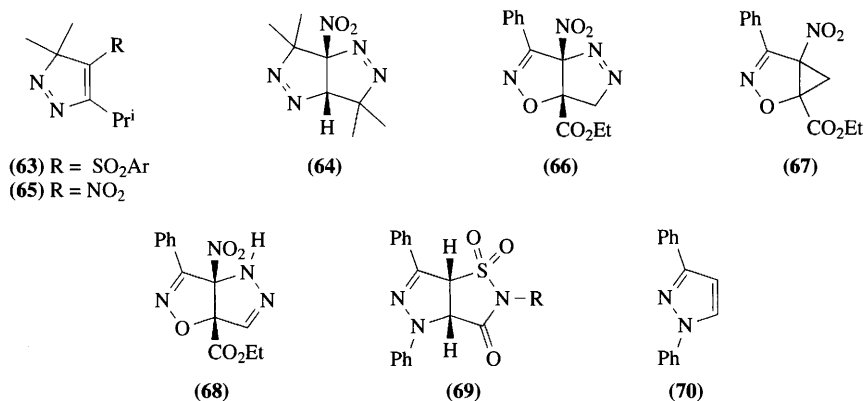
7.04.6 REACTIVITY OF NONCONJUGATED RINGS

7.04.6.1 Thermal and Photochemical Reactions

Irradiation of compound (25) gave the isomeric heterocycle (26) (51%) as the major product <89TL4825>. Thermolysis of compound (61) at 350°C under vacuum gave a product for which the structure (62) has been proposed <83JA4519>.

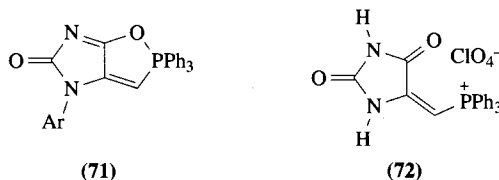


A number of tetraaza heterocycles undergo thermal and photochemical fragmentation reactions. Thus, heating compound (18) gave compound (63) (85%) <90T1145>, and heating compound (64) gave heterocycle (65) (75%) <84TL2909>. Several related reactions have been reported <83MI 704-01>. Heterocycle (66) has been postulated as a transient reaction intermediate which is converted into a mixture of the fragmentation product (67) and the tautomer (68) in equal proportions <87CC1077>. Compounds of the type (69) yielded 1,3-diphenylpyrazole (70), sulfur dioxide, and the corresponding isocyanate (RNCO) when heated <92C335>.

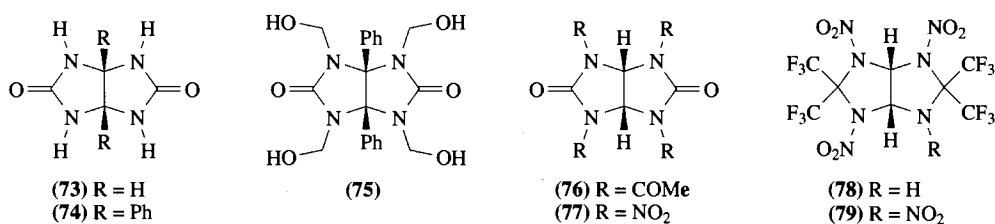


7.04.6.2 Electrophilic Attack at Nitrogen

Treatment of heterocycle (71) with perchloric acid gave the product (72) <85KGS1051>.

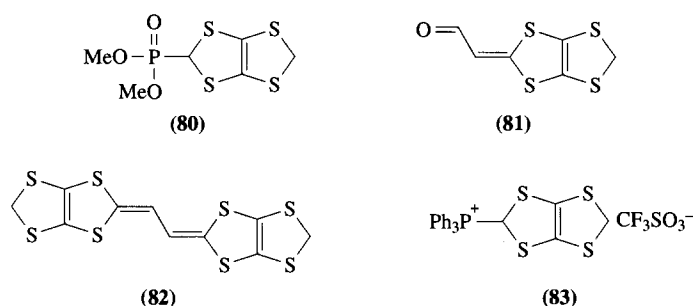


Numerous electrophilic reactions at nitrogen in glycouril derivatives (73) have been reported. Treatment of compound (74) with paraformaldehyde yielded the tetrahydroxymethyl derivative (75) <86TL243>. Acylation of glycouril (73) gave a tetraacyl derivative (76) and nitration (HNO_3 , 20–60°C) afforded the dinitro product (29) <86BSF465>. This dinitro compound (29) can also be obtained from mixed acid nitration of the tetraacyl derivative (76). Acylation of compound (29) gave heterocycle (30). The tetranitro derivative (77) can be obtained by treatment of compound (29) with $\text{HNO}_3\text{--N}_2\text{O}_5$ at 15°C. Compound (23) afforded the dinitro derivative (24) (42%) with HNO_3 at –35°C from which the trinitro derivative (78) (90%) can be obtained by treatment with $\text{HNO}_3\text{--Ac}_2\text{O}$ <87JOC1113>. With $\text{HNO}_3\text{--P}_2\text{O}_5$ compound (78) gave the tetranitro product (79) (65%). Nitrosation of compound (23) afforded a mononitroso derivative (43%) <87JOC1113>.



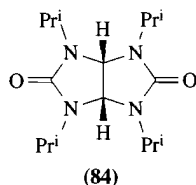
7.04.6.3 Nucleophilic Attack at Hydrogen

Phosphonate (80) is deprotonated by *n*-butyllithium and the resulting anion has been reacted with the aldehyde (81), giving the diene derivative (82). Aldehyde (81) can be prepared from the phosphonium salt (83) and glyoxal <91JCS(P1)2873>.



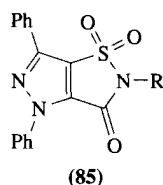
7.04.6.4 Reduction

Reduction (LAH) of compound (84) yielded the unstable heterocycle (6; R = Prⁱ) (77%) <87JOC1113>.



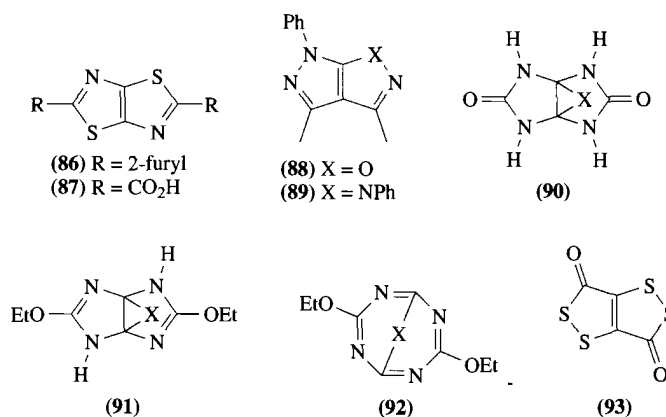
7.04.6.5 Oxidation

Heterocycle (69) and related compounds were oxidized (ddq, NiO_2 , MnO_2) to compounds (85) <89HCA1416>.



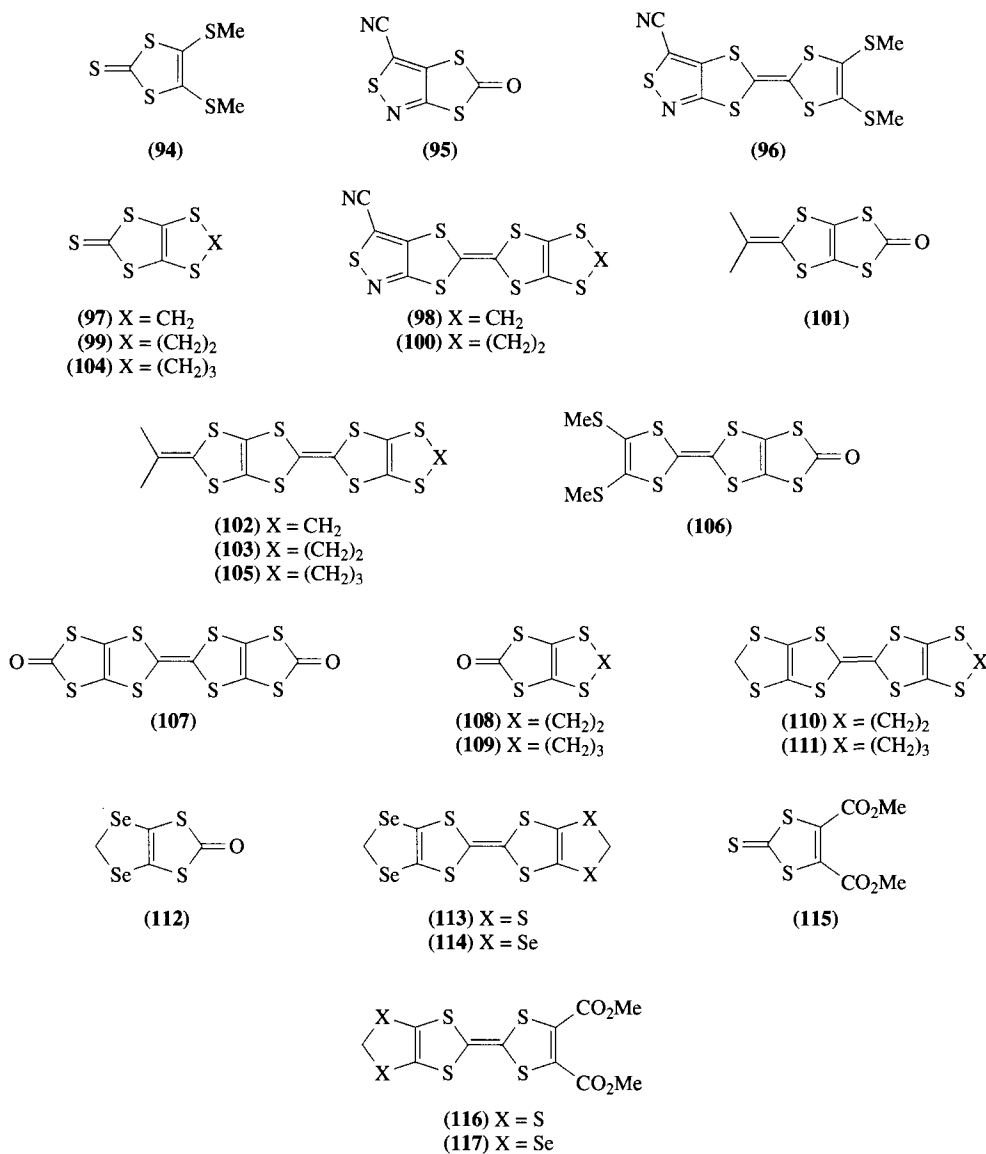
7.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Oxidation (KMnO_4) of the thiazolo[5,4-*d*]thiazole derivatives (86) gave thiazolo[5,4-*d*]thiazole dicarboxylic acid (87) <90MCLC297>. The methyl groups in the 1*H*-pyrazolo[4,3-*d*]isoxazole derivative (88) and the 1*H*,6*H*-pyrazolo[4,3-*d*]pyrazole derivative (89) can be activated toward condensation reactions with *N*-methylpyridinium iodide to give cyanine dye derivatives <90DP269>. Bridged glycouril derivatives (90; $\text{X} = (\text{CH}_2)_n$, $n = 2, 4, 5$ or $\text{X} = 1,8\text{-naphthyl}$) reacted with triethyloxonium tetrafluoroborate in the presence of potassium carbonate giving the *O*-ethylated derivatives (91), which underwent oxidative ring opening with *N*-bromosuccinimide, affording heterocycles (92) <87AG(E)1039>. Treatment of compound (40) with methyl iodide gave heterocycle (93) <91M71>.

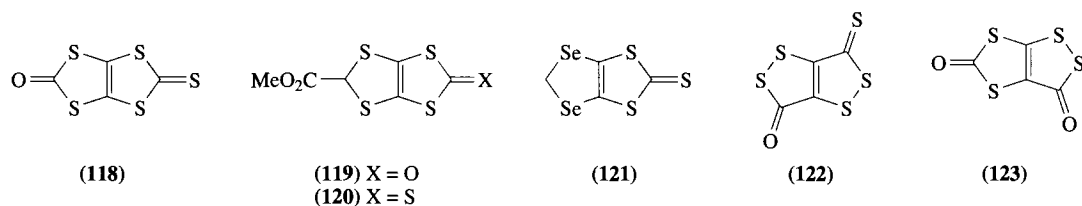


Many examples of triethyl phosphite or trimethyl phosphite symmetrical and unsymmetrical coupling reactions of sulfur-containing heterocycles have been reported. The products of these reactions have been prepared as analogues of tetrathiafulvalene (8). The following examples illustrate the scope of this reaction: (94) and (95) to (96); (95) and (97) to (98); (95) and (99) to (100) <87ZN(B)1050>; (97) and (101) to (102); (99) and (101) to (103); (101) and (104) to (105) <92CC1408>; (94) and (106) to (16) <92CL2321>; (54) to (107) <83JPR957, 91SM2381>; (61) to (7) <84CL993>; (61) and

(108) to (110) <87CC335>; (61) and (109) to (111) <87TL4153>; (61) and (112) to (113) <91ZN(B)1269>; (112) to (114) <89CS123>; (61) and (115) to (116); (112) and (115) to (117) <89CS123>.

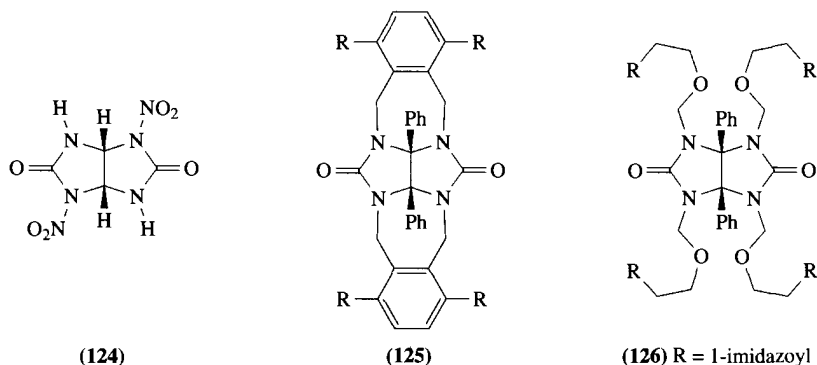


Desulfurization of many heterocycles which possess a thiocarbonyl group have been reported. The thiocarbonyl group is converted into a carbonyl group in this reaction, which is invariably achieved by treatment of the thiocarbonyl-containing heterocycle with mercuric acetate. The following transformations illustrate this desulfurization reaction: (97) to (61) <87CC335, 89CS71>; (118) to (54) <83JPR957>; (120) to (119) <88CS365>; (121) to (112) <89CS123>; (9) to a mixture of (93) (60%) and (122) (30%) <83TL3577> and (14) to (123) <86EGP236317>.



7.04.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

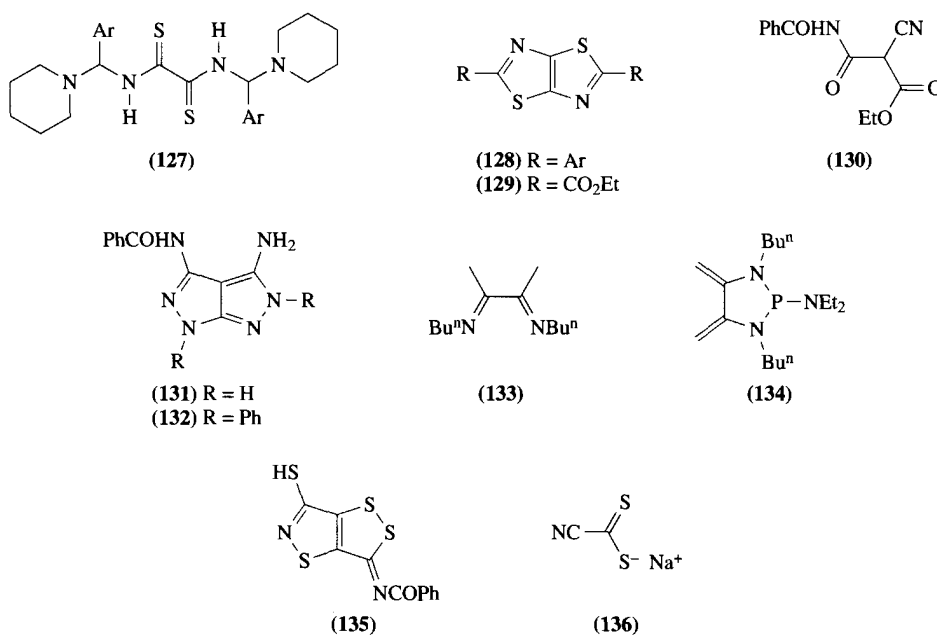
Nitration ($\text{H}_2\text{SO}_4\text{--HNO}_3$, 65°C) of the tetraacylglycouril derivative (**76**) gave the dinitro product (**124**) <86BSF465>. Glycouril derivative (**75**) reacted with benzene and substituted benzenes yielding "basket-shaped" heterocycles of the general structure (**125**; $\text{R} = \text{H, OH, OMe}$) (35–75%) <87JA928, 89JOC3710>. The metallo-enzyme mimic (**126**) has also been prepared from derivative (**75**) <88JA172>.



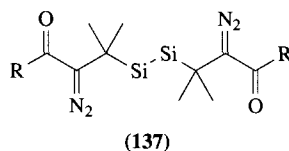
7.04.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

7.04.9.1 From Acyclic Compounds

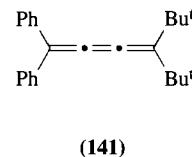
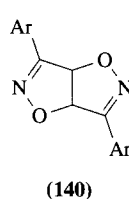
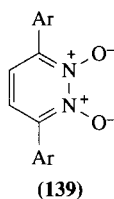
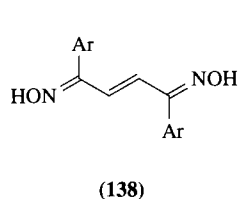
2,5-Diarylthiazolo[5,4-*d*]thiazole derivatives (**31**) have been prepared by treatment of appropriately substituted benzaldehyde derivatives with dithiooxamide <90MCLC297>. The dithione derivatives (**127**; $\text{Ar} = \text{substituted phenyl}$) and phenyl isothiocyanate yielded the heterocycles (**128**) in good yield <82EGP154987>. The diester derivative (**129**) (52%) was prepared from ethyl isocyanoacetate and S_2Cl_2 <87S1138>. Imide (**130**) gave 1*H*,5*H*-pyrazolo[3,4-*c*]pyrazoles (**131**) (72%) and (**132**) (70%) when treated with hydrazine and phenylhydrazine, respectively <87S228>. Treatment of diimine (**133**) with $(\text{Et}_2\text{N})_2\text{PCl}$ gave a mixture of the monocyclic product (**134**) (43%) and the bicyclic product (**11**) (23%) <87DOK(297)376>. Heterocycle (**135**) has been prepared from benzoyl chloride and the nitrile (**136**) in 95% yield <81EGP148341>. Heterocycle (**9**) can be prepared from hexachlorobutadiene and Na_2S_5 (40%) <85SUL25> or from 2,3-di-*t*-butylthiofumarate and P_2S_5 (15%) <83TL3577, 89T125>.



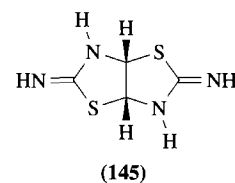
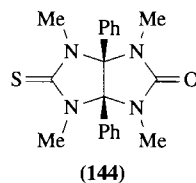
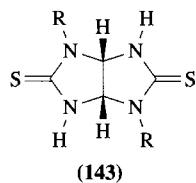
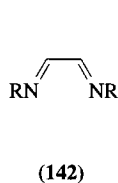
Photolysis of the diazo compound (**137**; R = Bu^t) gave heterocycle (**19**) in modest yield <90JOM(398)229>. Compounds (**137**; R = Prⁱ, 1-adamantyl) yielded similar products. When dimethyl alkynedicarboxylate was treated with Sn[N(TMS)₂]₂, heterocycle (**20**) (48%) was obtained <91POL1203>.



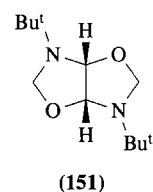
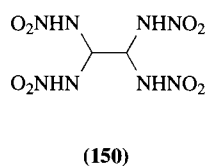
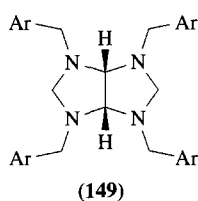
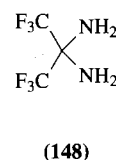
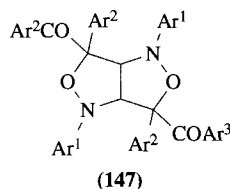
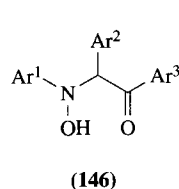
Oxidation (PhI(O₂CCF₃)₂) of dioximes (**138**) has been reported to give a mixture of the *N,N*-dioxides (**139**) in low yield and the 3a,6a-dihydroisoxazolo[5,4-*d*]isoxazoles (**140**) <82MI 704-01>. The 1,2,3-triene (**141**) gave compound (**25**) (48%) when heated with elemental sulfur <89TL4825>.



Diimines (**142**) and trimethylsilyl isothiocyanate gave glycouril derivatives (**143**) (10–60%) <90H(31)883> and *N,N*-dimethylthiourea and benzil afforded heterocycle (**144**) together with other products <91JCS(P2)1501>. Glyoxal and thiourea gave heterocycle (**145**) <82MI 704-02> and glyoxal and *N,N'*-diisopropylurea gave heterocycle (**84**) (50%) <87JOC1113>.



Hydroxylamine derivatives (**146**) were oxidized (PbO₂) to give products for which the structure (**147**) has been proposed <84JOC2654>. Glyoxal and diamine (**148**) yielded heterocycle (**23**) (87%) <87JOC1113>. A high-yielding (80–90%) synthesis of glycouril derivatives (**149**) from substituted benzylamines, formaldehyde and glyoxal has been reported <92JOC6756>. The tetranitro derivative (**150**) reacted with formaldehyde and *t*-butylamine at pH 3–6 to give heterocycle (**151**) in low yield <91ZOB2778>.

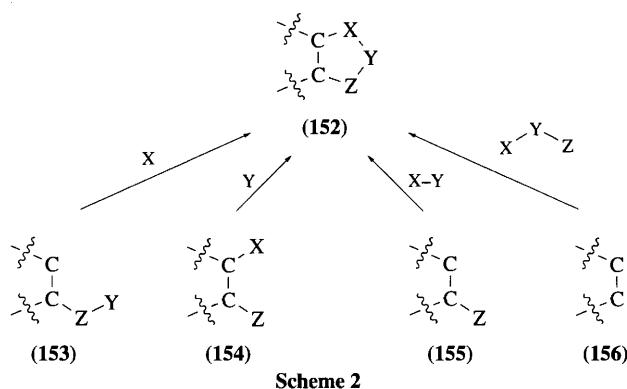


7.04.9.2 From Monocyclic Compounds

Numerous methods of preparing bicyclic systems from monocyclic precursors have been reported and four general strategies can be identified. These are: (i) intermolecular cyclization reactions which do not involve 1,3-dipolar cycloaddition reactions; (ii) intermolecular 1,3-dipolar cycloaddition reactions; (iii) nonoxidative intramolecular cyclizations; and (iv) oxidative intramolecular cyclization reactions. These four general methodologies are now considered.

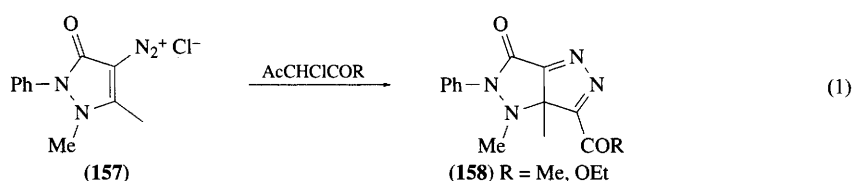
7.04.9.2.1 Intermolecular cyclization reactions which do not involve 1,3-dipolar cycloaddition reactions

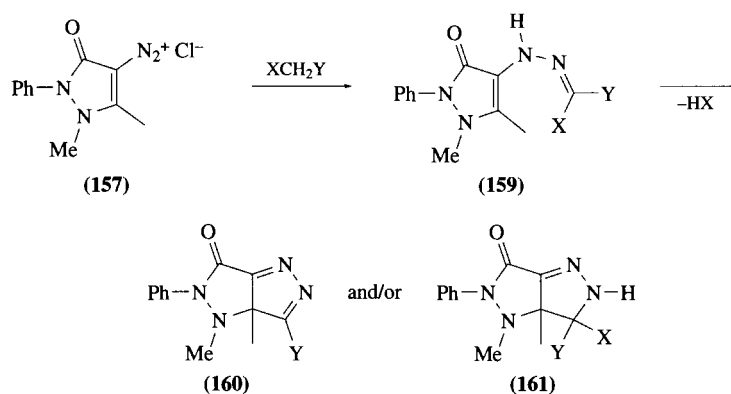
Intermolecular cyclizations which do not involve 1,3-dipolar cycloadditions form the largest of the four general types of cyclization reaction. If a general structure (152) is considered, where X, Y, and Z represent the component atoms or groups of the ring formed in the cyclization process, then several possible ways of constructing this ring from the monocyclic precursors (153)–(156) are apparent (Scheme 2). Methods which add the fragment X–Y–Z are restricted to 1,3-dipolar cycloaddition reactions, which are discussed in Section 7.04.9.2.2.



(i) Synthesis from [4 + 1] atom fragments by addition of fragment X

Diazonium salts (157) (Equation (1)) have been reacted with 2-chloro-1,3-dicarbonyl compounds yielding heterocycles (158) (50–75%) <82JCS(P1)989>. In a similar reaction sequence (Scheme 3), salt (157) yielded products (160) and/or (161) with activated methylene compounds <89ZN(B)951>. The formation of compound (160) involves elimination of a molecule XH, which is usually hydrogen cyanide.

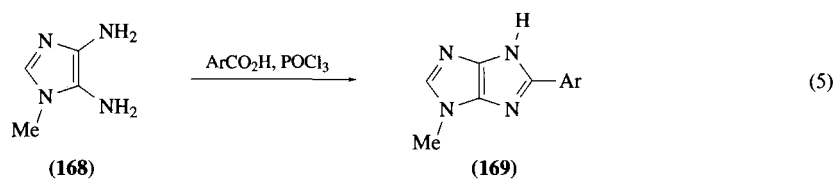
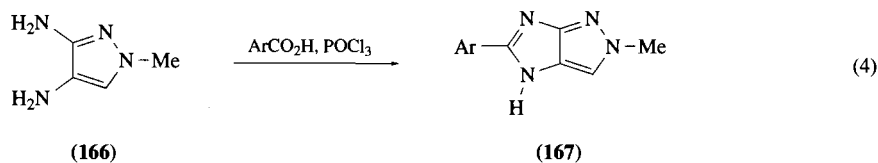
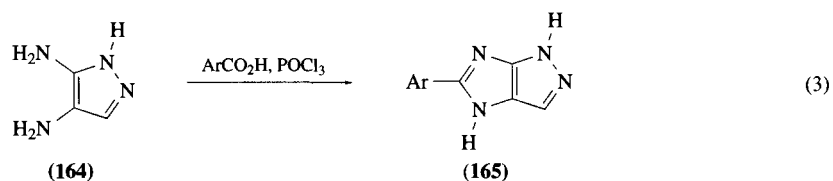
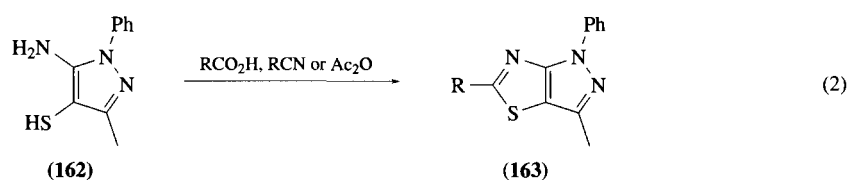


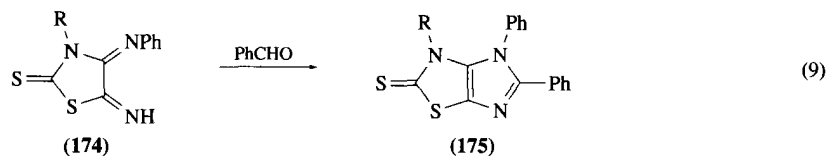
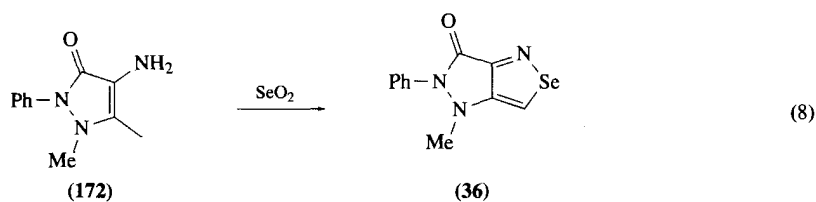
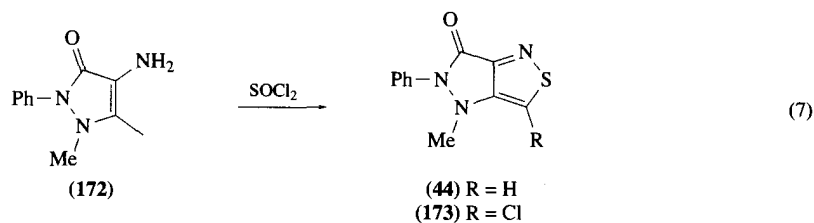
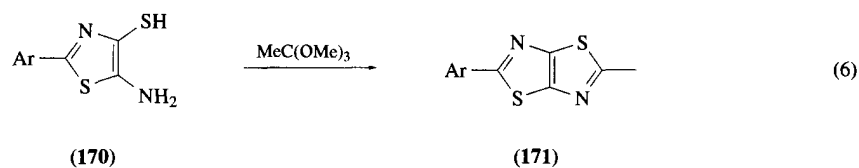


Scheme 3

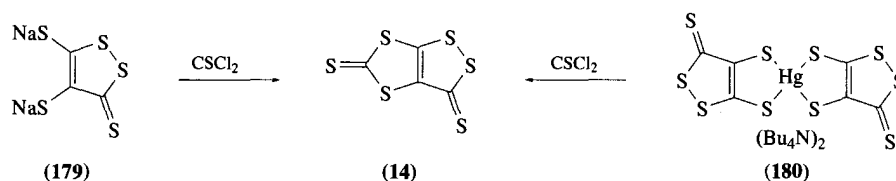
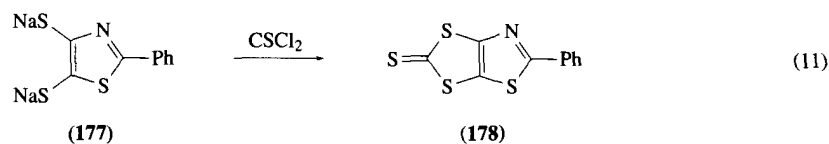
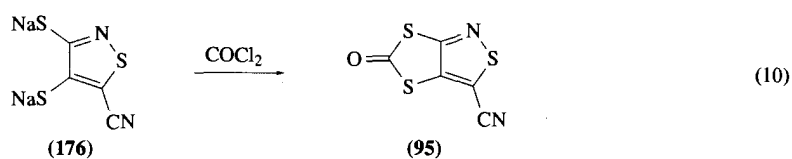
(ii) Synthesis from $[4 + 1]$ atom fragments by addition of fragment Y

Diazole derivatives (162), (164), (166), (168), and (170) have been reacted with carboxylic acids or their equivalents, giving the corresponding bicyclic heterocycles (163) (Equation (2)) <85BCJ785>, (165) (Equation (3)) <92AP(325)225>, (167) (Equation (4)) <92AP(325)225>, (169) (Equation (5)) <92AP(325)225> and (171) (Equation (6)) <84EGP210457>. Antipyrine (172) has been treated with thionyl chloride yielding a mixture of compounds (44) and (173) (Equation (7)) <86JHC1773> and with selenium dioxide giving heterocycle (36) (Equation (8)) <84JAP5920274, 85CPB3065, 87CPB398, 87TL4579>. Benzaldehyde can provide the Y component in a ring synthesis, as illustrated by the transformation of diimine (174) into compound (175) (Equation (9)) <85JOC3431>.

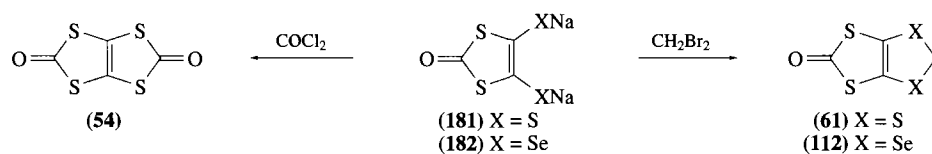




Phosgene and thiophosgene are popular reagents for synthesizing bicyclic heterocycles which possess either the carbonyl or the thiocarbonyl group. Thus isothiazole (176) and phosgene gave heterocycle (95) (Equation (10)) <87ZN(B)1051, 90MCLC171> and thiophosgene gave the corresponding thiocarbonyl product <87ZN(B)1051>. Similarly, thiazole (177) gave compound (178) with thiophosgene (Equation (11)) <84EGP210910>. Thiophosgene has also been used as a reagent in the preparation of compound (14) from salts (179) and (180) (Scheme 4) <85CS167, 86EGP236317, 89JOC2165>. Salt (181) and phosgene yielded heterocycle (54) (Scheme 5) <83JPR957>.

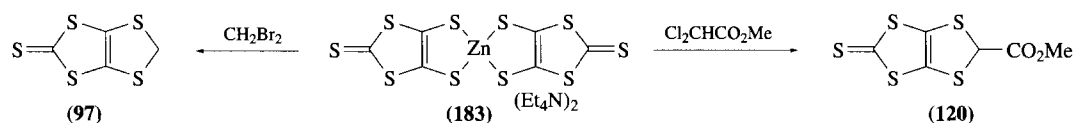


Scheme 4



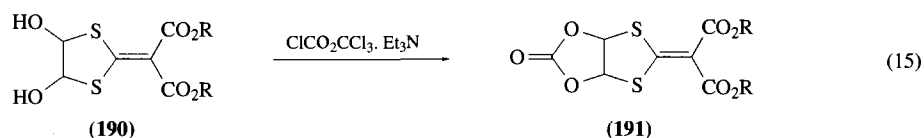
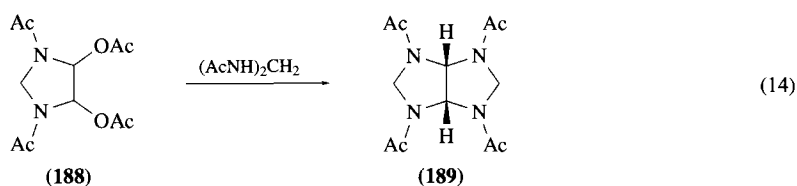
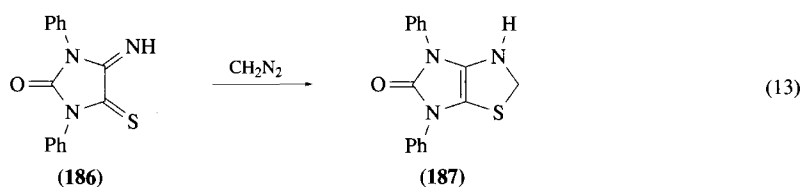
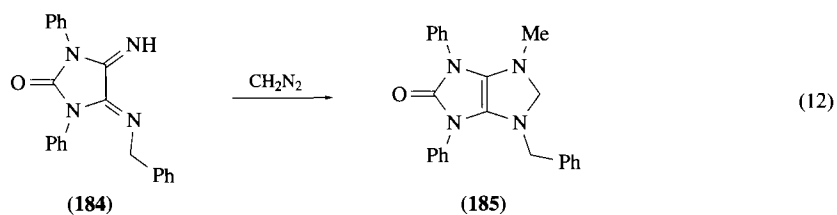
Scheme 5

Dibromomethane has been used to provide the Y component in several heterocyclic syntheses. Salts (181)–(183) reacted with dibromomethane giving heterocycles (61) (91SM2381), (112) (Scheme 5) (89CS123) and (97) (Scheme 6) (87CC335) respectively, and salt (183) gave compound (120) in a similar reaction with methyl 2,2-dichloroacetate (Scheme 6) (88CS365). Dibromomethane has also been used to provide the methylene fragments in a synthesis of the selenium-containing heterocycle (114) (89CC169).



Scheme 6

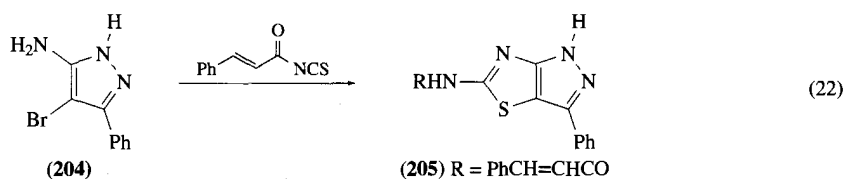
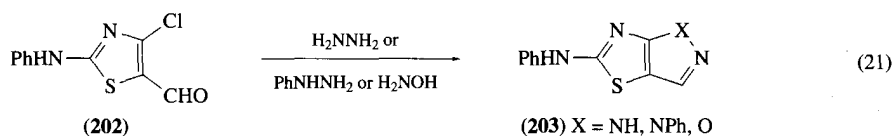
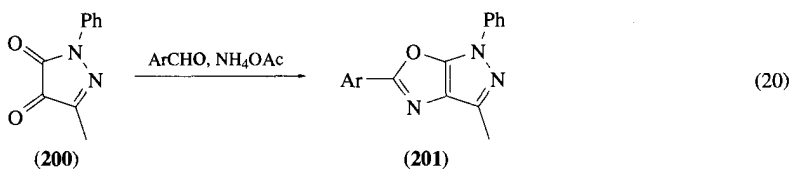
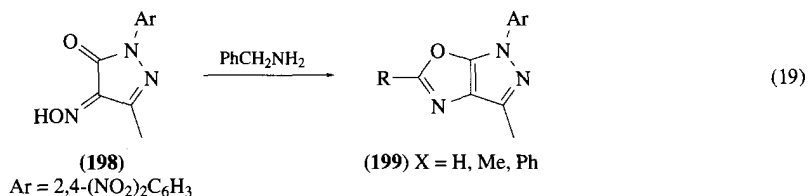
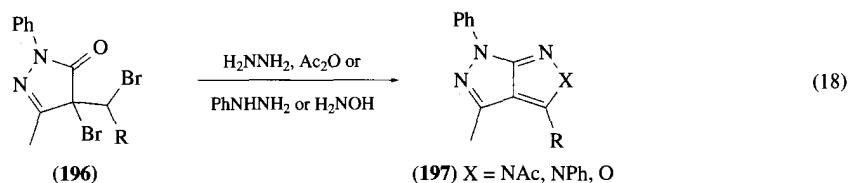
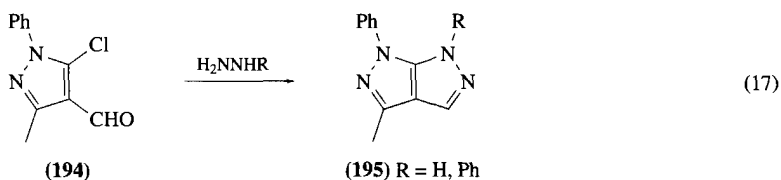
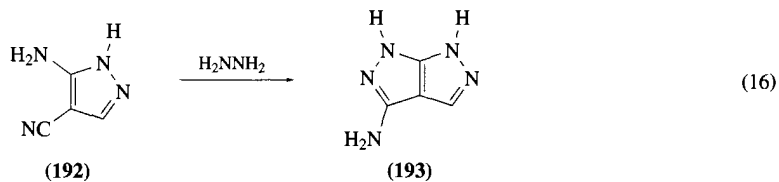
Diimine (184) and iminethione (186) both reacted with diazomethane yielding heterocycles (185) (Equation (12)) (90MI 704-01) and (187) (Equation (13)) (90MI 704-01) respectively. Compounds (189) (58%) and (191) (95%) have been prepared from the diacetate (188) (85JAP6006691) and the diol (190) (87JOC1113) respectively (Equations (14) and (15)).

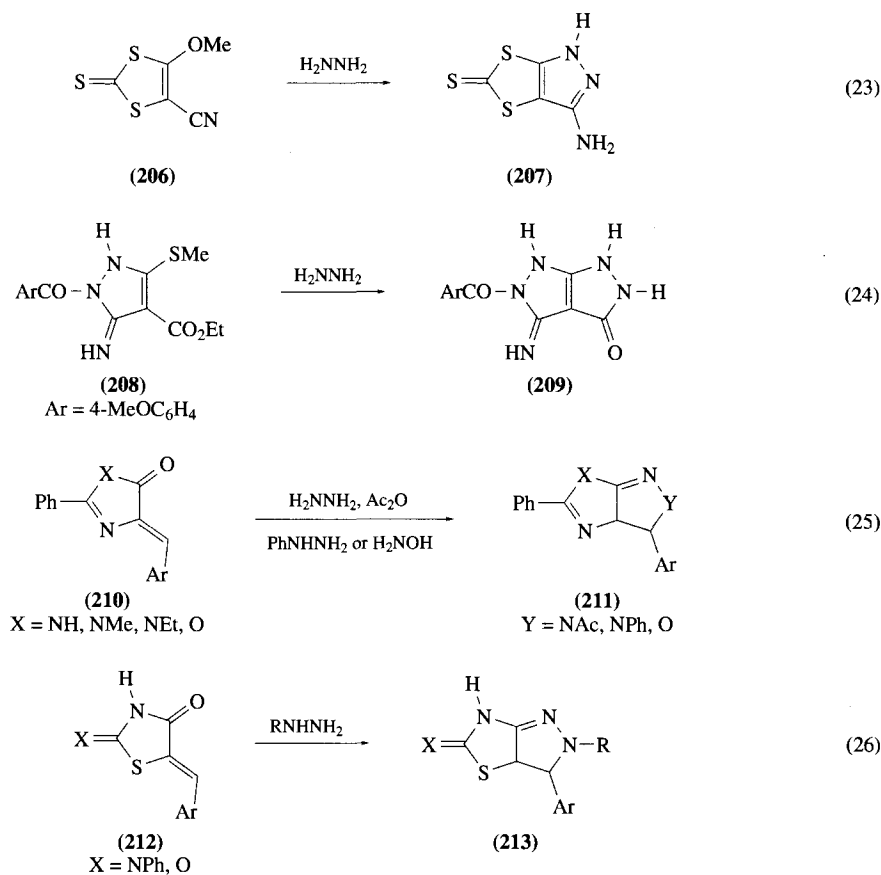


(iii) Synthesis from [3 + 2] atom fragments by addition of fragment XY

Hydrazine, substituted hydrazines, and hydroxylamine are popular reagents which can provide the X—Y components of a heterocyclic ring in the general transformation (155) to (152). Pyrazole

derivatives **(192)**, **(194)**, **(196)** and **(208)** were converted into heterocycles **(193)** <90CCC728>, **(195)** <93MI 704-01>, **(197)** <84JPR811> and **(209)** <82JPR639>, respectively, with these reagents (Equations (16), (17), (18), and (24)). Similarly, heterocycles **(210)** yielded products **(211)** (Equation (25)) <82JIC867, 85JSC135>. Thiazole derivatives **(202)** and **(212)** similarly yielded the corresponding heterocycles **(203)** (Equation (21)) <89IJC(B)866> and **(213)** (Equation (26)) <85JIC306, 91JIC167>, and compound **(206)** gave product **(207)** with hydrazine (Equation (23)) <83ZC333>. Ketoxime **(198)** and diketones **(200)** yielded 1*H*-pyrazolo[4,3-*d*]oxazole derivatives **(199)** (Equation (19)) <83H(20)1335, 84JHC1747> and **(201)** (Equation (20)) <84JHC1747>, respectively. The 5-aminopyrazole derivative **(204)** gave 1*H*-pyrazolo[4,3-*d*]thiazole derivative **(205)** (50%) (Equation (22)) when treated with $\text{PhCH}=\text{CHCONCS}$ <87LA65>.





(iv) *Synthesis from [2 + 3] atom fragments by addition of fragment XYZ*

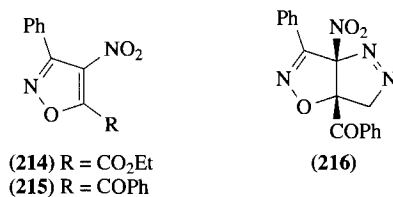
No new examples of this mode of cyclization have been reported.

7.04.9.2.2 Intermolecular cyclization reactions which involve 1,3-dipolar cycloaddition reactions

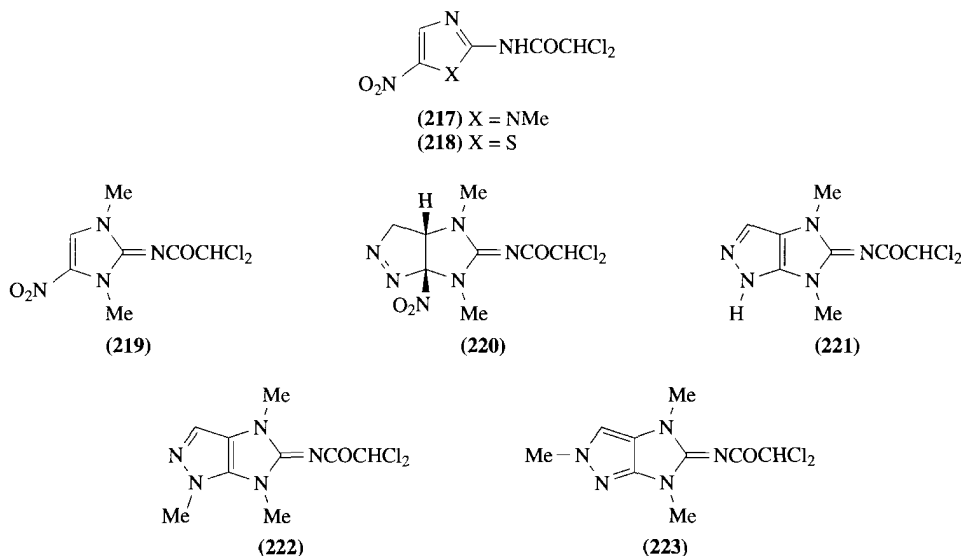
The intermolecular 1,3-dipolar cycloaddition route to bicyclic heterocycles has received considerable attention since 1983. Diazoalkanes, *N*-oxides, nitrile imines, and nitrile oxides have all been used as the 1,3-dipole component in the synthesis of these heterocycles.

(i) *Diazoalkanes*

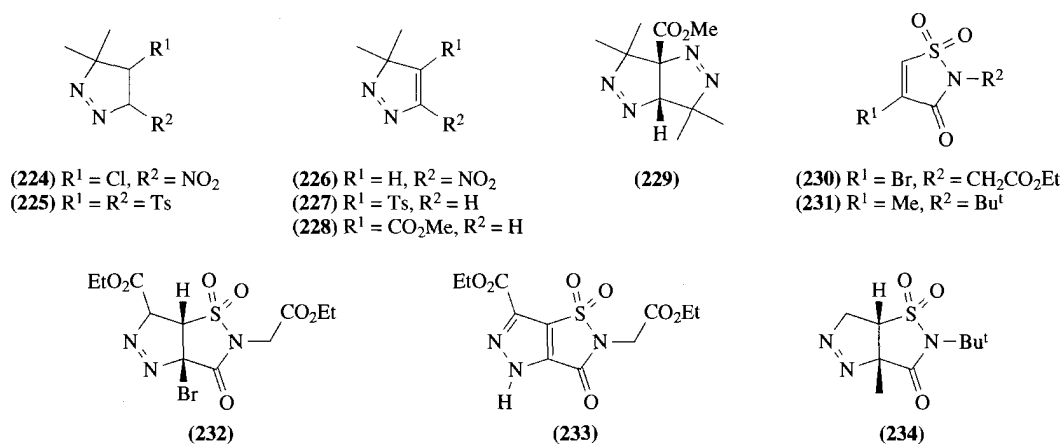
The isoxazole derivative (214) reacted with diazomethane to give the intermediate cycloadduct (66), which subsequently either fragmented with loss of nitrogen giving compound (67) or tautomerized to yield heterocycle (68) <87CC1077>. Isoxazole derivative (215) similarly participated in a 1,3-dipolar cycloaddition reaction with diazomethane giving a cycloadduct (216) in which the benzoyl group migrated and HNO₂ was lost yielding the 2*H*-pyrazolo[3,4-*d*]isoxazole derivative (10) (47%) <88S884>.



The imidazole derivative (**217**) underwent a series of reactions with diazomethane which resulted in the formation of products (**222**) and (**223**). Thus, *N*-methylation of compound (**217**) gave compound (**219**), which participated in a 1,3-dipolar cycloaddition giving cycloadduct (**220**). This cycloadduct then eliminated nitrous acid and the resulting product tautomerized giving heterocycle (**221**), which was further methylated giving a mixture of the products (**222**) and (**223**) <82IJC(B)997>. Thiazole derivative (**218**) underwent a similar reaction.



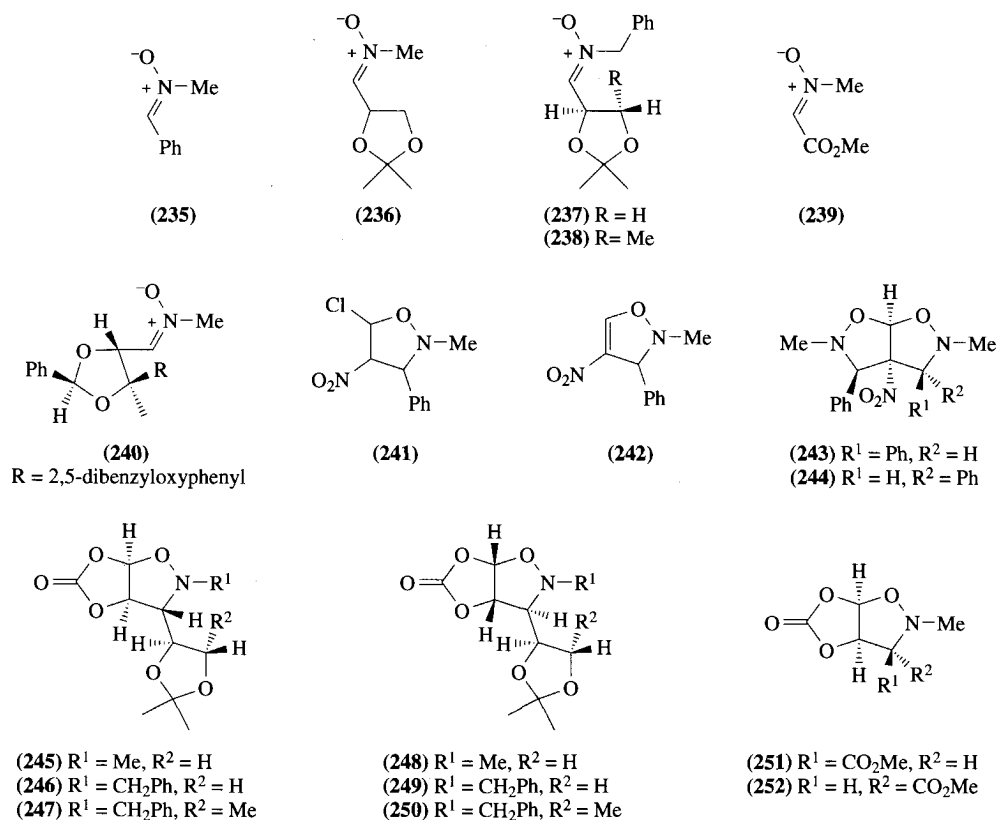
2-Diazopropane reacted with 2-chloronitroethene yielding diazole (**224**), which subsequently eliminated hydrogen chloride giving heterocycle (**226**). Compound (**226**) then reacted with a second molecule of 2-diazopropane giving heterocycle (**64**) <84TL2909>. In a related reaction sequence, 2-diazopropane and *cis*-1,2-ditosylethene gave product (**18**) (50%) via the initial cycloadduct (**225**) and heterocycle (**227**) <91T6139>. 2-Diazopropane reacted with methyl propiolate giving product (**229**) (6%) via the initial cycloadduct (**228**) <83AJC593>. Other alkynes and 2-diazopropane yield similar 2:1 adducts (60–85%) <83MI 704-02>. Ethyl diazoacetate and heterocycle (**230**) gave a cycloadduct (**232**), which eliminated hydrogen bromide and then tautomerized giving heterocycle (**233**) as the reaction product <89HCA1416>. Heterocycle (**231**) gave the cycloadduct (**234**) with diazomethane <89HCA1416>.



(ii) N-Oxides

The *N*-oxide derivatives (**235**)–(**240**) have all found use in the synthesis of bicyclic heterocycles. 2-Chloronitroethene reacted with *N*-oxide (**235**) in benzene at reflux temperature giving a mixture

of the diastereoisomers (243) and (244) in good yield <84JOC276>. In this reaction, the initial cycloadduct (241) eliminated hydrogen chloride giving heterocycle (242), which then underwent a second cycloaddition. Vinylene carbonate has been used as the alkene component in several 1,3-dipolar cycloaddition reactions of *N*-oxides. Thus, *N*-oxide (236) gave a 1:1 mixture of diastereoisomers (245) and (248) (85%) <84JA5598>; *N*-oxide (237) gave a 2:1 mixture of diastereoisomers (246) and (249) (81%) <84JA5598>; *N*-oxide (238) gave a 9:1 mixture of diastereoisomers (247) and (250) (80%) <84JA5598> and *N*-oxide (239) gave a 2:3 mixture of diastereoisomers (251) and (252) <90JOC3427>. Vinylene carbonate and *N*-oxide (240) gave a 1:2 mixture of diastereoisomers (27) and (28) (55%) at 120°C and ambient pressure and a 1:4 mixture of these products in 60% yield at ambient temperature and 12 kbar.

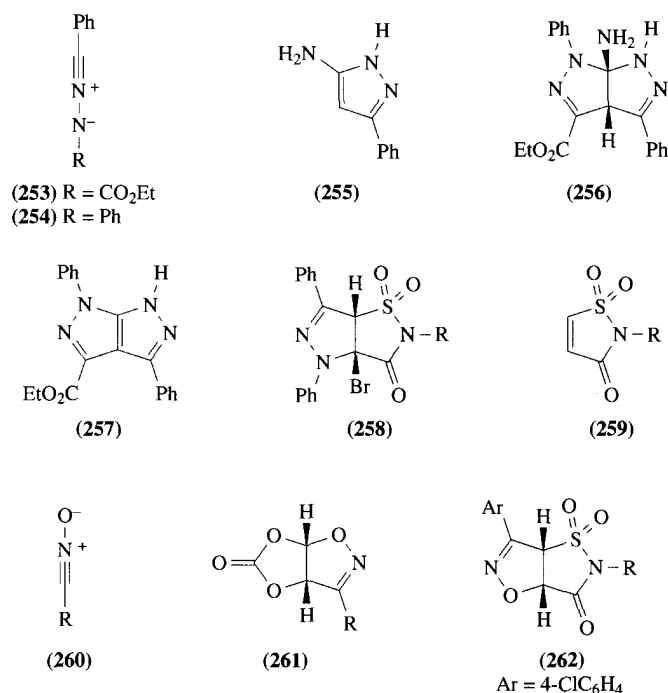


(iii) Nitrile imines

Nitrile imine (253) reacted with the aminopyrazole derivative (255) giving heterocycle (257) via loss of ammonia from the initial cycloadduct (256) <88IJC(B)836>. Similarly, nitrile imine (254) reacted with heterocycle (230) and gave product (85) via elimination of hydrogen bromide from the initial cycloadduct (258) <89HCA1416>. With heterocycle (259), nitrile imine (254) gave the cycloadduct (69) <89HCA1416, 92C335>.

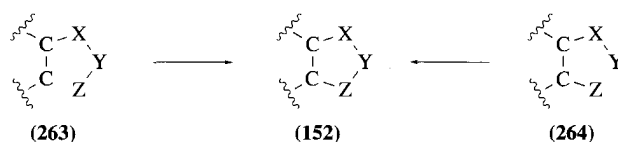
(iv) Nitrile oxides

Nitrile oxides (260; R = CPh, CO₂Et, COMe) reacted with vinylene carbonate yielding the cycloadducts (261) <85H(23)2479>. With the heterocycles (259), the nitrile oxide (260; R = 4-ClC₆H₄) gave the cycloadducts (262) (17–55%) <89HCA1416>.



7.04.9.2.3 Nonoxidative intramolecular [5 + 0] cyclizations

The two strategies for preparing bicyclic heterocycles of the general type (152) by nonoxidative intramolecular reactions have been used and these involve cyclization of the generalized structures (263) or (264) (Scheme 7). Cyclizations of the type (263) to (152) include the transformation of the dipolar compound (265) into the 1*H*-pyrazolo[3,4-*d*]oxazole derivative (266) (40–90%) <84H(22)2309> under photochemical conditions and the cyclization of the hydrazone (267) into the 1*H*-pyrazolo[4,3-*d*]oxazole derivative (268) <89IJC(B)782>. Heterocycles (269) can be cyclized, giving three types of products depending on the reaction conditions <92MI 704-01>. Under basic conditions compounds (270) were obtained, whilst under acidic conditions compounds (271) were formed. Treatment of compounds (269) with methyl iodide gave products (272). Similarly, heterocycles (273) gave the products (274)–(276) <87IJC(B)1200>.

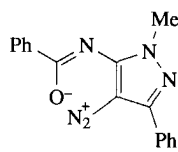


Scheme 7

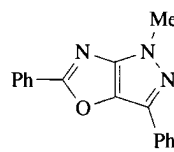
Several cyclizations of the type (264) to (152) (Scheme 7) have been reported. Heating the nitroso compounds (277) in pyridine at reflux temperature afforded the 1*H*-pyrazolo[3,4-*d*]imidazole derivatives (278) <86EUP190457, 90T5777>. Thiylimine (279) was converted to the thiazolo[5,4-*d*]thiazole derivative (128; Ar = Ph) when heated in nitrobenzene <84EGP216241> and azides (280) and (282) were transformed into the corresponding 2*H*-pyrazolo[3,4-*d*]thiazoles (281) (80–85%) and thiazolo[4,5-*c*]isoxazole (283) (61%) when heated under reflux in toluene and bromobenzene solutions, respectively <92JCS(P1)973>. Heterocycle (284) gave the salt (53) with Lawesson's reagent <89CC1716>. Thermally induced cyclization of heterocycle (285) gave compound (135) via a Dimroth rearrangement <89MI 704-01> and hydrazone (286) was cyclized to heterocycle (287) under basic conditions <89IJC(B)470>.

7.04.9.2.4 Oxidative intramolecular [5 + 0] cyclizations

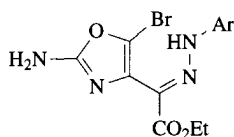
Since 1985 examples of oxidative intramolecular cyclizations have all been transformations of the general transformation type (264) to (152) (Scheme 7). Most examples involve the formation of a



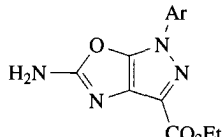
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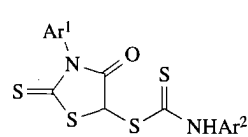
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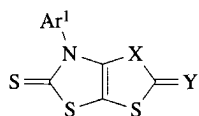
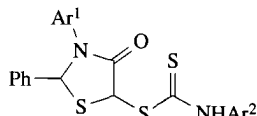
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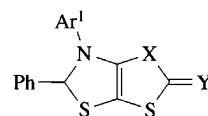
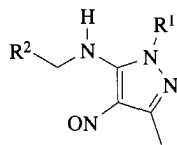
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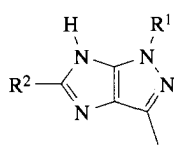
(269)

(270) X = NAr², Y = S(271) X = S, Y = NAr²(272) X = O, Y = NAr²

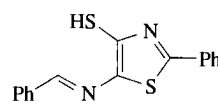
(273)

(274) X = NAr², Y = S(275) X = S, Y = NAr²(276) X = O, Y = NAr²

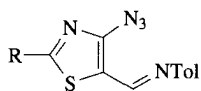
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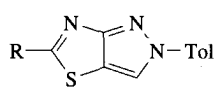
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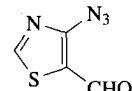
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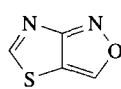
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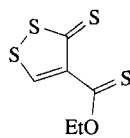
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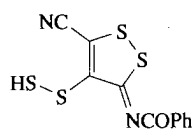
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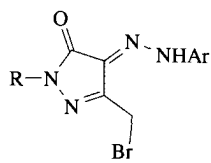
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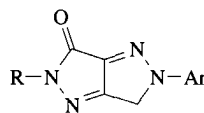
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(285)

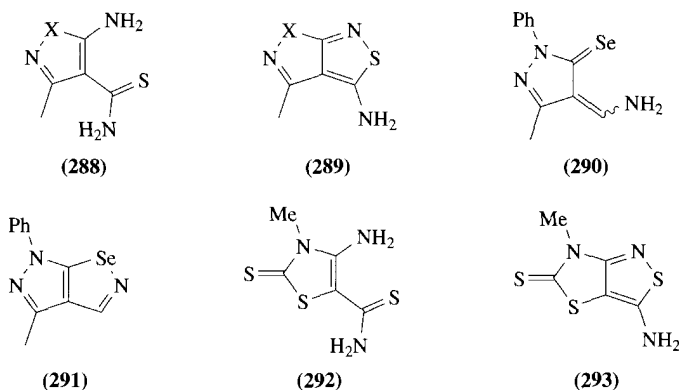


(286)



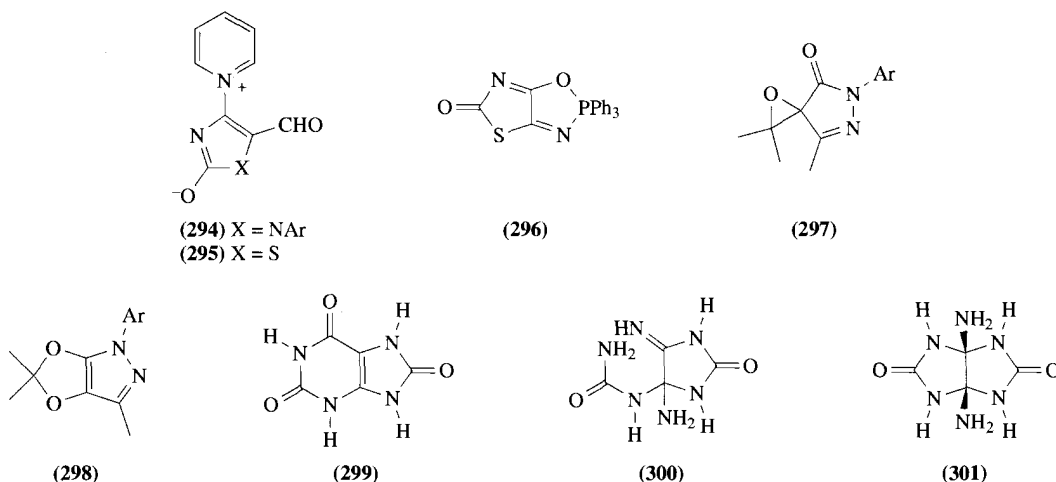
(287)

bond between the sulfur atom of a thioamide group and an appositely located heteroatom. Pyrazole derivatives (**288**; X = NR) were oxidized by either iodine or hydrogen peroxide giving the 1*H*-pyrazolo[5,4-*c*]isothiazole derivatives (**289**; X = NR) <87FES133>. Isoxazoles (**288**; X = O) were similarly cyclized <90JHC1481>. Photochemical oxidation of heterocycle (**290**) in the presence of oxygen gave the substituted 1*H*-pyrazolo[5,4-*d*]isoseleazole (**291**) <85ZOB2258>. Hydrogen peroxide has also been used as the oxidizing agent in the conversion of thioamides (**49**) and (**292**) into heterocycles (**33**) <91JPR19> and (**293**) (80%) <81EGP152937>, respectively. Nitrosium tetrafluoroborate and compound (**58**) gave the salt (**57**) <89SM537>.



7.04.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Several examples of ring transformations of sulfur-containing heterocycles have been reported. Thus, compound (9) is converted into a mixture of heterocycles (32) and (33) when treated with amines <89T125>, and heterocycles (50) are converted into isothiazolo[5,4-*d*]isothiazoles (51) (10–80%) when treated with hydroxylamine <89ZC17>. Heterocycle (32; R = 4-Me₂NC₆H₄) gave the isomer (33; R = 4-Me₂NC₆H₄) under photochemical conditions or when treated with a Lewis acid <90JPR387>. The zwitterionic heterocycles (294) and (295) gave products (71) (56%) and (296) (67%), respectively, when heated under reflux with triphenylphosphine in acetic acid <85ZOB195>. Epoxide (297; Ar = 4-NO₂C₆H₄) gave the 1*H*-[1,3]dioxolo[4,5-*c*]pyrazole derivative (298) when heated at 160°C <85JPR35>. Treatment of uric acid (299) with potassium ferricyanide and aqueous ammonia gave an intermediate (300) which cyclized to the glycouril derivative (301) <91T317>. Methylated uric acid derivatives gave similar products (50–60%).



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

Most of the compounds described in this chapter have been prepared by one route and a critical comparison of available routes for specific compounds cannot therefore be made. Some general trends can, however, be recognized which relate to the synthesis of heterocycles with particular substitution patterns. If one heterocyclic ring of a bicyclic system is associated with 1,2-heterosubstitution, binucleophiles such as substituted hydrazines and hydroxylamine are frequently used to introduce these two heteroatoms. 1,3-Dipolar cycloaddition reactions can also be used to construct a heterocyclic ring with 1,2-heterosubstitution. If one heterocyclic ring of a bicyclic system is associated with 1,3-heterosubstitution, compounds represented by the general structure (154), where X and Z

are the heteroatoms, are often used as binucleophiles and are reacted with suitable electrophiles to construct the 1,3-heterosubstituted ring. 1,3,4,6-Tetraaza heterocycles such as glycouril derivatives can readily be prepared in a three-component reaction involving a 1,2-dicarbonyl compound and two molecules of an appropriate 1,3-binucleophile.

7.04.12 IMPORTANT COMPOUNDS AND APPLICATIONS

One of the most striking advances in this area of chemistry is the synthesis and investigation of sulfur-containing heterocycles as potential "organic metals" because of their relationship to tetrathia fulvalene (**8**) <86T1209, 87SR155, 88AG(E)1747, 94AM(6)439>. In this context many 5:5 ring systems have been prepared and evaluated.

Many uses of thiazolo[5,4-*d*]thiazole derivatives in the fields of photographic processing and photoconductors have been reported in the patent literature.

Several fully saturated heterocyclic systems which have been formed by cycloaddition reactions have found use in natural product synthesis. Cycloadducts (**27**) and (**28**) were prepared as part of an investigation into the synthesis of the benzoxocin fragment of the antitumor anthracycline nogalomycin <91JOC1364> and cycloadducts (**245**) and (**248**) were intermediates in the synthesis of amino sugar derivatives <84JA5598>.

Many applications of polynitroglycouril derivatives as high explosives have been described in the patent literature.

Many of the heterocycles described in this chapter have been tested for biological activity, which is not surprising in view of the wide variety of novel structural types.

7.05

Bicyclic 5-5 Systems: Five Heteroatoms 2 : 3 and Six Heteroatoms 3 : 3

FRANCES HEANEY

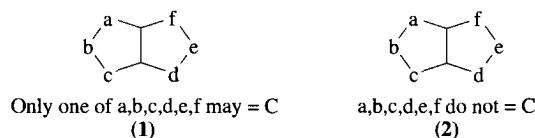
University College Galway, Republic of Ireland

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7.05.1 INTRODUCTION

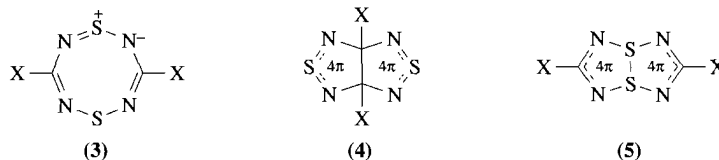
The chemistry of 5,5-fused heterocycles has not been reviewed since its discussion in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). At that time thirteen 5,5-fused heterocycles containing five or six heteroatoms without a bridgehead heteroatom were recorded in the ring index and, although no single chapter was devoted to this group of molecules, much of the known chemistry was included in Chapters 4.36 and 4.37 of CHEC-I. A number of review articles dealing with selected aspects of this topic exist <77T3203, 78AHC183>. The interest in these systems continues and in 1996 almost three times this number of such 5,5-fused heterocycles are documented in the literature. The aim of this chapter is to survey and correlate this work. Specifically it is concerned with 5,5-fused heterocycles containing five or six heteroatoms arranged 2 : 3 or 3 : 3 with no heteroatoms occupying the bridgehead position, i.e., general structures (1) and (2). Both aromatic and nonaromatic systems are considered. The number of compounds in this category is potentially huge, yet it will become obvious that most work has been carried out on systems with N, S, and O as the heteroatoms. A smaller number of compounds exist where P, Se, and B are incorporated into the ring system. The major focus of this work surveys material published post CHEC-I, but a number of ring systems from earlier years not included in the first edition are also discussed.



7.05.2 THEORETICAL CONSIDERATIONS

Only scant reference has been made to model studies on these types of compounds. Thus *ab initio* (STO-3G) and MNDO calculations on 1,5-dithia-2,4,6,8-tetrazocine propound a preference for the 10 π -electron planar monocyclic structure (3) (X = H), and suggest that the bicyclic [1,2,5]thiadiazolo[3,4-c][1,2,5]thiadiazole-2,5-S(IV) (4), an 8 π system with a transannular C—C bond could never be the stable structure for this molecule. Hence it is proposed the preparation of

compounds (4) would be feasible only if formation of the eight-membered ring were prevented, i.e., by initial formation of the C—C bond. On the other hand, a delicate balance in energy between structure (3) and the bicyclic structure (5), an 8π system with a transannular S—S bond is reported, such that electron-donating substituents ($X = \text{NH}_2, \text{NMe}_2$) favor the latter <84JA3437>.

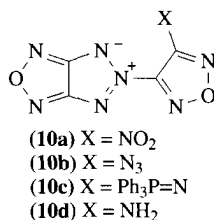


Tajiri and Winkler have conducted quantum mechanical calculations on some thiadiazolo-thiadiazoles (6)–(9) within the framework of the Parriser–Paw–Pople (PPP) method and have successfully employed their theoretical results to assist in the interpretation and prediction of the magnetic circular dichroism (MCD) spectra of these molecules <83ZN(A)1263>. Despite the fact that sulfur $3d$ orbital participation is more or less unimportant in the prediction of dipole moments, electronic absorption spectra, or photoelectron spectra, the authors suggest that its significance for the evaluation of magnetic moments of sulfur-containing heterocycles merits further consideration.

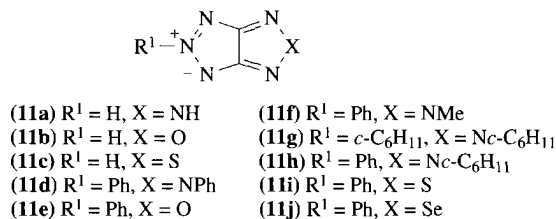


The aromatic character of [1,2,3]triazolo[4,5-*d*]-1,2,3-triazole and its 2,5-dioxide has been the subject of a quantum chemical study; thus MNDO/3 and MNDO calculations present the opinion that the parent compound has antiaromatic character with C_{2h} and not D_{2h} symmetry, while its 2,5-dioxide has a preference for aromatic structure and D_{2h} symmetry <91IZV1825>.

The density, detonation velocity, and detonation pressure of the triazoloxadiazole (10a) has been the subject of calculation; results suggest that this molecule may be a good candidate as a super energetic material <93HAC521>.



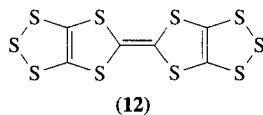
A series of heteroazapentalenes (11a–c) have been studied using the CNDO/2 method. The results of these studies allowed a prediction of molecular geometry and have been used in conjunction with x-ray photoelectron spectroscopy to predict charge densities of compounds (11a,b) and their derivatives (11d,e); experimental and theoretical results were in good agreement. The study of molecule (11c) by CNDO/2 gave no useful results—an accepted drawback of this method is its unreliability with molecules containing second-row elements. It is concluded that although compounds (11d,e) may have been regarded as *meso*-ionic compounds, the degree of charge polarization is not very large <77BCJ1917>.



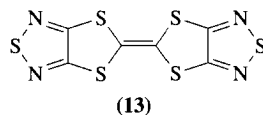
The observed linear correlation of the energy of the LUMO of the 2,5-disubstituted triazolo[4,5-*d*]-1,2,3-triazol-2-ium-3-ides (11d,f,g,h) with their polarographic reduction potentials is in keeping

with that expected for aromatic hydrocarbons. The calculations performed by the HMO (Hückel Molecular Orbital) method also suggested that the aryl substituents would be co-planar with the bicyclic nucleus, a prediction borne out by the UV and NMR spectroscopic analysis <74BCJ1490>.

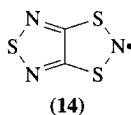
The effect of a range of substituents on the electron-donor capability of TTFs (tetrathiafulvalenes) was the subject of a report by Bowadt and Jensen <89SM179>. Semiempirical MNDO calculations have been conducted on 5-[1,3]dithiolo[4,5-*d*]-1,2,3-trithiol-5-ylidene (**12**) and the following conclusions were adopted: the molecule is planar and has D_{2h} symmetry; its vertical ionization potential is 8.61 eV and its adiabatic ionization potential is 8.02 eV. The calculated ionization potentials are in good agreement with the experimental values measured in solution.



5-[1,3]Dithiolo[4,5-*d*][1,2,5]thiadiazol-5-ylidene (**13**) has been studied using the MNDO method. A calculation of its HOMO (input structure was derived from the geometry obtained from x-ray analysis) showed it to be similar to that of unsubstituted TTF, with an important observation being the large coefficient on the sulfur atom of the thiadiazole ring. This property confers an advantage in the construction of multidimensional organic conductors <93H(35)69>.



[1,2,5]Thiadiazolo[3,4-*d*]-1,3,2-dithiazol-2-yl (**14**) failed to be a suitable candidate for calculation for ESR properties and isotropic and anisotropic hyperfine interactions <91MRC625>. However, the MNDO method successfully predicted, in line with experimental findings, that the p spin density is essentially located on the unique nitrogen atom.



7.05.3 EXPERIMENTAL STRUCTURAL METHODS

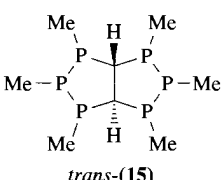
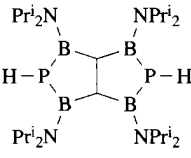
7.05.3.1 X-ray Diffraction

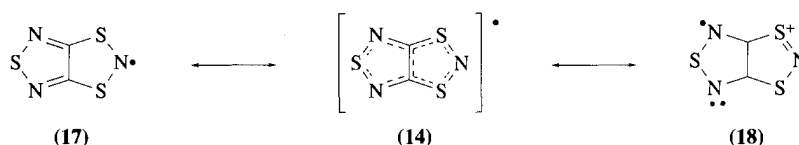
X-ray crystal structure analysis has proved to be the essential tool for unambiguous assignment of the structure of a number of new ring systems. Structures (**6**), (**10b**), (**13**)–(**16**) have been determined by x-ray studies, the results of which are presented in Table 1. A number of unexpected structural features have been detected. The tetrasubstituted tetrathiafulvalene (TTF) (**13**) showed S—N and C—N bond lengths which are longer and shorter, respectively, than those expected for a corresponding monocyclic 1,2,5-thiadiazole. An important point is the short intermolecular S—N and S—S contact distances observed in the crystal, which facilitate network formation through heteroatom contacts. The crystals are packed along the short b axis. Compound (**14**) (Scheme 1), a stable sulfur–nitrogen radical, represents a novel pentalene analogue deemed to be suitable for the synthesis of conductive systems. The S—N, C—N, and C—S measured bond lengths suggest that these bonds are single bonds with partial double bond character. This conclusion suggests that of the possible resonance forms of the radical (**14**), that of (**17**) is more likely than that of (**18**).

Perhydro[1,2,5]phosphadiboro[3,4-*c*][1,2,5]phosphadiborole (**16**) has been the subject of detailed spectroscopic analysis and its structure unveiled by these studies has been confirmed by x-ray crystallographic determination <93CB1291>.

[1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazole-5-S(IV) (**6**) is an example of a unique aromatic compound with no hydrogen atoms. This completely planar molecule was first reported by Komin and co-workers <75JOC2749, 81CSC1403>.

Table 1 Some bicyclic 5,5-fused ring systems whose conformations have been determined by x-ray studies.

Molecule	Structural features	Ref.
(6) (10b) (13) (14)	Fully planar molecule Planar geometry Planar system	81CSC1403 93HAC521 93H(35)69 89AG(E)920
 <i>trans</i> -(15)	Skew chair conformation; all methyl groups axial	78ZN(B)698
 (16)	Nonplanar	93CB1291

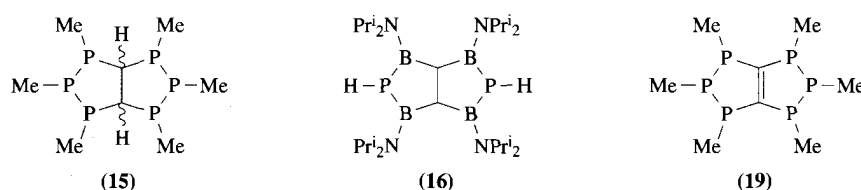
**Scheme 1**

7.05.3.2 Molecular Spectra

Spectroscopic analysis has been central to the characterization of all new ring systems and new derivatives of older systems included in this chapter. Many compounds display spectral data entirely as would be predicted; however, a number of points merit discussion. Original publications should be consulted for data relevant to the individual molecules.

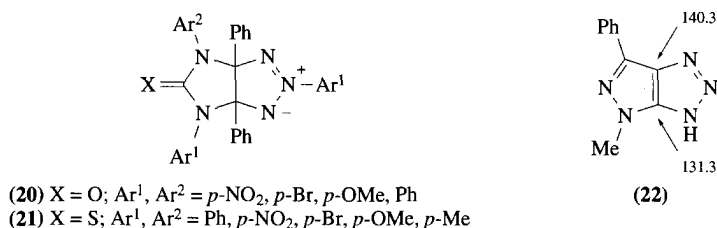
7.05.3.2.1 Nuclear magnetic resonance spectroscopy (^1H , ^{13}C , ^{15}N , ^{31}P , ^{11}B)

Nuclear magnetic resonance spectroscopy has assisted in assigning the structure of almost all new compounds illustrated in this chapter, and ^1H , ^{13}C , ^{15}N , ^{31}P , and ^{11}B nuclei have been studied where appropriate. The perhydrohexamethyl[1,2,3]triphospholo[4,5-*d*]-1,2,3-triphosphole (15) exists in two diastereomeric forms; details of ^1H , ^{13}C , and ^{31}P spectra together with an x-ray crystal structure of *trans*-(15) allowed unambiguous assignment of each isomer. Spectral data of the isomers differ considerably; for example, in the ^1H NMR spectra the resonance position of the methine protons were δ 3.85 (s) for the *trans* isomer and δ 3.46 (s) for the *cis* isomer (78ZN(B)691). The ^{31}P spectra of both these isomers and of the corresponding dehydro derivative (19) showed a series of complex multiplets arising from A_2B spin systems (79ZC418).



Multinuclear NMR spectroscopy has been used for the structural elucidation of the boron heterocycle (16). The ^{11}B NMR spectrum of compound (16) exhibited one signal, a singlet at δ 52.1. The ^{31}P NMR spectrum also showed one signal, a doublet at δ 180.2 with $^1J_{\text{PH}} = 214.9$ Hz. ^{13}C NMR displayed seven sets of signals, $4 \times \text{q}$ representing $4 \times \text{CH}_3$, $2 \times \text{d}$, $2 \times \text{NCH}$, and $1 \times \text{d}$, δ 48.13 ($J = 129$ Hz) being the $\text{B}-\text{C}-\text{H}$ carbon signal. ^1H NMR spectral data are as expected, though it is interesting to note that four-bond coupling between the P and the CH proton is significant at $J = 2.6$ Hz. $\langle 93\text{CB}1291 \rangle$.

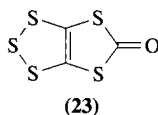
The 5-oxo- (20) and 5-thia-hexahydroimidazo[4,5-*d*]-1,2,3-triazol-2-ium-3-ides (21) represent novel ring systems. These new products have been assigned on the basis of their spectral data and, in particular, it is noted that in the thia series (21) the ^{13}C signals for $\text{C}=\text{S}$ appeared at δ 182–185.5. The corresponding signals for the oxo series had their resonance positions at δ 155–157.5. In the entire series the ^{13}C bridgehead signals were observed at δ 89–102, which is characteristic for these types of molecules $\langle 92\text{JCS(P)}12159 \rangle$. The bridgehead ^{13}C signals for 3,4-dihydro-4-methyl-6-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (22) occur at δ 140.3 and 131.3 $\langle 85\text{JHC}951 \rangle$.



7.05.3.2.2 Mass spectrometry

Mass spectrometry has been a useful tool in structural evaluation of a number of unusual heterocyclic compounds.

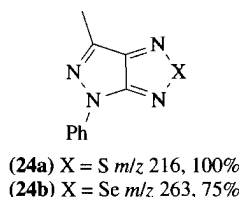
[1,3]Dithiolo[4,5-*d*]-1,2,3-trithiole-5-thione (23), obtained unexpectedly upon electrochemical reduction of carbon disulfide, was identified largely on the basis of its mass spectrum, which showed a molecular ion, m/z 228 (47%) with the base peak at m/z 76 $\langle 81\text{JOC}775 \rangle$.



Mass spectral data obtained for the radical (14) at low ionization energies showed an intense molecular ion $\langle 89\text{AG(E)}920 \rangle$. The hexaphosphabicycles (15), analyzed as a mixture of *cis* and *trans* isomers, also displayed an intense molecular ion (100%) together with characteristic fragment ions in its mass spectrum: $(\text{M} - \text{Me})^+$, $(\text{M} - \text{PMe})^+$, $[\text{M} - (2\text{PMe})]^+$ $\langle 78\text{ZN(B)}691 \rangle$.

The highly symmetrical perhydrophosphadiborolophosphadiborole (16) exhibited a low-intensity molecular ion in its mass spectrum, m/z 534 (7%), yet the $[\text{M} - \text{B}_2(\text{NPr}^i)_2]^+$ fragment ion, seen as a strong peak at m/z 311 (67%), confirms the identity of this compound $\langle 93\text{CB}1291 \rangle$.

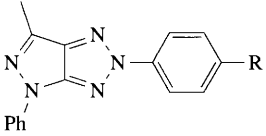
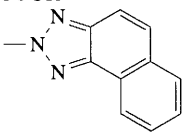
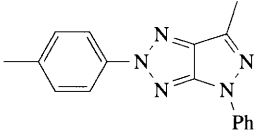
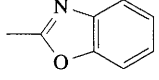
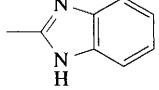
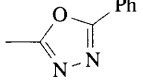
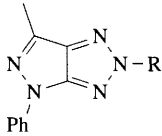
The presence of the molecular ion as an intense peak in the mass spectra of the pyrazolo[3,4-*c*][1,2,5]thiadiazole (24a) and pyrazolo[3,4-*c*][1,2,5]selenadiazole (24b) was central to their structural identification $\langle 81\text{JOC}4065 \rangle$.

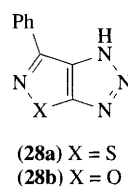
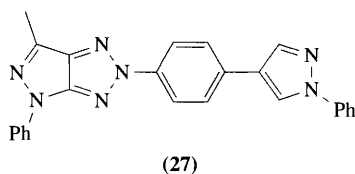


7.05.3.2.3 Ultraviolet spectroscopy

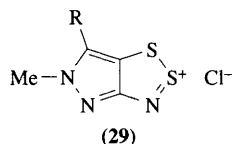
The UV properties of a number of molecules discussed in this chapter make them useful in the fabrics industry where they function as fluorescent brightners (see Section 7.05.12). The absorption and fluorescence emission maxima of an interesting range of 2-substituted 2,4-dihydro-6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazoles (**25**), (**26**) are included in Table 2. The triazole (**27**) displayed a strong violet fluorescence <87JJC(B)616>. The wavelength of maximum absorption of the isothiazolo[4,5-*d*]-1,2,3-triazole (**28a**) occurred at 299 nm with a shoulder at 290 nm: in contrast, the corresponding isoxazotriazole (**28b**) had its UV absorption maximum at 266 nm <78HCA108>.

Table 2 UV properties of some pyrazolotriazoles.

Pyrazolotriazole	Absorption maxima (nm)	Fluorescence maxima (nm)	Ref.
 (25)			86DP289
a; R = Me	300	432	
b; R = OMe	305	445	
c; R = COOH	297	427	
d; R = 	358	449	
e; R = 	328	460	
f; R = 	338	458	
g; R = 	342	457	
h; R = 	312	451	
 (26)			88JHC1663
a; R = 2-pyridyl	374	442	
b; R = 2-[1,3]thiazole	426	530	



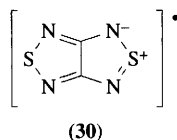
Structural proof for the Herz salts (5*H*-pyrazolo[3,4-*d*]-1,2,3-dithiazol-2-ium chlorides) (**29**) rests on their UV spectra and chemical reactivity. Two bands were observed in the UV spectra of this series of compounds, one of which was very sensitive to the nature of the substituent at position 6. The similarity between these spectra and those for the known Herz salts of aniline derivatives suggest a similar chromophore <84JOC1224>. The stable sulfur–nitrogen radical (**14**) has a broad-band absorption at 595.5 nm, giving it a blue color <89AG(E)920>.



R = H	452 nm	(ϵ 1590)	326 nm	(ϵ 10 200)
R = Br	500 nm	(ϵ 1180)	328 nm	(ϵ 8660)
R = CO ₂ Me	442 nm	(ϵ 1470)	328 nm	(ϵ 8100)

7.05.3.2.4 Electron spin resonance spectroscopy

Examination of the solution and powder ESR spectra of the stable [1,2,5]thiadiazolo[3,4-*d*]-1,3,2-dithiazole radical (**14**), permitted a deeper understanding of its electronic structure. The similarity between the nitrogen coupling constants of radical (**14**) ($a(\text{N}) = 11.21$ G for the unique nitrogen and $a(\text{N}) = 0.85$ G for the two equivalent nitrogens) with that of the [1,3,2]dithiazole radical anion ($a(\text{N}) = 10.4\text{--}11.4$ G) suggests that radical (**14**) exists as a π -radical with most of the electron density concentrated in out-of-plane valence *p* orbitals in the dithiazole part of the molecule <89AG(E)920, 91MRC625>. In contrast, nitrogen coupling constants for the 1,2,5-dithiazole radical anion are much smaller ($a(\text{N}) = 5.3$ G). On the other hand, examination of the ESR spectrum of the radical ion of the highly symmetrical [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole-5-S(IV) (**30**) showed four equivalent nitrogen atoms, which was as expected for this aromatic heterocycle <76JPC1786>.



Delocalization of the unpaired electron was also found on analysis of the ESR spectrum of 1*H*-isothiazolo[4,5-*d*]-1,2,3-dithiazolo-1-ium, described as one of a group of new persistent radicals <84CCC684>.

7.05.3.2.5 X-ray photoelectron spectroscopy

The charge distribution in a number of heteroazapentalenes (**11d,e,i,j**) has been established by x-ray photoelectron spectroscopy, recorded in the solid state (CNDO calculations on the parent molecules are described above). The chemical shifts of core electron levels were measured and analyzed employing Siegbahn's electrostatic potential model. The spectra showed that for derivatives (**11e,i,j**) the nitrogen atom at position 5 had a less negative charge than the nitrogen atoms at positions 1,3,4, and 6, and for compound (**11d**) the nitrogen atoms at positions 2 and 5 had less negative charge than those at positions 1,3,4, and 6 <77BCJ1917>.

7.05.3.2.6 Magnetic circular dichroism spectroscopy

The UV and MCD <72MI 705-01> spectra for the [1,2,5]thiadiazolo[3,4-*c*][1,2,5]-thiadiazole-5-S(IV) (**6**) have been recorded in ethanol. The observed MCD spectrum showed positive and negative extrema at 29900 cm⁻¹ and 33700 cm⁻¹, respectively. The inflection point appears to coincide with the absorption maximum of the UV spectrum (32200 cm⁻¹). Since the molecule (**6**) has C_{2v} symmetry, the MCD spectrum is due only to the Faraday *B* term, and thus the MCD experiment reveals two components of absorption in the lowest-wavenumber absorption band of compound (**6**). The electronic transition associated with this absorption, judged from the intensity of absorption and

the MCD spectrum, is considered to be $\pi \rightarrow \pi^*$. Values are reported for the Faraday B constants and the theoretical results correlate reasonably well with the experimental observations $\langle 83ZN(A)1263 \rangle$.

7.05.3.2.7 Cyclic voltammetry

The cyclic voltagram of the tetrasubstituted tetrathiafulvalene (**13**), measured in dichloromethane, showed this molecule to have higher oxidation potentials than the unsubstituted parent. The observed change is in keeping with the electron-withdrawing property of the fused 1,2,5-thiadiazole and may be expected to improve the ability of this molecule to behave as an organic conductor $\langle 93H(35)69 \rangle$. Attempts to obtain structural information from the cyclic voltagram of [1,3]dithiolo[4,5-*d*]-1,2,3-trithiole-5-thione (**23**) in DMF were unsuccessful. The investigation, however, could successfully rule out the presence of any elemental sulfur in the sample of compound (**23**) $\langle 81JOC775 \rangle$.

7.05.4 THERMODYNAMIC ASPECTS

7.05.4.1 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

[1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazole-5-S(IV) (**6**) has been part of a study undertaken to assess aromatic character of a range of bicyclic heterocycles. In this study, Bird's calculation of the aromatic character of a suppressed aromatic molecule is based upon a statistical evaluation of the deviations in peripheral bond orders. Compound (**6**), the only member of this class to be considered, was calculated to have an aromaticity index $I_{5,5}$ of 96, representing a very high degree of aromatic character, cf. 1,2,3-thiadiazole with an I_5 of 54 and 1,3,4,6-tetraphenylthiolo[3,4-*c*]-2-thiole with an $I_{5,5}$ of 81 $\langle 85T1409, 87T4725 \rangle$.

7.05.4.2 [1,3]Dithiolo[4,5-*d*]-1,2,3-trithioles

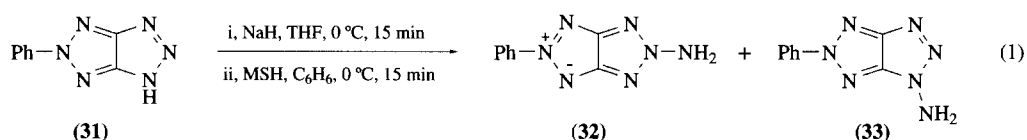
The low solubility and apparent decomposition of the dithiolotrithiole (**23**) in solution prohibited voltammetric investigation of its structure $\langle 81JOC775 \rangle$.

7.05.5 REACTIVITY OF FULLY CONJUGATED RINGS

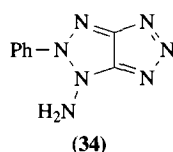
7.05.5.1 Electrophilic Attack at Nitrogen

7.05.5.1.1 Triazolo[4,5-*d*]-1,2,3-triazoles

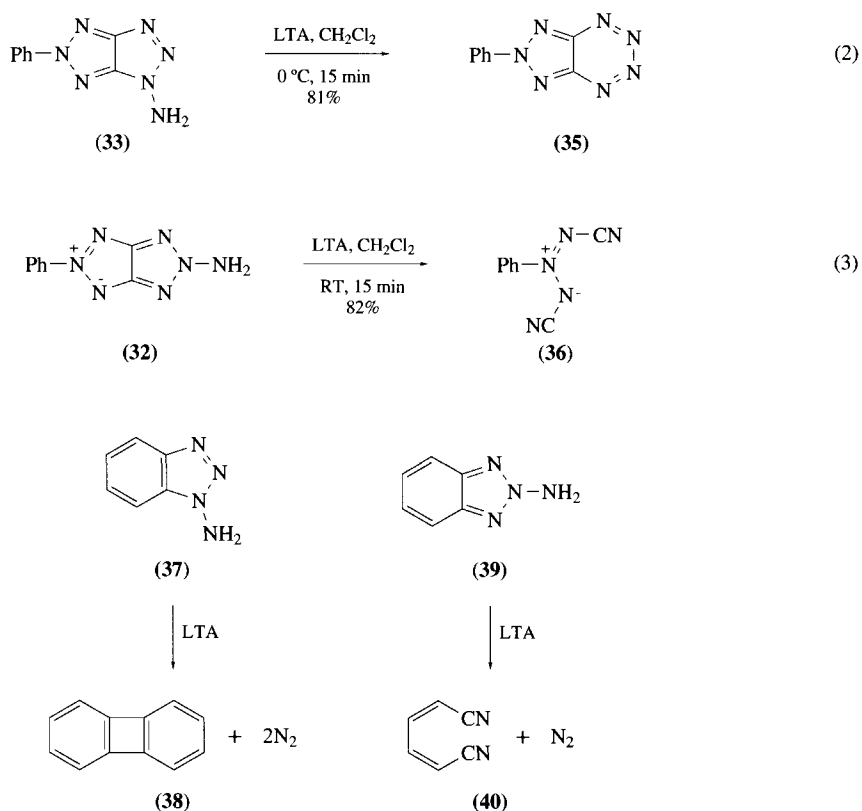
The amination of 5-phenyl-1,5-dihydro[1,2,3]triazolo[4,5-*d*]-1,2,3-triazole (**31**) with *o*-(mesitylsulfonyl)hydroxylamine afforded two *N*-aminated products distinguishable on the basis of their ^{13}C NMR spectra (Equation (1)). The major product (46%), showed one carbon signal other than those from the phenyl ring and was therefore assigned as the symmetrical 2-amino derivative (**32**). The minor product showed two ^{13}C signals in addition to those from the phenyl ring and was believed to be represented by structure (**33**) or (**34**): (**33**) is the preferred isomer on the basis of the similarity of its NMR spectrum to that of known 1-acetyl-5-phenyltriazolotriazole.



MSH = *o*-(methylsulfonyl)-hydroxylamine



Oxidation of these isomeric amino triazolotriazoles revealed interesting chemistry. Treatment of compound (33) with lead tetraacetate (LTA) afforded the ring-expanded product (35), the first example of an aromatic 1,2,3,4-tetrazine (Equation (2)) (see also Chapter 7.14). This compound, reddish brown in color, was reported to be rather unstable in solution and explosive upon heating or impact. However, its structure has been unequivocally established by x-ray crystallography. This experiment is significant in that it demonstrates, for the first time, the ability of the 1,2,3,4-tetrazine ring to exist (at least in the ring-fused form) <88CC1608>. LTA oxidation of the 2-amino derivative (32) displayed entirely different chemistry and (*E,Z*)-1,3-dicyano-2-phenyltriazeniumide (36), a ring-opened product of the intermediate *N*-nitrene, resulted (Equation (3)) <91JCS(P1)2045>. A precedent for this difference in behavior has been recorded; thus, oxidation of the isomeric 1- and 2-amino-benzotriazoles (37) and (39) afforded biphenylene (38) and mucononitrile (40) respectively (Scheme 2).

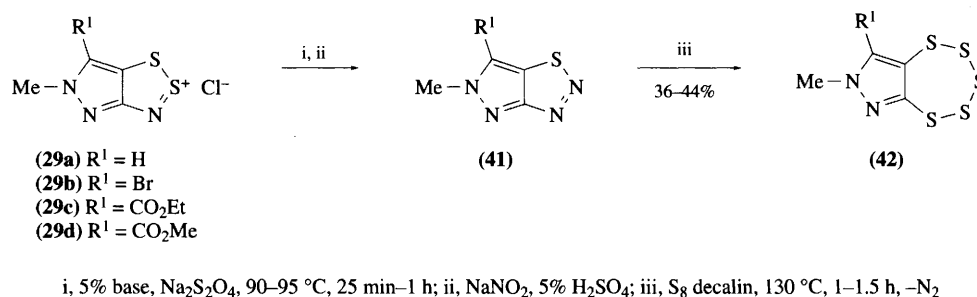


Scheme 2

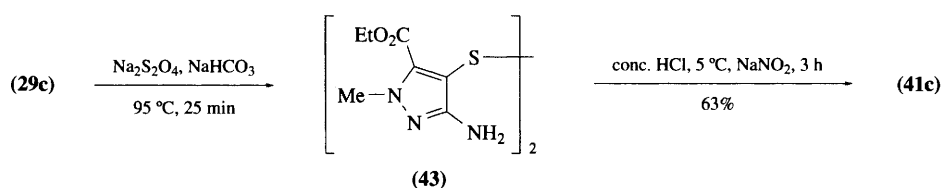
7.05.5.2 Reduction

7.05.5.2.1 Pyrazolo[3,4-d]-1,2,3-dithiazolium chlorides

A new heterocyclic ring system, 5*H*-pyrazolo[3,4-*d*]-1,2,3-thiadiazoles (41), results from a one-pot, two-step reaction of the pyrazolodithiazolium chlorides (29). Sequential treatment of the derivatives (29) with base, sodium dithionite, and sodium nitrite followed by acidification afforded (41) (Scheme 3). For substrates (29a,b) potassium hydroxide was chosen, whilst for (29c,d) sodium bicarbonate was found to be superior. In the latter cases, potassium hydroxide caused appreciable hydrolysis of the ester substituent. A further point of interest is the significant quantity of disulfide (43) which can form on reaction of 6-carboethoxy-5-methylpyrazolodithiazolium chloride (29c). This, however, need not represent a problem since compound (43) can be converted *in situ* or isolated and converted to the desired product (41c) in good yield (Scheme 4) <84JOC1224>.



Scheme 3

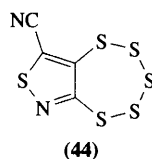


Scheme 4

7.05.5.3 Ring Expansion

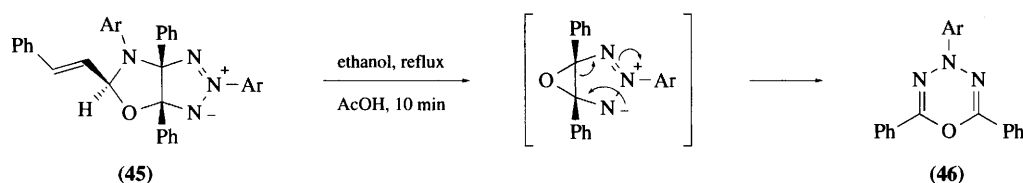
7.05.5.3.1 Pyrazolo[3,4-d]-1,2,3-thiadiazoles

The serendipitous discovery that cyanoisothiazolopentathiepin (**44**) had antifungal activity lead to the preparation of a range of fused pentathiepins including the pyrazolopentathiepins (**42**) which can be obtained by thermolysis of 5-methylpyrazolo[3,4-*d*]-1,2,3-thiadiazoles (**41**) with sulfur (Scheme 3). The reaction progresses in moderate yield and is superior to the corresponding reaction with 6,5-fused 1,2,3-benzothiadiazoles. The increased reactivity was attributed to greater inherent strain present in the 5,5-fused system <85EUP138633, 85JA3871>.



7.05.5.3.2 Oxazolo[4,5-d]-1,2,3-triazoles

The tetrahydro-oxazolo[4,5-*d*]-1,2,3-triazoles (**45**), which are stable under ambient conditions, rapidly change into 4*H*-1,3,4,5-oxatriazines (**46**) following a short reflux in ethanol. These red colored products (**46**) are 8π six-atom ring systems which are rather uncommon and normally difficult to obtain yet can be formed in excellent yield from the derivatives (**45**) (Scheme 5) <90JCS(P1)2527>.



Scheme 5

7.05.5.4 Cycloadditions

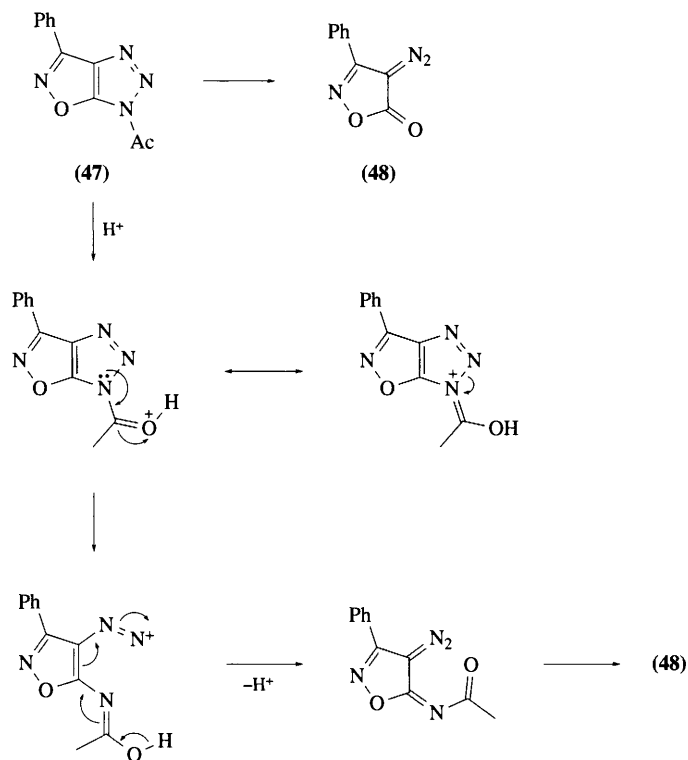
7.05.5.4.1 *Pyrazolo[3,4-c][1,2,5]thiadiazoles*

Heteropentalenes with a nonclassical ring structure have been observed to partake in interesting dipolar cycloaddition reactions <75ACR139, 77T3203>. It is believed that by increasing the number of heteroatoms in the ring the resultant chemical reactivity decreases as a consequence of increased stability of the system. This hypothesis was reinforced when no evidence was found for cycloaddition of dipolarophiles to 6-methyl-4-phenylpyrazolo[3,4-c][1,2,5]thiadiazole (**24a**) <81JOC4065>.

7.05.5.5 Hydrolysis

7.05.5.5.1 *Isoxazolo[4,5-d]-1,2,3-triazoles*

3-Phenyl-6-acetylisoisoxazolo[4,5-d]-1,2,3-triazole (**47**), prepared under mild conditions, was unstable in acid solution and changed rapidly to 3-phenyl-4-diazo-5-isoxazolone (**48**). The mechanism proposed for cleavage of the triazole ring is outlined in Scheme 6 <70T1393>.



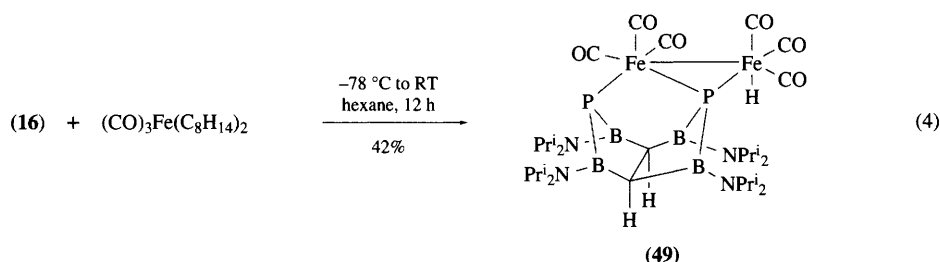
Scheme 6

7.05.5.6 Metal Complexation

7.05.5.6.1 *[1,2,5]Phosphadiboro[3,4-c][1,2,5]phosphadiboroles*

An unusual diiron complex (**49**) resulted from the reaction of compound (**16**) with $(CO)_3Fe(C_8H_{14})_2$ (Equation (4)). The structure of this complex (**49**) was unambiguously established as a result of

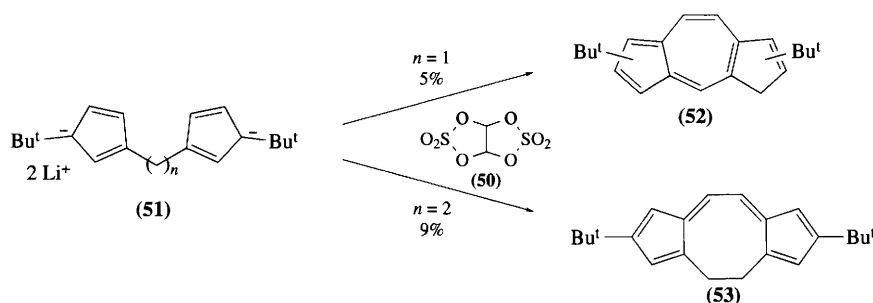
spectral studies (^1H , ^{13}C , ^{31}P , and ^{11}B NMR, IR, and electron impact ionization mass spectrometry) and a single-crystal x-ray structure determination <93CB1291>.



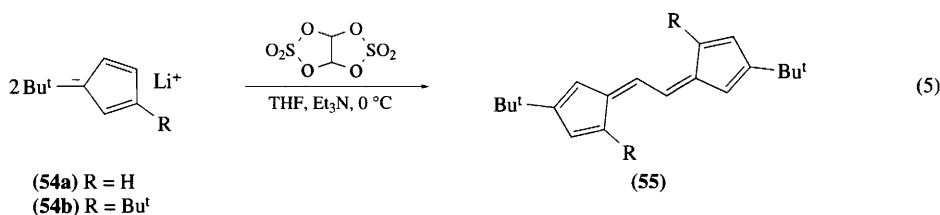
7.05.6 REACTIVITY OF NONCONJUGATED RINGS

7.05.6.1 [1,3,2]Dioxothiolo[4,5-*c*]-1,3,2-dioxathioles

Glyoxal sulfate (**50**), a cyclic ester of sulfur, condensed with dilithium salts (**51**; $n = 1$) to afford low yields (5%) of the isomeric tricycles (**52**). Compound (**53**) is formed similarly on reaction of the salt (**51**, $n = 2$) (Scheme 7) <76TL2155, 85TL2567, 88AG(E)1191>. In contrast, lithium *t*-butylcyclopentadienide (**54a**) or the 1,3-dibutylcyclopentadienide (**54b**) upon reaction with glyoxal sulfate under the same conditions yielded (*E,E*)-pentafulvadienes (**55**) in 15% and 79% yield, respectively (Equation (5)) <82TL5131, 90JCS(P1)2527>.



Scheme 7

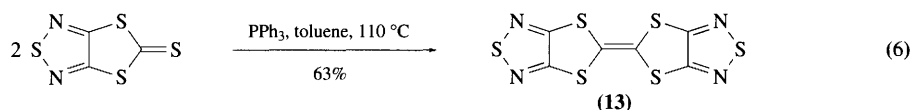


7.05.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBONS

7.05.7.1 Desulfurization

7.05.7.1.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

Upon heating in boiling toluene in the presence of excess triphenylphosphine, 1,3-dithiolo[4,5-*c*][1,2,5]thiadiazole-5-thione underwent desulfurization to afford 5-[1,3]dithiolo[4,5-*c*][1,2,5]thiadiazol-5-ylidene (**13**) (Equation (6)). When trialkylphosphines were used instead of triphenylphosphine a complex mixture of products resulted <93H(35)69>.

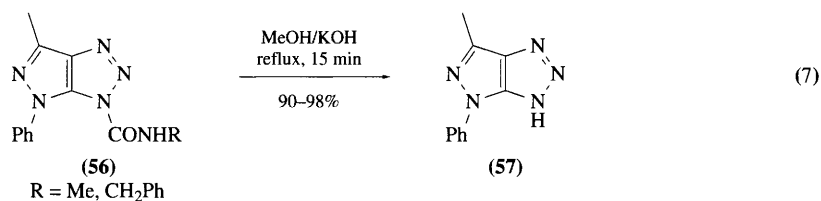


7.05.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

7.05.8.1 Hydrolysis

7.05.8.1.1 Pyrazolo[3,4-*d*]-1,2,3-triazoles

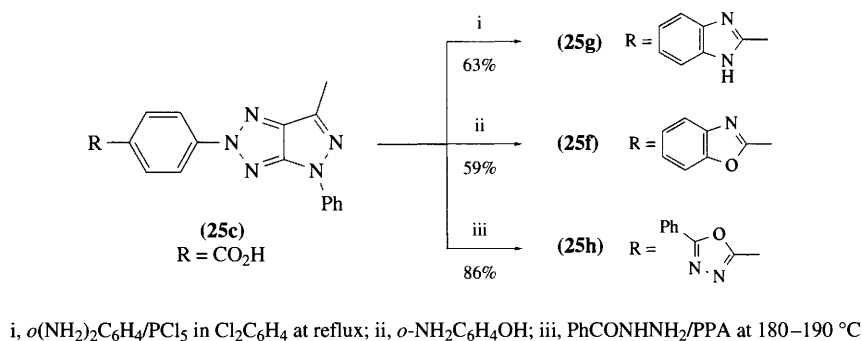
Alkaline hydrolysis of pyrazolo[3,4-*d*]-1,2,3-triazole-1-(*N*-alkyl)carboxamides (**56**) afforded the corresponding unsubstituted product (**57**) in almost quantitative yield (Equation (7)) <91H(32)727>.



7.05.8.2 Condensation Reactions

7.05.8.2.1 Pyrazolo[3,4-*d*]-1,2,3-triazoles

The 2-(4-carboxyphenyl)pyrazolo[3,4-*d*]-1,2,3-triazole (**25c**), considered to be useful in construction of a range of heterocycles with interesting fluorophores, underwent condensation with suitably substituted aryl amines (e.g., 2-aminophenol, 1,2-diaminobenzene, and benzhydrazide) to furnish, respectively, the extended heterocycles (**25f,g,h**) (Table 2) in good yield (Scheme 8) <86DP289>.

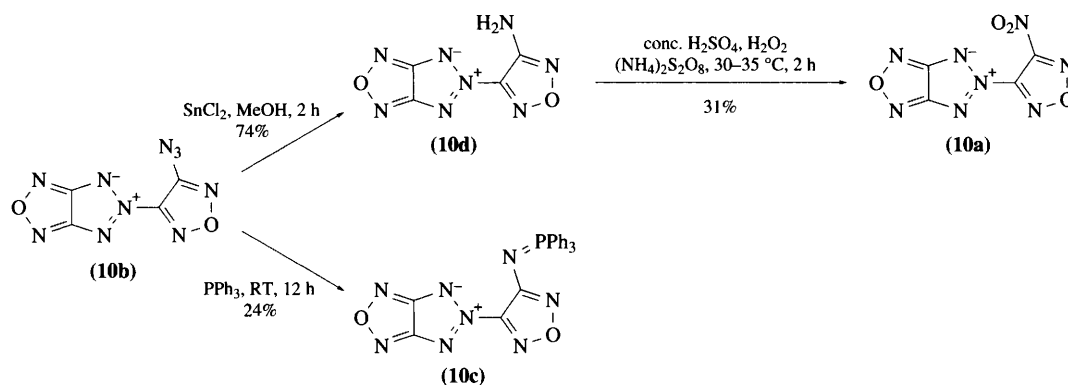


Scheme 8

7.05.8.3 Nitrogen Extrusion

7.05.8.3.1 Triazolo[4,5-*c*][1,2,5]oxadiazoles

The azido group of 5-(4-azido-1,2,5-oxadiazolyl)-5*H*-[1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazole (**10b**) reacted at room temperature with triphenylphosphine to furnish the phosphorimino derivative (**10c**) as orange needles (24%) (Scheme 9) <93HAC521>.



Scheme 9

7.05.8.4 Reduction

7.05.8.4.1 Triazolo[4,5-c][1,2,5]oxadiazoles

Treatment of compound (10b) with stannous chloride effected reduction giving the amino analogue (10d) (Scheme 9) <93HAC521>.

7.05.8.5 Oxidation

7.05.8.5.1 Triazolo[4,5-c][1,2,5]oxadiazoles

Oxidation of the amine functionality in compound (10d) to the nitro group was achieved by reaction with ammonium persulfate; (10a) was obtained in 31% yield (Scheme 9) <93HAC521>.

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

7.05.9.1 Synthesis from Monocyclic Precursors

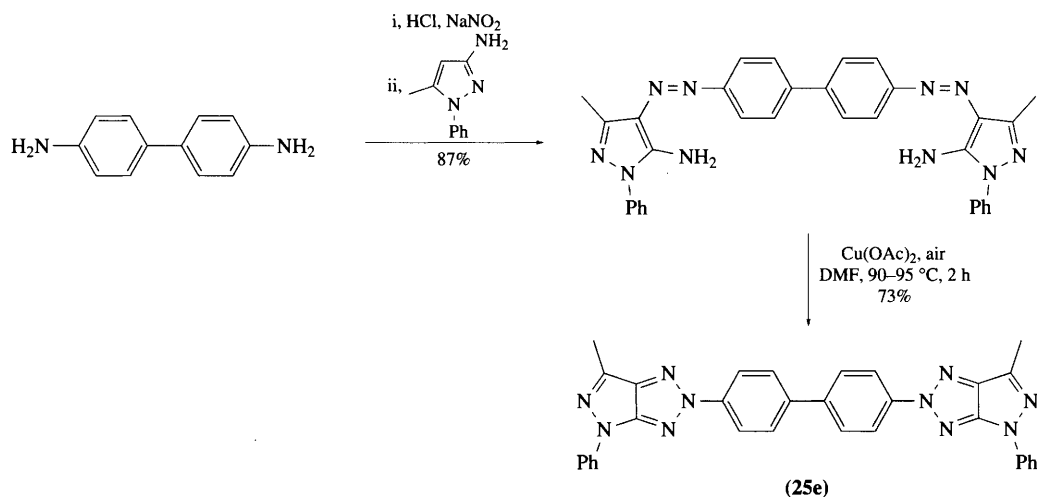
The most common routes to the bicyclic systems discussed in this chapter involve the reaction of suitably substituted monocyclic parents. In this section the formation of the second heterocyclic ring is considered; methods of synthesis of the first ring can be found by consultation of Volumes 3 and 4 and CHEC-II or in CHEC-I.

7.05.9.1.1 Synthesis from [5 + 0] atom fragments

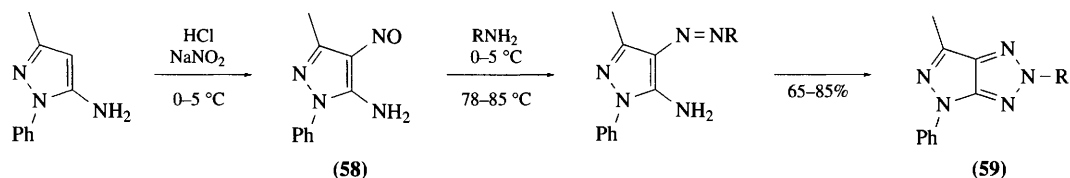
(i) Pyrazolo[3,4-d]-1,2,3-triazoles

The synthesis of 2,4,6-trisubstituted 2,6-dihydropyrazolo[3,4-d]-1,2,3-triazoles by the oxidation of 5-amino-4-azopyrazoles is well documented <86DP289, 87IJC(B)616, 88JHC1663>. In a typical procedure, diazotized arylamines were coupled with 5-aminopyrazoles affording the required 5-amino-4-azo compounds, which were readily oxidized to the desired bicycle <86DP289, 87IJC(B)616>. Scheme 10 illustrates the preparation of a symmetric bispyrazolo[3,4-d]-1,2,3-triazole (25e) <86DP289>. Alter-

natively, condensation of the 4-nitroso-5-amino-1*H*-pyrazole (**58**) with suitable heteroaryl amines gave good yields of the required 5-amino-4-azo precursor, which may be converted to the pyrazolotriazole (**59**) (Scheme 11) <88JHC1663>. The oxidation process was carried out using cupric acetate in DMF (or pyridine) in a stream of air. Treatment of the *o*-aminoazopyrazole (**60**), prepared by a diazotization–coupling procedure, with K_2CO_3 and $Ni(NO_3)_2$ furnished compound (**61**) upon heating at 130 °C (Equation (8)) <80KGS1524>.

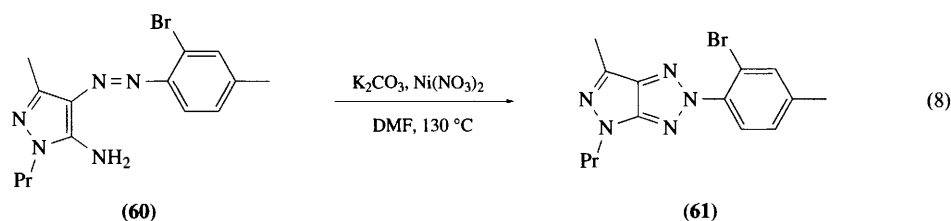


Scheme 10

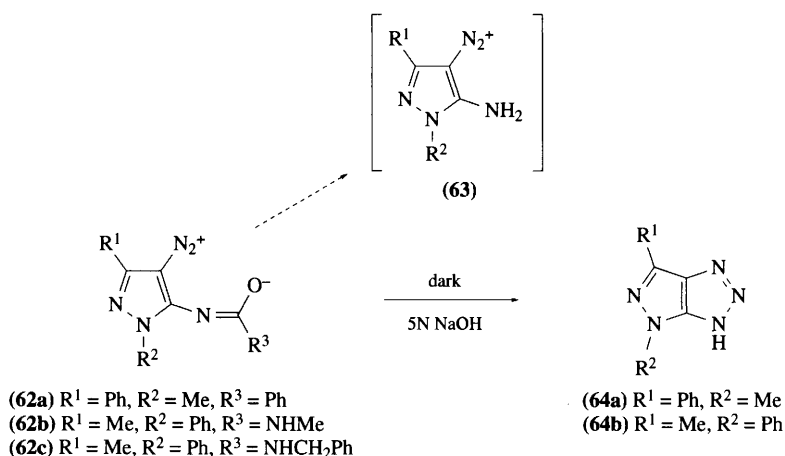


R = 2-pyridyl, 2[1,3]thiazole, 5-(3-methyl-5-phenylpyrazole)

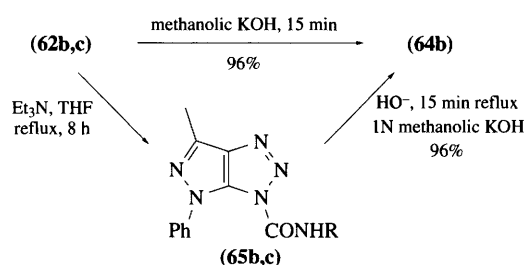
Scheme 11



5-Benzoylamido-4-diazo-1-methyl-3-phenylpyrazole (**62a**), which exists in the zwitterionic form, reacted under alkaline conditions to furnish 4-methyl-6-phenyl-3,4-dihydropyrazolo[3,4-*d*]-1,2,3-triazole (**64a**) as the sole reaction product (Scheme 12). This reaction, which is believed to proceed via a 5-amino-4-diazo intermediate (**63**), needs to be carried out in the dark since compound (**62a**) itself is very sensitive to irradiation <84H(22)2309>. The urea derivatives (**62b,c**) react analogously, affording compound (**64b**) after a short reflux in KOH solution. Treatment of the same substrate with triethylamine yielded the carboxyamides (**65b,c**), hydrolysis of which gave the unsubstituted pyrazolo[3,4-*d*]-1,2,3-triazole (**64b**) (Scheme 13) <91H(32)727>.



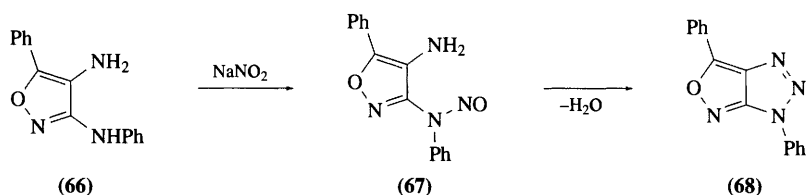
Scheme 12



Scheme 13

(ii) Isoxazolo[3,4-d]-1,2,3-triazoles

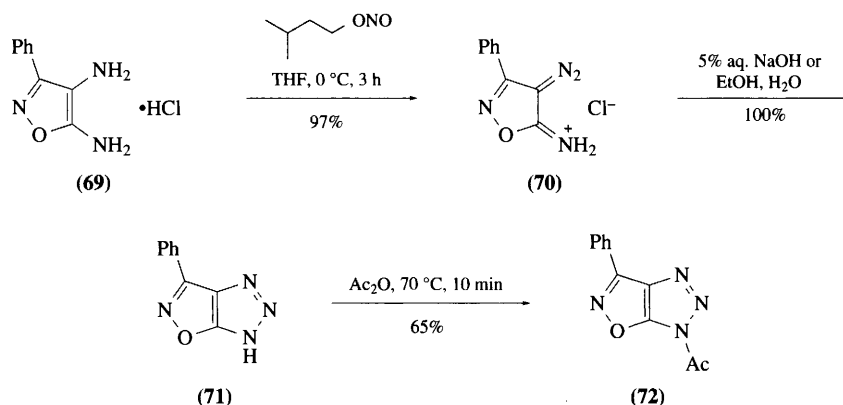
Treatment of 3-aminophenyl-4-amino-5-phenylisoxazole (66) with sodium nitrite afforded the nitroso compound (67), which lost water to furnish 3,6-diphenylisoxazolo[3,4-d]-1,2,3-triazole (68) (Scheme 14) <10LA(375)297>.



Scheme 14

(iii) Isoxazolo[4,5-d]-1,2,3-triazoles

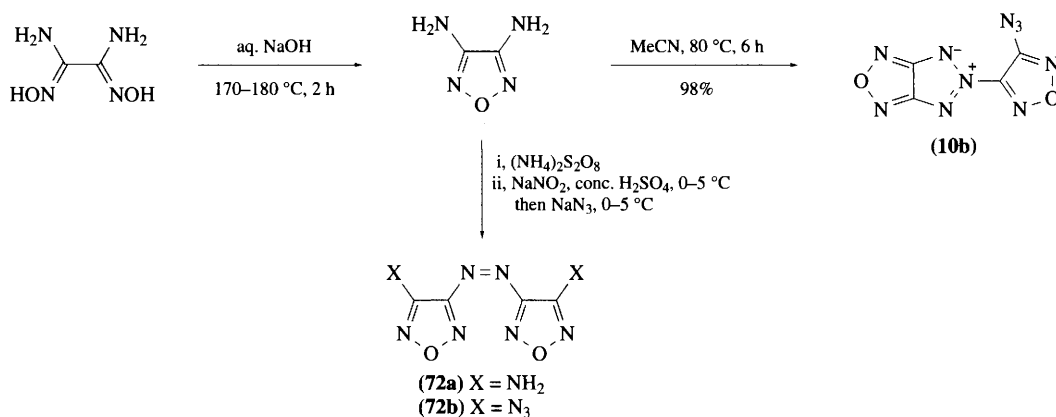
3-Phenyl-4,5-diaminoisoxazole hydrochloride (69) reacted with isoamyl nitrite in THF to afford the diazo compound (70), which underwent immediate closure on treatment with aqueous base (5% NaOH) to furnish 3-phenylisoxazolo[4,5-d]-1,2,3-triazole (71). The isoxazolotriazole, which resulted in essentially quantitative yield, is a relatively stable compound <70T1393>. Treatment of (71) with acetic anhydride afforded the 6-acetyl derivative, which does not share the stability of its precursor and decomposes rapidly in acid solution (Scheme 15).



Scheme 15

(iv) Triazolo[4,5-c][1,2,5]oxadiazoles

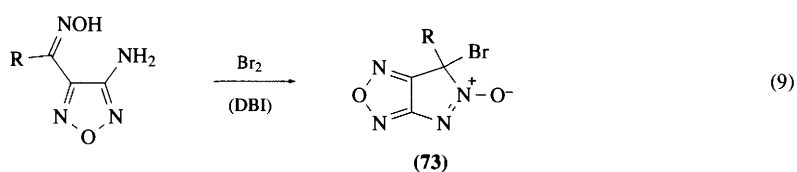
Mild thermolysis (80°C) of the diazidoazofurazan (**72b**), prepared as shown in Scheme 16, afforded the triazoloxadiazole (**10b**) in 98% yield <93HAC521>.



Scheme 16

(v) Pyrazolo[3,4-c][1,2,5]oxadiazoles

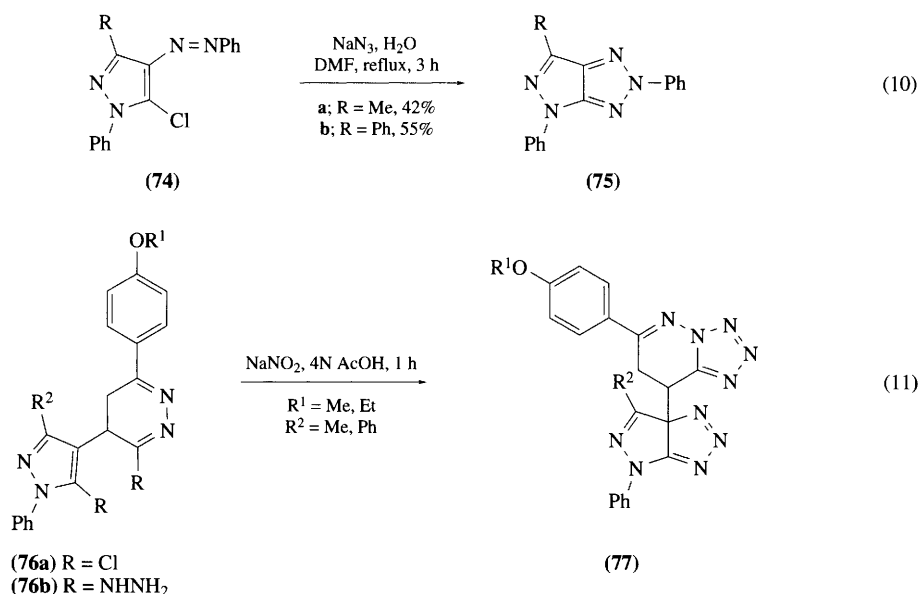
Pyrazolo[3,4-c][1,2,5]oxadiazole-5-oxides (**73**) have been prepared from the corresponding 3-amino-4-(hydroxyiminomethyl)-1,2,5-oxadiazoles by sequential treatment with bromine and dibromoisocyanurate (DBI) (Equation (9)) <93MC120>.



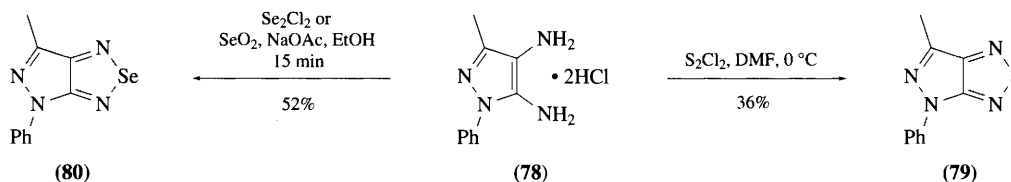
7.05.9.1.2 Synthesis from [4 + 1] atom fragments

(i) Pyrazolo[3,4-d]-1,2,3-triazoles

A number of synthetic routes to pyrazolotriazoles have been outlined by Gonzalez and co-workers <75JHC279>. The treatment of 5-chloro-4-phenylazopyrazoles (**74**) with sodium azide furnished corresponding 2,4-dihydropyrazolo[3,4-*d*]-1,2,3-triazoles (**75**) (40–55%) (Equation (10)). The mechanism is believed to involve thermal decomposition of an initially formed 5-azide derivative. An analogous process is known to lead to 1,2,3-triazoles, but this is its first application to the synthesis of the bicyclic pyrazolotriazole ring system <83JHC1501>. Pyrazolotriazoles (**77**) resulted, in moderate yield, from the reaction of 5-hydrazinopyrazoles (**76b**) (formed from (**76a**) by treatment with hydrazine hydrate) with nitrous acid (sodium nitrite and AcOH) (Equation (11)) <90AQ808, 91BCJ2032, 91MI 705-01>.

(ii) Pyrazolo[3,4-*c*][1,2,5]thiadiazoles

4,5-Diamino-1-phenyl-3-methylpyrazole dihydrochloride (**78**) reacted with sulfur monochloride in DMF at 0°C to afford 6-methyl-4-phenylpyrazolo[3,4-*c*][1,2,5]thiadiazole (**79**) in 36% yield (Scheme 17) <81JOC4065>.



Scheme 17

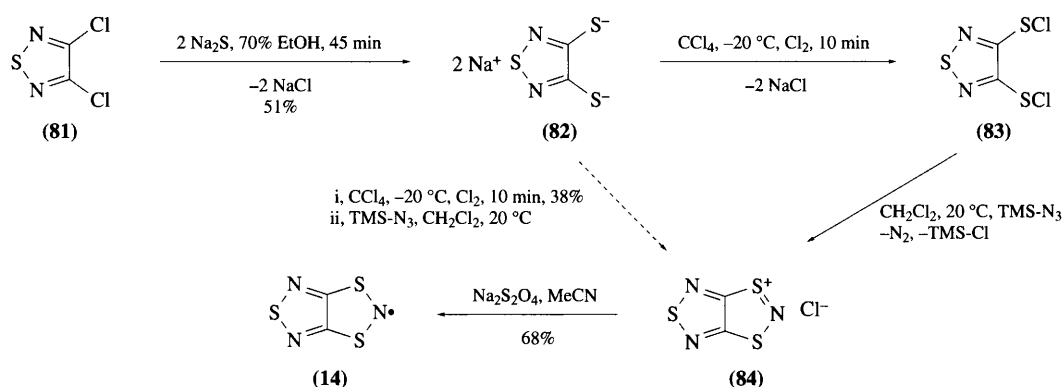
(iii) Pyrazolo[3,4-*c*][1,2,5]selenadiazoles

6-Methyl-4-phenylpyrazolo[3,4-*c*][1,2,5]selenadiazole (**80**) has been obtained from 4,5-diamino-1-phenyl-3-methylpyrazole by two methods (Scheme 17). The pyrazole dihydrochloride (**78**) on

treatment with sodium acetate followed by selenium dioxide furnished (**80**) in 52% yield. Alternatively the salt (**78**) and selenium monochloride reacted to give compound (**80**) as bright yellow needles (Scheme 17) <81JOC4065>.

(iv) [1,2,5]Thiadiazolo[3,4-d][1,3,2]dithiazoles

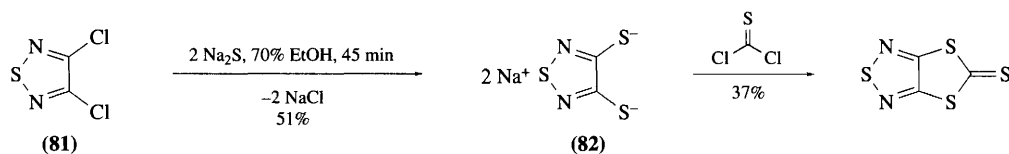
A three-step reaction sequence starting from 3,4-dichloro-1,2,5-thiadiazole (**81**) led to the formation of the stable sulfur–nitrogen radical [1,2,5]thiadiazolo[3,4-d][1,3,2]dithiazol-1-ium (**14**). Treatment of thiadiazole (**81**) with two equivalents of Na_2S afforded the sodium salt (**82**), which reacted with chlorine gas to furnish the sulphenyl chloride (**83**). The reaction of this intermediate (**83**) with trimethylsilyl azide yielded the salt (**84**), reduction of which afforded the novel pentalene analogue (**14**) as black needle-like crystals (Scheme 18) <89AG(E)920>.



Scheme 18

(v) [1,3]Dithiolo[4,5-c][1,2,5]thiadiazoles

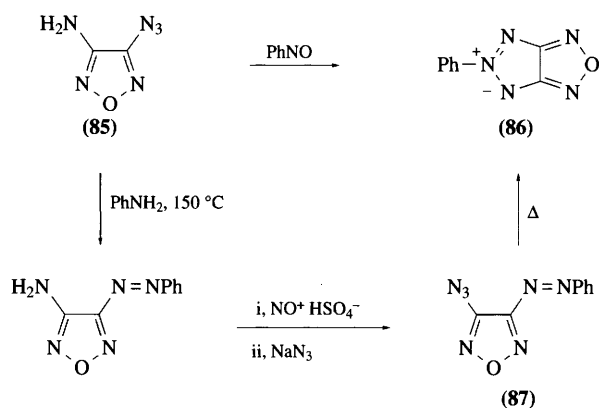
The disodium salt (**82**) prepared from the dichloride (**81**) reacted with thiophosgene to afford 1,3-dithiolo[4,5-c][1,2,5]thiadiazole-2-thione in 37% yield (Scheme 19) <93H(35)69>.



Scheme 19

(vi) Triazolo[4,5-c][1,2,5]oxadiazoles

1*H*-2-Phenyl-1,2,3-triazolo[4,5-c][1,2,5]oxodiazol-2-ium-1-ide (**86**) has been formed by treatment of the azide (**85**) with nitrosobenzene. An alternative route to compound (**86**) is via thermally induced cyclization of the azide (**87**) itself obtained from azide (**85**) by sequential treatment with aniline, NO^+ , HSO_4^- , and finally sodium azide (Scheme 20) <81ZOR1123>.

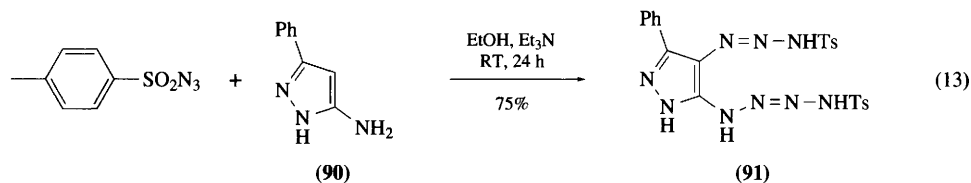
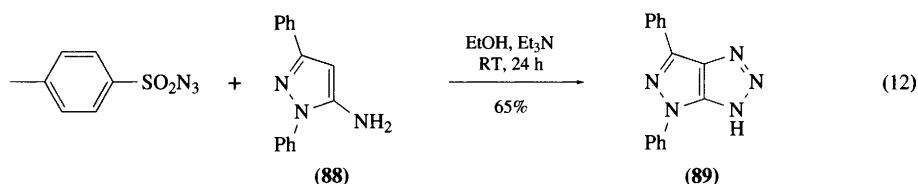


Scheme 20

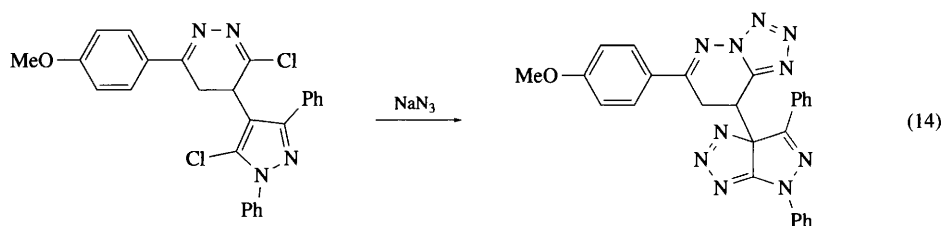
7.05.9.1.3 Synthesis from [3 + 2] atom fragments

(i) Pyrazolo[3,4-d]-1,2,3-triazoles

The product of reaction between *p*-tosylazide and substituted 5-aminopyrazoles was observed to be dependent on the extent of the substitution on the heterocyclic ring. Thus 1,3-diphenyl-5-aminopyrazole (88) reacted with tosylazide in ethanol, in the presence of NEt₃, to afford the pyrazolotriazole (89) (Equation (12)). On the other hand, the 3-phenyl substituted pyrazole (90) reacted under the same conditions to furnish the tetrazene derivative (91) (Equation (13)) <85MI 705-01>.

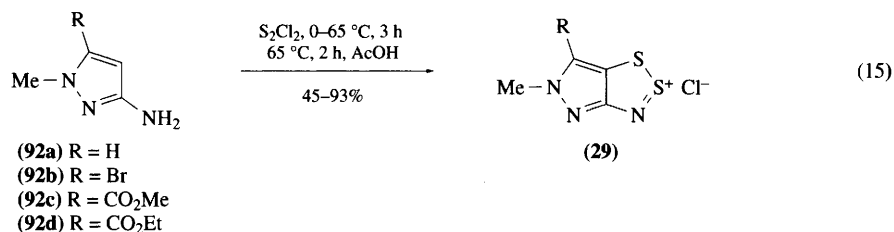


Another popular route to substituted pyrazolo[3,4-d]-1,2,3-triazoles involves treatment of substituted 5-chloro pyrazoles with sodium azide in refluxing aqueous DMF; yields are moderate (Equation (14)) <90AQ808, 91BCJ2032, 91MI 705-01>.

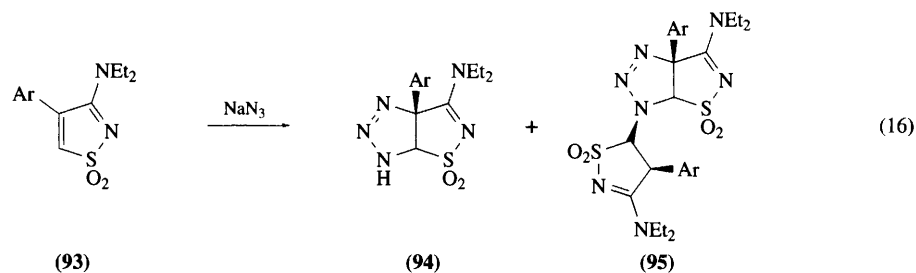


(ii) *Pyrazolo[3,4-d]-1,2,3-dithiazoles*

The 5-methylpyrazolo[3,4-*d*]-1,2,3-dithiazol-2-ium chlorides (**29**), identified as the products of reaction between the 1-methyl-3-aminopyrazoles (**92**) and sulfur monochloride, were highly colored, moisture-sensitive salts which were obtained in good yield (Equation (15)). The slightly lower yields of derivatives (**29c,d**) may reflect a reduced electrophilicity due to the carboalkoxy substituent in the 6-position <84JOC1224>.

(iii) *Isothiazolo[4,5-d]-1,2,3-triazoles*

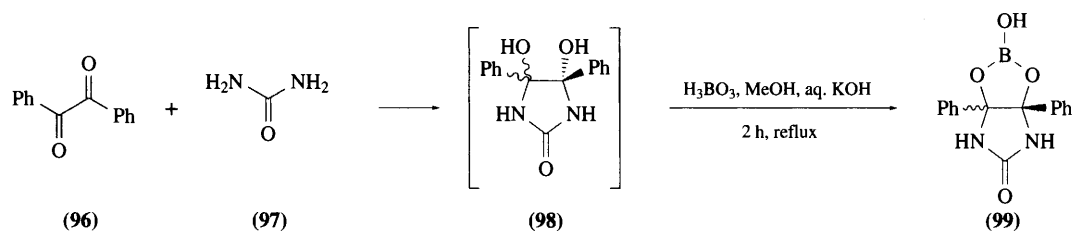
The isothiazolo[4,5-*d*]-1,2,3-triazoles (**94**) and (**95**), identified by HPLC, were minor products in the reaction between the isothiazole (**93**) and NaN_3 in ethanol (Equation (16)) <93T9117>.



7.05.9.2 Synthesis from Acyclic Precursors

7.05.9.2.1 [1,3,2]Dioxaborolo[4,5-d]imidazoles

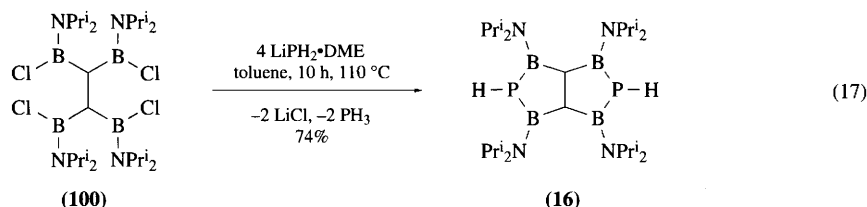
The cyclic boron esters (**99**) resulted from the three-component reaction between benzil (**96**), urea (**97**), and boric acid (Scheme 21). The stereoisomeric products arose as a consequence of boric acid addition to the intermediate cyclic amides (**98**) <89PHA110>. Carbon-13 NMR spectroscopy and mass spectrometry are consistent with structure (**99**).



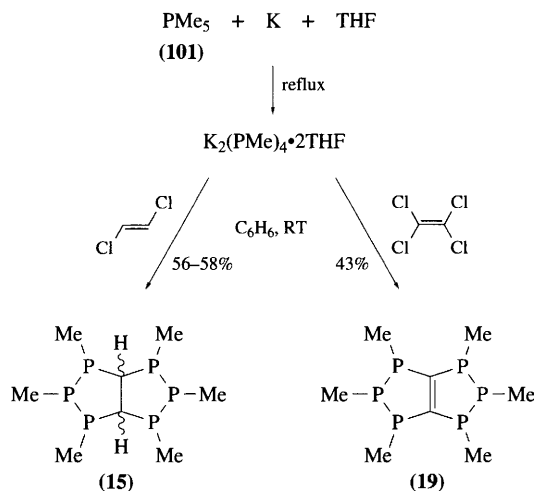
Scheme 21

7.05.9.2.2 [1,2,5]Phosphadiborolo[3,4-*c*][1,2,5]phosphadiboroles

1,1,2,2-Tetrakis(chlorodiisopropylaminoboryl)ethane (**100**) upon treatment with lithium phosphide in refluxing toluene yielded the novel bicyclic [1,2,5]phosphadiborolo[3,4-*c*][1,2,5]phosphadiborole (**16**) with two fused phosphadiborolane rings (Equation (17)) <93CB1291>.

7.05.9.2.3 [1,2,3]Triphospholo[4,5-*d*]-1,2,3-triphospholes

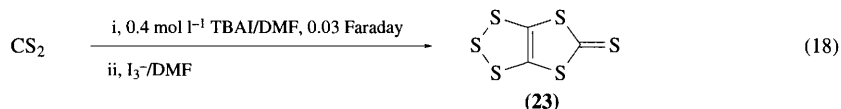
The novel cyclocarbaphosphanes, octahydro-1,2,3,4,5,6-hexamethyl[1,2,3]triphospholo[4,5-*d*]-1,2,3-triphosphole (**15**) and its corresponding dehydro derivative (**19**) were synthesized by reaction of K₂(PMe)₄·THF with chloroethenes (Scheme 22). Thus *cis*- or *trans*-1,2-dichloroethene reacted with K₂(PMe)₄·2THF, formed *in situ* from potassium and pentamethylphosphide (**101**), to furnish a mixture of diastereoisomers (**15**) separation of which was achieved by repeated crystallizations <78ZN(B)691, 79ZC418>. Analogous reaction with tetrachloroethene lead to the formation of compound (**19**) in 43% yield (Scheme 22).



Scheme 22

7.05.9.2.4 [1,3]Dithiolo[4,5-*d*]-1,2,3-trithioles

An off-yellow solid, obtained in almost quantitative yield by electrochemical reduction of CS₂ and subsequent oxidation, is tentatively assigned (on the basis of MS and IR data) as [1,3]dithiolo[4,5-*d*]-1,2,3-trithiole-5-thione (**23**) (Equation (18)) <81JOC775>.

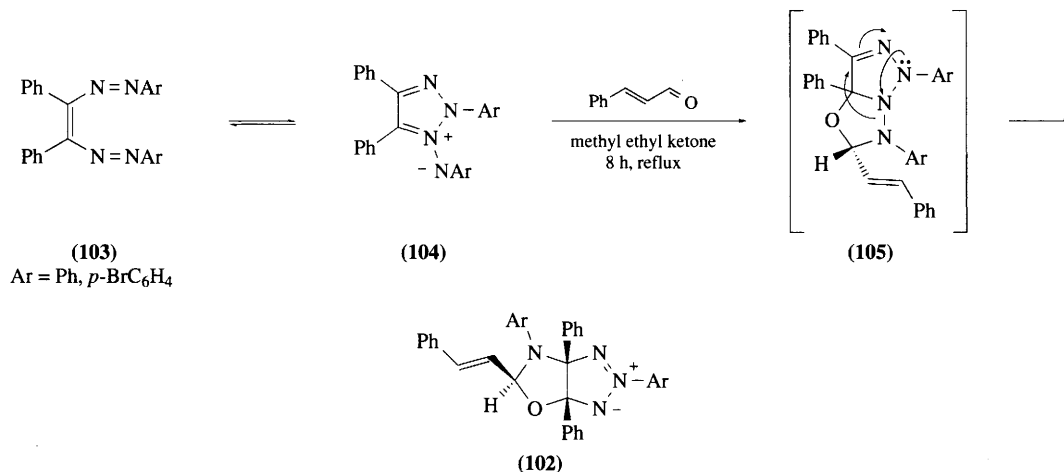


TBAI = tetra-*n*-butylammonium iodide

7.05.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

7.05.10.1 Oxazolo[4,5-*d*]-1,2,3-triazoles

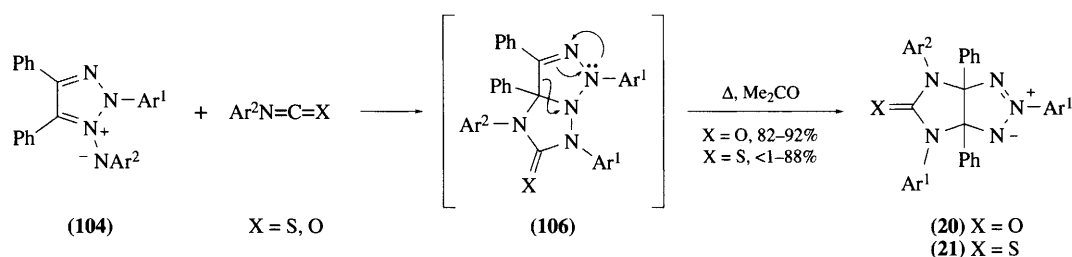
The synthesis of a new series of tetrahydro-oxazolo[4,5-*d*]-1,2,3-triazoles (**102**) has been reported. The triazolium imide 1,3-dipole (**104**) reacted with (*E*)-cinnamaldehyde in refluxing ethyl methyl ketone. It is significant that it was to the C=O bond of the α,β -unsaturated aldehyde that the cycloaddition took place, yet analogous addition to benzaldehyde or aliphatic ketones was not possible. The primary products of the cycloaddition reaction (**105**) underwent a sigmatropic rearrangement to furnish the new ring system (**102**) as shown in Scheme 23 <90JCS(P1)2527>.



Scheme 23

7.05.10.2 Imidazolo[4,5-*d*]-1,2,3-triazoles

New ring systems based on imidazo[4,5-*d*]-1,2,3-triazoles have been synthesized as the result of a tandem 1,3-dipolar cycloaddition, 1,4-sigmatropic rearrangement sequence (Scheme 24). Thus, triazolium imide 1,3-dipoles (**104**) added to the C=N bond of isocyanates or isothiocyanates upon heating in refluxing acetone and sigmatropic rearrangement of the initial products furnished, respectively, oxo- and thioimidazolotriazoles (**20**) and (**21**). The wide ranging and generally lower yields of thioimidazolotriazoles obtained may be a reflection of the stability of the intermediate adduct (**106**). Both electron-withdrawing and electron-donating substituents on any of the *N*-aryl rings of intermediate (**106**) effectively reduced its stability and the highest yield of derivative (**21**) was obtained when Ar = Ph <92JCS(P1)2159>.

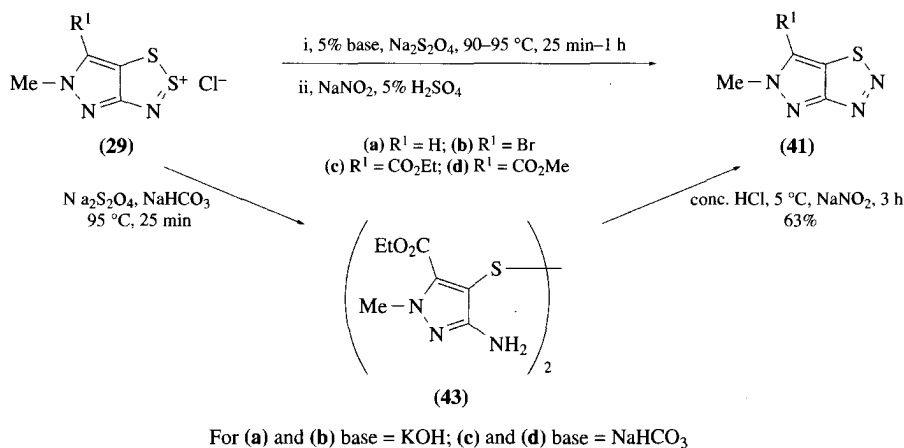


Ar¹, Ar² = Ph, *p*-NO₂C₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄

Scheme 24

7.05.10.3 Pyrazolo[3,4-*d*]-1,2,3-thiadiazoles

A one-pot, two-step reaction of the pyrazolodithiazolium chlorides (**29**) afforded the 5*H*-pyrazolo[3,4-*d*]-1,2,3-thiadiazoles (**41**), representing a new heterocyclic ring system (Scheme 25). Hydrolysis and reduction of the salts (**29**) with base and sodium dithionite followed by treatment with sodium nitrite and subsequent acidification afforded derivatives (**41**) (30–55%). Potassium hydroxide was the base of choice for substrates (**29a,b**), while sodium bicarbonate was found to be superior for substrates (**29c,d**). A significant quantity of disulfide (**43**) may form on reaction of compound (**29c**): this can be converted *in situ*, or isolated and converted to the desired product (**41c**) in good yield (Scheme 25) <84JOC1224>.



Scheme 25

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

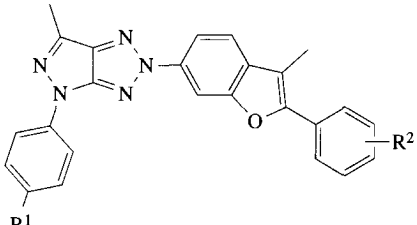
The interest in the pyrazolo[3,4-*d*]-1,2,3-triazole ring system is reflected in the number of synthetic routes available. These include synthesis of the second ring from [5 + 0], [4 + 1], and [3 + 2] atom fragments (see Section 7.05.9). The most common route involving Cu(OAc)₂ oxidation of 4-azo- or 4-nitroso-5-aminopyrazoles is significant in that a number of hydrocarbon and heteroatomic substituents can be introduced. The yields of products are generally good (65–85%) and the reaction simply involves heating in DMF at 90 °C in a stream of air for a short time <86DP289, 87IJC(B)616, 88JHC1663>. Other methods, for example thermal decomposition of a 5-azido-4-azopyrazole <83JHC1501> and base-induced cyclization of 5-benzoylamidopyrazoles <84H(22)2309> or *N*-alkyl-*N'*-(4-diazopyrazoyl)ureas <91H(32)727>, are less common routes and product yields are usually lower (40–100%). Synthesis beginning from 5-chloropyrazoles is also reported; the chloro derivative may be reacted directly with sodium azide to afford the corresponding pyrazolotriazole in moderate yield; alternatively it may be treated with hydrazine hydrate, furnishing a 5-hydrazino derivative which upon reaction with nitrous acid gives the same bicyclic product <85MI 705-01, 91BCJ2032, 91MI 705-01>.

7.05.12 IMPORTANT COMPOUNDS AND APPLICATIONS

A range of 2,5-disubstituted 6-methylpyrazolo[3,4-*d*]-1,2,3-triazoles (**25**) have been examined as optical brighteners. Selected results of these studies, carried out mainly on polyester fibers, are summarized in Table 3; optical brightening capacity ranged from nil to an excellent level (see also

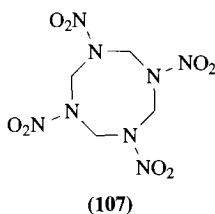
<86EGP240014>. Additionally, compound (27) was tested for pharmaceutical activity; no antipyretic properties were detected.

Table 3 Pyrazolotriazoles investigated as optical brighteners.

Pyrazolotriazole	Optical brightening capacity	Ref.
 $R^1 = \text{H, Me; } R^2 = o\text{-CN, } p\text{-CN}$ (25a,b) (25d-h) (27) (26a,b)	Useful fluorescent brighteners	77GEP(O)2529688
	Excellent fluorescent whitening properties Especially good	86DP289
	No promising fluorescence activity	87IJC(B)616
	Moderate whitening capacity	88JHC1663

Tetrathiafulvalene (TTF) derivatives containing fused 1,2,5-thiadiazole rings have been prepared in the interest of synthetic organic conductors. The extended π -conjugation and unique two-dimensional crystal network of the derivative (13) may be expected to confer useful conducting properties <93H(35)69, 93SM1914>.

The triazoloxadiazole (10a) is an excellent example of a high-energy molecule. It is restricted in composition to carbon, nitrogen, and oxygen and qualifies as a superior energetic material with density, detonation velocities, and detonation pressures comparing favorably with tetranitro-1,3,5,7-tetraazacyclooctane (107) <93HAC521>.



7.06

Bicyclic 5-6 Systems: Two Heteroatoms 1 : 1

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7.06.1 INTRODUCTION

This chapter covers bicyclic ring systems containing a five- and a six-membered ring where each ring contains one heteroatom; neither heteroatom is situated at the position of the ring junction. The major heterocyclic systems discussed are those containing nitrogen, oxygen, and sulfur heteroatoms. These compounds include pyrrolopyridines, thienopyridines, fuopyridines, thiopyranopyrroles, pyranopyrroles, fuopyrans, thienopyrans, furothiopyrans, and thienothiopyrans. In addition, where appropriate, mention is made of benzo derivatives as well as of bicyclic systems containing other heteroatoms such as selenium, tellurium, and phosphorus.

7.06.1.1 Scope and General Reviews

A large number of compounds is covered by this chapter. However, for some of these compounds little or no information is available in the chemical literature. Since some of the information concerning these compounds was not covered in the first edition of *Comprehensive Heterocyclic*

Chemistry (CHEC-I), chemical literature references prior to 1980 are included where necessary. An attempt has been made to classify the compounds into categories containing pyridine, pyrrole, and pyran and thiopyran rings. Generally, a large volume of chemical literature is available for the pyridine and pyrrole compounds, but for most of the pyran and thiopyran compounds much less information is available. This is noted in the text where appropriate.

Some general reviews were found for bicyclic 5-6 ring systems. These compounds are interesting to study because they contain a π -electron-deficient ring fused to a π -electron-rich ring. A few excellent reviews of pyrrolopyridines can be found in the literature <68AHC(9)27, 68RCR551, 80RCR428, 84CHEC-I(4)497>. Pyrido[2,3-*b*]indoles have been reviewed <84CHE345>. Bicyclic systems containing sulfur and oxygen have been reviewed collectively <84CHEC-I(4)973>. Some of the sulfur compounds have been incorporated into a general review of thiocompounds <72IJS(B)309> and more specific reviews of the thienopyridines <77AHC(21)65, 81H(15)1285>. No major reviews were found for the other compounds.

7.06.1.2 Isomeric Structures

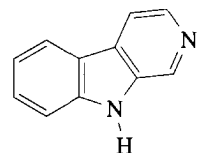
7.06.1.2.1 Pyrrolopyridines

The pyrrolopyridines contain one nitrogen heteroatom in the five-membered pyrrole ring and one nitrogen atom in the six-membered pyridine ring. A more common name is azaindoles, with 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine (**1**)) being the most widely studied isomer of the series. Twelve isomers of pyrrolopyridines are listed in the *Chemical Abstracts* Ring Formula Index. Table 1 lists the pyrrolopyridines with their *Chemical Abstracts* Registry Numbers. The 1*H*-pyrrolopyridines (**1**)–(**6**) are the most frequently prepared, but some work has also been carried out on the isomers (**7**), (**8**), and (**10**). Isomers (**8**), (**9**), (**11**), and (**12**) are tautomeric structures which are considered later (see Section 7.06.4.4).

Table 1 Pyrrolopyridine isomers.

1 <i>H</i> -Pyrrolo[2,3- <i>b</i>]pyridine (1) [271-63-6]	1 <i>H</i> -Pyrrolo[2,3- <i>c</i>]pyridine (2) [271-29-4]	1 <i>H</i> -Pyrrolo[3,2- <i>c</i>]pyridine (3) [271-34-1]	1 <i>H</i> -Pyrrolo[3,2- <i>b</i>]pyridine (4) [272-49-1]
1 <i>H</i> -Pyrrolo[3,4- <i>b</i>]pyridine (5) [653-38-2]	1 <i>H</i> -Pyrrolo[3,4- <i>c</i>]pyridine (6) [270-71-3]	2 <i>H</i> -Pyrrolo[3,4- <i>c</i>]pyridine (7) [270-70-2]	4 <i>H</i> -Pyrrolo[3,2- <i>b</i>]pyridine (8) [20464-17-9]
5 <i>H</i> -Pyrrolo[3,2- <i>c</i>]pyridine (9) [20444-05-7]	6 <i>H</i> -Pyrrolo[3,4- <i>b</i>]pyridine (10) [271-01-2]	6 <i>H</i> -Pyrrolo[2,3- <i>c</i>]pyridine (11) [271-28-3]	7 <i>H</i> -Pyrrolo[2,3- <i>b</i>]pyridine (12) [89267-19-6]

The most commonly studied benzo derivative in the pyrrolopyridine series is 9*H*-pyrido[3,4-*b*]indole (**13**), known as β -carboline. The α -, γ -, and δ -derivatives are also known but they have not been as widely investigated.



(13)
9*H*-Pyrido[3,4-*b*]indole

7.06.1.2.2 Furopyridines

Furopyridine derivatives contain a nitrogen atom in a six-membered pyridine ring and an oxygen atom in a five-membered furan ring. Table 2 lists the six parent furopyridine isomers, (**14**)–(**19**), with their registry numbers. In this series, compounds (**14**)–(**17**) are the most widely investigated isomers.

Table 2 Furopyridine isomers.

Furo[2,3- <i>b</i>]pyridine (14) [272-01-5]	Furo[2,3- <i>c</i>]pyridine (15) [19539-50-5]	Furo[3,2- <i>b</i>]pyridine (16) [272-62-8]
Furo[3,2- <i>c</i>]pyridine (17) [271-92-1]	Furo[3,4- <i>b</i>]pyridine (18) [271-04-5]	Furo[3,4- <i>c</i>]pyridine (19) [270-77-9]

7.06.1.2.3 Thienopyridines

Thienopyridines contain a six-membered pyridine ring fused to a five-membered thiophene ring. Table 3 lists the possible parent thienopyridine isomers, (**20**)–(**25**). Similarly to the furopyridine series, compounds (**20**)–(**23**) have been studied extensively and there has been very little emphasis on isomers (**24**) and (**25**).

7.06.1.2.4 Pyranopyrroles

Structures for possible pyranopyrrole isomers are given in Table 4. The pyranopyrrole ring system consists of a five-membered pyrrole ring joined to a six-membered pyran ring. Little chemistry of these pyranopyrrole systems has been investigated.

In addition to the neutral pyranopyrrole species, a number of pyranopyrrolium ions have been identified where the oxygen atom bears the positive charge. These are given in Table 5.

Table 3 Thienopyridine isomers.

Thieno[2,3- <i>b</i>]pyridine (20) [272-23-1]	Thieno[2,3- <i>c</i>]pyridine (21) [272-12-8]	Thieno[3,2- <i>b</i>]pyridine (22) [272-67-3]
Thieno[3,2- <i>c</i>]pyridine (23) [272-14-0]	Thieno[3,4- <i>b</i>]pyridine (24) [271-06-7]	Thieno[3,4- <i>c</i>]pyridine (25) [270-83-7]

Table 4 Pyranopyrrole isomers.

Pyrano[2,3- <i>b</i>]pyrrole [271-84-1]	Pyrano[2,3- <i>c</i>]pyrrole [271-14-7]	Pyrano[3,2- <i>b</i>]pyrrole [272-73-1]
Pyrano[3,4- <i>b</i>]pyrrole [271-30-7]	Pyrano[3,4- <i>c</i>]pyrrole [270-73-5]	Pyrano[4,3- <i>b</i>]pyrrole [20437-21-2]

Table 5 Pyranopyrrolonium and furopyridinium ions.

1 <i>H</i> -Pyrano[3,2- <i>b</i>]pyrrol-4-ium [272-74-2]	1 <i>H</i> -Pyrano[4,3- <i>b</i>]pyrrol-5-ium [49668-06-6]	1 <i>H</i> -Pyrano[3,4- <i>c</i>]pyrrol-5-ium [86423-29-2]
2 <i>H</i> -Pyrano[2,3- <i>b</i>]pyrrol-1-ium [42316-45-0]	1 <i>H</i> -Furo[3,4- <i>b</i>]pyridin-6-ium [42304-30-3]	

7.06.1.2.5 Thiopyranopyrroles

The thiopyranopyrrole ring system consists of a five-membered pyrrole ring joined to a six-membered thiopyran ring. Some of these isomers have been discussed only in the chemical literature from the 1980s and 1990s. Table 6 lists thiopyranopyrrole isomers.

Table 6 Thiopyranopyrrole isomers.

Thiopyrano[2,3- <i>b</i>]pyrrole [67165-66-6]	Thiopyrano[2,3- <i>c</i>]pyrrole [28647-68-9]	Thiopyrano[3,2- <i>b</i>]pyrrole [126581-22-4]
Thiopyrano[3,4- <i>b</i>]pyrrole [271-31-8]	Thiopyrano[3,4- <i>c</i>]pyrrole [88212-51-5]	Thiopyrano[4,3- <i>b</i>]pyrrole [16989-50-7]

7.06.1.2.6 Furopyrans

Six furopyran structures are listed in Table 7. Each of the isomers contains a six-membered pyran ring attached to a five-membered furan ring. Not many studies have been carried out on these furopyran compounds.

A few charged parent compounds have been prepared. The oxygen atom in either ring can bear the positive charge.

Table 7 Furopyran isomers.

2 <i>H</i> -Furo[3,2- <i>b</i>]pyran [272-76-4]	2 <i>H</i> -Furo[2,3- <i>c</i>]pyran [271-90-9]	2 <i>H</i> -Furo[3,4- <i>b</i>]pyran [271-16-9]
3 <i>H</i> -Furo[3,4- <i>c</i>]pyran [270-78-0]	4 <i>H</i> -Furo[2,3- <i>b</i>]pyran [272-06-0]	4 <i>H</i> -Furo[3,2- <i>c</i>]pyran [271-94-3]

7.06.1.2.7 Thienopyrans

The structures of the thienopyrans include a six-membered ring with an oxygen atom and a five-membered sulfur heterocycle (Table 8). For the charged species, it is always the oxygen atom which bears the positive charge (Table 9).

Table 8 Thienopyran isomers.

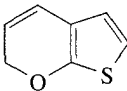
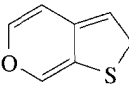
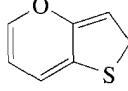
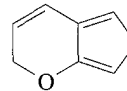
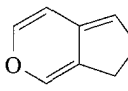
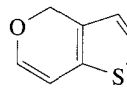
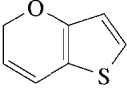
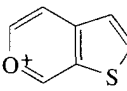
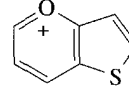
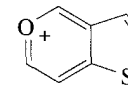
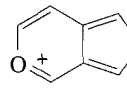
			
2H-Thieno[2,3-b]pyran [272-28-6]	2H-Thieno[2,3-c]pyran [42376-91-0]	2H-Thieno[3,2-b]pyran [42376-92-1]	2H-Thieno[3,4-b]pyran [103282-57-1]
			
3H-Thieno[3,4-c]pyran [42376-93-2]	4H-Thieno[3,2-c]pyran [55209-33-9]	5H-Thieno[3,2-b]pyran [272-81-1]	

Table 9 Thienopyrylium isomers.

			
Thieno[2,3-c]pyrylium [4145-33-9]	Thieno[3,2-b]pyrylium [35760-58-8]	Thieno[3,2-c]pyrylium [35766-05-3]	Thieno[3,4-c]pyrylium [35631-26-6]

7.06.1.2.8 Thiopyranofurans

The thiopyranofurans contain a six-membered sulfur heterocyclic ring and a five-membered oxygen heterocyclic ring (Table 10). Another common name for these isomers is furothiopyrans. Not much chemical literature exists regarding the thiopyranofuran compounds.

As with the thienopyrans, the charged species always include the positive charge on the oxygen atom. For the thiopyranofurans, the common charged species are shown in Table 11.

Table 10 Thiopyranofuran isomers.

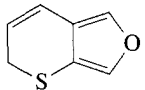
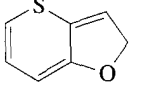
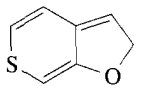
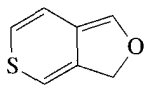
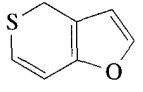
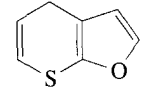
		
2H-Thiopyrano[2,3-c]furan [271-20-5]	2H-Thiopyrano[3,2-b]furan [106596-87-3]	2H-Thiopyrano[3,4-b]furan [42377-20-8]
		
3H-Thiopyrano[3,4-c]furan [270-79-1]	4H-Thiopyrano[4,3-b]furan [59718-25-1]	4H-Thiopyrano[2,3-b]furan [63105-73-7]

Table 11 Thiopyranofurylium ion isomers.

Thiopyrano[2,3- <i>b</i>]furylium [59718-25-1]	Thiopyrano[3,4- <i>b</i>]furylium [59718-29-5]	Thiopyrano[4,3- <i>b</i>]furylium [59718-27-3]

7.06.1.2.9 Thienothiopyrans

The final group of compounds to be considered here comprises compounds containing a sulfur atom in each of the rings. Thienothiopyran isomers are shown in Table 12.

Thienothiopyrylium and thiopyranothiolium ionic species that have been identified are shown in Table 13.

Table 12 Thienothiopyran isomers.

2 <i>H</i> -Thieno[2,3- <i>c</i>]thiopyran [42377-02-6]	2 <i>H</i> -Thieno[3,2- <i>b</i>]thiopyran [42377-03-7]	2 <i>H</i> -Thieno[3,4- <i>b</i>]thiopyran [34359-24-5]	3 <i>H</i> -Thieno[3,4- <i>c</i>]thiopyran [42377-04-8]
4 <i>H</i> -Thieno[2,3- <i>b</i>]thiopyran [272-29-7]	4 <i>H</i> -Thieno[3,2- <i>c</i>]thiopyran [3104-82-3]	6 <i>H</i> -Thieno[2,3- <i>b</i>]thiopyran [21339-38-8]	7 <i>H</i> -Thieno[2,3- <i>c</i>]thiopyran [53073-21-5]

Table 13 Thienothiopyrylium and thiopyranothiolium isomers.

Thieno[2,3- <i>b</i>]thiopyrylium [24194-68-1]	Thieno[2,3- <i>c</i>]thiopyrylium [27677-54-9]	Thieno[3,2- <i>b</i>]thiopyrylium [24194-69-2]
Thieno[3,2- <i>c</i>]thiopyrylium [27677-55-0]	Thiopyrano[2,3- <i>b</i>]thiolium [24194-70-5]	Thiopyrano[3,2- <i>b</i>]thiolium [24194-71-6]

7.06.2 THEORETICAL METHODS

Overall, very few theoretical studies can be found in the literature pertaining to this class of compounds. For the compounds actually studied, only simple analyses have been carried out. Literature references were found only for those systems incorporating a pyridine ring, i.e., pyrrolopyridines, furopyridines, and the thienopyridines.

7.06.2.1 Semiempirical and *Ab Initio* Methods

One theoretical study of pyrrolopyridines was carried out using an SCF-CI π -electron semiempirical method <76RRC1007> but it did not include the complete set of isomeric structures. Calculations for the compounds (1)–(4) show that, in all cases, the nitrogen of the pyrrole ring acts as a π donor and a σ acceptor whereas the nitrogen of the pyridine ring acts as both π and σ acceptor. As a result, the negative charge associated with the pyrrole nitrogen is of considerably smaller magnitude than that on the pyridine nitrogen. Overall atomic charges were useful for reactivity and basicity predictions.

A later study using *ab initio* calculations was carried out. Unlike the previous study, this one incorporated σ bonding and, as a result, significantly different conclusions could be drawn from the analysis. Some limitations in the calculations were found since the molecules were too large to completely optimize their molecular geometries <83T2851>. This study also included only compounds (1)–(4). In this series it was found that the geometry of the five-membered pyrrole ring was fairly insensitive to the position of the nitrogen in the adjacent six-membered ring. Furthermore, charge distribution in the pyrrole ring was not affected by the position of the nitrogen atom in the pyridine ring. As with the earlier study, lower negative charges were found to be associated with the pyrrole nitrogen than with the pyridine ring nitrogen. For the pyrrolopyridines, C-3 was found to have the highest electron density; a finding which agrees with the relative reactivity at position 3. Position C-2 was found to have the highest positive charge. These results contradict those obtained from the earlier study, probably due to the exclusion of σ -effects in the earlier work. Table 14 gives the charge densities for the pyrrolopyridines examined in the study.

Table 14 Charge densities of pyrrolopyridines and tautomers.

Atom	Pyrrolopyridine isomer							
	(1)	(12)	(2)	(11)	(3)	(9)	(4)	(8)
C-1	–560	–674	–559	–623	–567	–639	–562	–635
C-2	+231	+230	+242	+247	+234	+228	+239	+263
C-3	+24	–20	+16	–26	+21.5	–6	0	–63
C-4	+108	+142	+53	+53	+259	+290	–555	–505
C-5	+24	+12	+224	+239	–583	–516	+231	+274
C-6	+250	+276	–561	–517	+247	+238	+50	+17
C-7	–594	–515	+221	+278	+16	+40	+70	+122
C-8	+378	+395	+200	+156	+249	+244	+204	+179
C-9	+29	+34	+78	+90	+29	+14	+216	+244
H-1	+189		+175		+173		+173	
H-2	–5	–34	–7	–35	–7	–32	–10	–36
H-3	–2	–9	–3	–12	–2	–10	+7	–2
H-4	–20	–15	–14	–8	–32	–10		+169
H-5	–11	–5	–30	–12		+169	–32	–8
H-6	–30	–8		+169	–32	–12	–15	–5
H-7		+182	–25	0	–6	+4	–15	–11

Other findings from the *ab initio* study concern the migration of charge from the pyridine to the pyrrole ring as a consequence of prototropic tautomerism. The accumulation of charge is found at C-3, the most basic carbon atom, and at N-1. This concentration of charge at C-1 or N-3 is illustrated in the mesomeric structures contributing to the tautomer (12) in Figure 1. As a result of the charge distribution, basicity and the dipole moments at these two centers are noticeably affected.

An *ab initio* study of some methyl derivatives of pyrrolopyridines was also conducted. In addition to confirming some of the findings of the unsubstituted pyrrolopyridine study, this study also found that basicity increases with methyl substitution <82T3693, 88JA2699>.

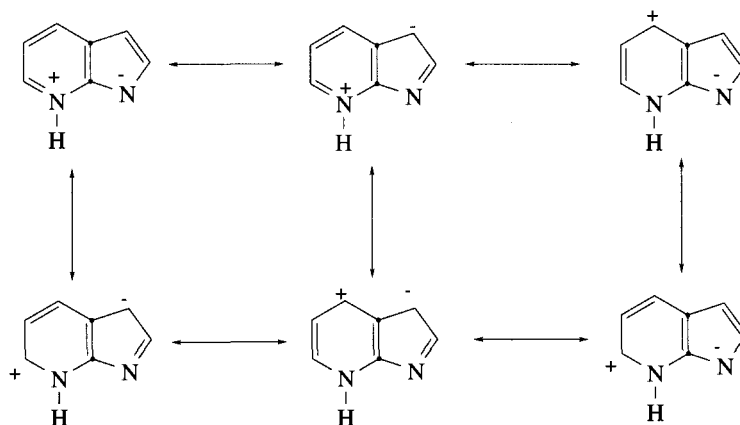


Figure 1 Mesomeric structures for 7*H*-pyrrolo[2,3-*b*]pyridine (12).

A semiempirical AM1 study was also carried out on substituted pyridoindole derivatives. Overall the results showed that the effects of substituents were independent of the aromaticity of the ring and typical trends for the substituents observed in other ring systems were also found in the pyridoindole derivatives (90JCS(P2)65, 90JCS(P2)1881, 91JCS(P2)1729).

A study using the CNDO/2 method was carried out for structure (17) and the results are shown in Figure 2 (80AP(313)1048). Based on simple HMO calculations for a number of furopyridines using superdelocalizability to predict reactivity, electrophilic substitution is preferred on the furan ring for the neutral and protonated compounds.

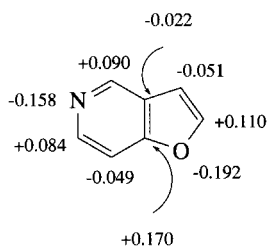


Figure 2 CNDO/2 charge densities for furo[3,2-*c*]pyridine (17).

Simple HMO calculations were also carried out for a series of thienopyridines. Again using superdelocalizability to predict reactivity, electrophilic substitution should be preferred in the thiophene nucleus (72ACS2601).

Using the PPP method, dipole moments, diamagnetic susceptibilities, ^1H , ^{13}C , and ^{14}N chemical shifts, and energies of the lowest singlet-singlet transitions were calculated for thienopyridines. Considering the ring current, the calculations showed that the nitrogen heteroatom substitution (in comparison to carbon for the analogous benzene derivative) had no effect on the ring current distribution (87CHE454). Further, the thienopyridines examined in the study have nearly identical aromatic character. The results are summarized in Table 15.

PPP and CNDO/2 calculations have been carried out for thienopyridines. Electron densities are shown in Table 16 (72ACS2601).

Table 15 Ring current distribution.

Compound	Thiol ring current	Pyridine ring current
(20)	0.905	1.069
(21)	0.910	1.071
(22)	0.906	1.071
(23)	0.909	1.068

Source: Vysotskii *et al.* (87CHE454).

Table 16 Electron density distribution for thienopyridines.

Atom no.	Thienopyridine isomer					
	(20)	(21)	(22)	(23)	(24)	(25)
1	1.374	1.340	1.360	1.351	1.349	1.265
2	1.090	1.083	1.084	1.088	0.913	1.111
3	1.193	1.188	1.203	1.182	1.068	1.246
4	0.940	1.035	1.320	0.903	0.933	0.915
5	1.053	0.995	0.923	1.317	1.256	1.300
6	0.925		1.056	0.996	1.105	1.011
7	1.311	0.903	0.938	1.032	1.264	1.024
8	1.039	1.080	1.078	1.056	1.025	1.068
9	1.075	1.054	1.039	1.076	1.086	1.060

Source: Helland and Skancke <72ACS2601>.

7.06.3 EXPERIMENTAL STRUCTURAL METHODS

7.06.3.1 NMR Spectroscopy

7.06.3.1.1 Proton NMR spectroscopy

(i) Pyrrolopyridines

Proton NMR data are given in Table 17 for a number of pyrrolopyridine derivatives. Upon heating in D₂SO₄, the isomers (3) and (4) underwent deuterium exchange of the proton attached to C-3. Reaction at other ring positions occurred only with very forcing conditions, along with side reactions <73JCS(P2)1072>. For 4-methyl-1*H*-pyrrolo[2,3-*b*]pyridine, deuterium exchange also occurred initially at the 3-position of the ring. However, at higher temperatures exchange was also observed at the 2- and 5-positions of the ring.

Another study investigated compound (3), 1-phenylpyrrolo[3,2-*c*]pyridine and some dihydro 1*H*-pyrrolo[3,2-*c*]pyridine derivatives by ¹H NMR spectroscopy <73CHE705>. Protonation occurred in the pyridine ring on the nitrogen atom for all compounds investigated. A comparison of spectral data for compound (3) in dichloromethane and trifluoroacetic acid indicates that protonation results in a significant deshielding of the pyrrole protons of the order of 0.41–0.54 ppm. Further, the protons at the 2- and 3-positions relative to the pyridine nitrogen (α - and β -positions, respectively), experienced less change in chemical shift than the corresponding protons in pyridine under the same conditions. Protons of the pyridine ring were shifted further upfield for 2,3-dihydro derivatives in comparison to the pyrrolopyridine compounds. Table 18 gives a comparison of some of the 1*H*-pyrrolo[3,2-*c*]pyridine derivatives.

The most commonly studied pyrrolopyridine is compound (1). This compound is capable of self-association, a phenomenon that has led to much investigation, especially by NMR techniques. NMR data in carbon tetrachloride and benzene show that the chemical shift of the H-1 proton moves downfield as the concentration of solute is increased. This type of shift is typical for a proton that undergoes hydrogen bond formation. From the NMR data, the dimerization constant for 1*H*-pyrrolo[2,3-*b*]pyridine (1) has been determined to be $18.9 \pm 10.3 \text{ mol l}^{-1}$ <81JPC3181>.

(ii) Furopyridines

Proton NMR data for some parent furopyridines and a variety of derivatives are listed in Table 19. Some long-range coupling may occur between H-3 and H-7. Proton NMR data for a series of furodipyridines indicates that the chemical shift of each proton moves downfield from the similar proton in the parent furopyridine ring system (Table 20). This is due to larger anisotropic effects in the furodipyridine ring system <90JHC637>.

(iii) Thienopyridines

A considerable amount of proton spectral data exists for the parent thienopyridines and some of their derivatives. Table 21 lists data for the parent compounds and some derivatives. As in the

Table 17 Proton NMR chemical shift data (ppm) for pyrrolopyridine derivatives.

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	Ref.
(4)	D ₂ SO ₄	—	7.67	6.38	—	8.10	7.25	8.05	73JCS(P2)1072
2-Me-(4)	CD ₃ OD	—	2.47 ^a	6.27	—	8.12	6.97	7.62	81H(16)1473
3-Me-(4)	CD ₃ OD	—	7.12	2.35 ^a	—	8.20	7.05	7.73	81H(16)1473
3-Me-2-Ph-(4)	CD ₃ OD	—	7.3–7.7 ^e	2.51 ^a	—	8.24	—	7.04	81H(16)1473
2-Pyridyl-(4)	CD ₃ OD	—	7.0–7.9 ^g	—	—	—	8.57	8.3	81H(16)1473
7-NH ₂ -(4)	CD ₃ OD	—	7.38	6.43	—	7.87	6.40	—	92JHC359
(3)	CH ₂ Cl ₂	—	7.39	6.67	8.97	—	8.28	7.42	72TL2857
(3)	CDCl ₃	11.10 ^c	7.31	6.70	9.03	—	8.32	7.38	92JHC359
1-Me-4-MeO-(3)	CDCl ₃	3.7 ^a	6.87	6.57	4.1 ⁱ	—	7.84	6.84	83T1777
(2)	CDCl ₃	11.85 ^c	7.48	6.58	7.61	8.26	—	8.85	92JHC359
2-Me-(2)	CDCl ₃	11.21 ^c	2.44 ^a	6.13	7.30	—	—	8.56	77CHE1224
2-Me-3-CO ₂ Et-(2)	d ₆ -DMSO	—	1.89 ^a	4.28/1.37 ^d	7.85	8.14	—	8.72	78CHE402
2-Me-3-Ac-(2)	d ₆ -DMSO	—	2.54 ^a	1.90 ^b	7.82	8.18	—	8.65	78CHE402
2-Ph-3-COOEt-(2)	d ₆ -DMSO	12.9 ^c	7.71/7.51 ^e	4.22/1.26 ^d	7.92	8.28	—	8.78	78CHE402
1-Ac-(2)	d ₆ -DMSO	2.70 ^a	8.07	6.78	7.62	8.36	—	9.52	78CHE406
3-Ac-(2)	CD ₃ OD	—	8.42	2.61 ^a	8.24 ^f	—	—	7.89	78CHE406
3-COOH-(2)	d ₆ -DMSO	—	8.75	—	8.42 ^f	—	—	9.28	78CHE406
3-Br-(2)	CD ₃ OD	—	7.67	—	7.55	8.22	—	8.75	78CHE406
7-Me-(2)	CDCl ₃	—	7.42	6.60	7.48	8.16	—	2.79 ^a	92JHC359
1-Ac-(1)	CDCl ₃	3.11 ^b	8.20	6.73	8.06	7.35	8.73	—	76JHC585
1-Ac-(1)	CDCl ₃	2.99 ^b	7.87	6.47	7.77	7.07	8.27	—	82JHC665
3-Ac-(1)	d ₆ -DMSO	—	8.42	2.52 ^b	8.47	7.20	8.29	—	82JHC665
3-CHO-(1)	CD ₃ OD	—	8.18	9.83 ^b	8.45	7.23	8.26	—	82JHC665
3-BrAc-(1)	d ₆ -DMSO	12.7 ^c	8.60	4.70 ^b	8.42	7.22	8.30	—	84JHC421
3-Vinyl-(1)	CDCl ₃	10.4–11.0 ^c	7.39	5.20/5.68/ 6.86 ^k	8.34	7.14	8.21	—	92BCJ2992
4-Me-(1)	D ₂ SO ₄	—	7.20	6.25	2.21 ^a	6.90	6.90	—	73JCS(P2)1072
6-NH ₂ -(1)	CDCl ₃	8.5–9.0	7.0	6.34	7.69	6.35	5.0–5.5 ^j	—	92BCJ2992
6-Me-(1)	CDCl ₃	—	7.24	6.38	7.78	6.88	2.68 ^a	—	92JHC359

^aCH₃ chemical shift. ^bCH₃CO chemical shift. ^cNH chemical shift. ^dCH₃CH₂ chemical shift. ^eC₆H₅ chemical shift. ^fMultiplet of H-4. ^gC₃H₃N chemical shift. ^hCHO chemical shift. ⁱOCH₃ chemical shift. ^jNH₂ chemical shift. ^kCH₂=CH chemical shift.

Table 18 Proton NMR chemical shift data (ppm) for 1*H*-pyrrolo[3,2-*c*]pyridine derivatives.

Compound	Solvent	H-2	H-3	H-4	H-6	H-7
(3)	CH ₂ Cl ₂	7.39	6.67	8.97	8.28	7.42
	TFA	7.80	7.13	9.00	8.30	7.99
2,3-Dihydro-(3)	CH ₂ Cl ₂	3.63	3.03	8.05	8.00	6.44
	TFA	4.06	3.31	7.75	7.85	6.69
1-Ph-(3)	CH ₂ Cl ₂	—	6.76	8.93	8.29	—
	TFA	—	7.29	9.10	8.35	—
1-Ph-2,3-dihydro-(3)	CH ₂ Cl ₂	4.01	3.13	8.15	8.11	6.88
	TFA	4.44	3.44	7.86	7.92	6.82
1-Ac-2,3-Dihydro-(3)	CH ₂ Cl ₂	4.07	3.20	8.34	8.31	7.93
	TFA	4.54	3.59	8.49	8.65	8.52

Source: Dvoryantseva *et al.* <73CHE705>.

furopyridines series, long-range coupling between H-3 and H-7 is observed for the [2,3-*c*], [3,2-*c*], [3,2-*b*], and [3,4-*b*] isomers. The shift reagent Eu(fod)₃ was used to aid in the assignment of structures to products of the chlorination reaction of thienopyridines, including dichlorodihydrothienopyridine *N*-oxides and a trichloro derivative <74JHC535>.

(iv) Thienothiopyridines

Thienothiopyrylium perchlorate salts have been investigated by ¹H NMR. Long-range coupling, covering distances of five or six bonds, has been observed. Data are summarized in Table 22 <74G671>.

Table 19 Proton NMR chemical shift data (ppm) for furopyridine derivatives.

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	Ref.
(14)	CDCl ₃	—	7.75	6.79	7.92	7.19	8.35	—	71JHC735
2-CHO-(14)	CDCl ₃	—	9.90 ^c	7.53	8.13	7.34	8.54	—	86JHC1465
3-CHO-(14)	CDCl ₃	—	8.27	10.01 ^c	8.34	7.29	8.41	—	86JHC1465
3-Br-(14)	CDCl ₃	—	7.70	—	7.85	7.27	8.35	—	84JHC725
5-NH ₂ -(14)	CDCl ₃	—	7.72	6.67	7.29	3.64 ^a	7.84	—	71JHC735
2-CO ₂ H-(14)	d ₆ -Acetone d ₆ -DMSO	—	—	7.64	8.25	7.40	8.46	—	71JHC735
3-Me-(15)	CDCl ₃	—	7.42	2.19 ^b	7.35	8.30	—	8.71	86JHC549
(16)	CCl ₄	—	7.99	6.95	—	8.46	7.17	6.64	75ACS(B)233
2-NO ₂ -(16)	CDCl ₃	—	—	7.77	—	8.73	7.47	7.92	84JHC725
3-Me-(16)	CDCl ₃	—	7.54	2.27 ^b	—	8.46	7.11	7.62	86JHC665
5-CO ₂ H-(16)	d ₆ -DMSO	—	8.51	7.33	—	—	8.21	8.21	75ACS(B)233
5-Me-(16)	CCl ₄	—	7.73	6.84	—	2.57 ^b	6.91	7.50	75ACS(B)233
(17)	CDCl ₃	—	7.58	6.76	8.90	—	8.45	7.39	82JHC1207
2-CHO-4-Cl-(17)	d ₆ -DMSO	—	9.92 ^c	8.11	—	—	8.43	7.86	83T1777
(19)	CDCl ₃	8.20 ^d	—	7.99 ^d	9.03	—	7.79	7.13	77TL1741

^aNH₂ chemical shift. ^bCH₃ chemical shift. ^cCHO chemical shift. ^dH-1 or H-3 chemical shift.**Table 20** Proton NMR chemical shift data (ppm) for furodipyridines.

Dipyridine	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
Furo[2,3- <i>b</i> :4,5- <i>c'</i>]	—	8.488 (dd)	7.400 (dd)	8.332 (dd)	9.204 (d)	—	8.693 (d)	7.539 (dd)	—
Furo[3,2- <i>b</i> :4,5- <i>c'</i>]	—	8.632 (dd)	7.383 (dd)	7.815 (dd)	—	7.490 (dd)	8.706 (d)	—	9.439 (d)
Furo[2,3- <i>c</i> :4,5- <i>c'</i>]	9.346 (d)	—	8.792 (d)	7.606 (dd)	—	9.056 (dd)	—	8.690 (dd)	7.958 (dd)
Furo[3,2- <i>c</i> :4,5- <i>c'</i>]	9.345 (d)	—	8.743 (d)	7.580 (dd)	—	9.345 (d)	(H3)	—	(H1)

Source: Shiotani and Morita (90JHC637).

Table 21 Proton NMR chemical shift data (ppm) for thienopyridines.

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	Ref.
(20)	D ₂ SO ₄	—	8.56	8.28	9.40	8.60	9.40	—	78JCS(P2)861
6-CN-(20)	CDCl ₃	—	7.81	7.35	8.17	7.64	—	—	83JHC213
(21)	D ₂ SO ₄	—	8.70	7.95	8.50	8.50	—	8.95	78JCS(P2)861
(23)	D ₂ SO ₄	—	8.13	7.86	9.22	—	8.44	8.44	78JCS(P2)861
(22)	D ₂ SO ₄	—	8.67	7.90	—	8.92	8.05	9.25	78JCS(P2)861
(22)	CCl ₄	—	7.60	7.49	—	8.59	7.04	8.00	75ACS(B)233
2-CHO-(22)	CDCl ₃	—	10.22 ^a	8.25	—	8.82	7.42	8.27	84JHC785
2-I-(22)	CDCl ₃	—	—	7.79	—	8.60	7.20	8.07	84JHC785
2-CN-(22)	CDCl ₃	—	—	8.12	—	8.85	7.45	8.23	84JHC785
5-CO ₂ H-(22)	d ₆ -DMSO	—	8.33	7.76	—	—	8.11	8.70	75ACS(B)233
5-Me-(22)	CCl ₄	—	7.57	7.41	—	2.58 ^c	6.92	7.87	75ACS(B)233
(25)	CDCl ₃	8.02 ^b	—	7.64 ^b	9.12	—	8.04	7.38	72JHC843

^aCHO chemical shift. ^bH-1 or H-3 chemical shift assignment. ^cCH₃ chemical shift.

7.06.3.1.2 Carbon-13 NMR spectroscopy

With the exception of furopyridines, there have been no extensive studies using ¹³C NMR spectroscopy of these compounds. There is, however, a considerable volume of information concerning the ¹³C NMR data for furopyridines (91JHC1469). Table 23 lists ¹³C NMR data for the parent compounds and some simple derivatives. Based on analysis of the ¹³C NMR data, the C-2 and C-3 shifts are very similar to those for furan, indicating that the fused pyridine ring has minimal electronic effect upon those carbon atoms. Carbon-13 NMR data for a series of furodipyridines

Table 22 Proton NMR chemical shift data (ppm) for thienothiopyrans.

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	Ref.
[2,3- <i>b</i>] ^a	CCl ₄	—	9.99	8.70	9.50	8.21	8.60	—	74G671
[3,2- <i>b</i>] ^a	CCl ₄	—	9.98	8.70	9.62	—	9.03	8.42	74G671
[2,3- <i>c</i>] ^a	CCl ₄	10.70	—	9.36	9.26	8.22	9.14	—	74G671
[3,2- <i>c</i>] ^a	CCl ₄	10.62	—	9.43	9.47	—	8.52	8.21	74G671
2-Me-2H-[2,3- <i>b</i>]	—	—	2.35 ^b	6.40	6.27	5.53	3.35 ^c	—	80RTC23

^aPerchlorate salt. ^bCH₃ chemical shift. ^cTwo protons.

indicates that overall signals for the carbon atoms in the difuropyridine are shifted downfield from the corresponding signals for the parent compounds. This is attributed to the increased π -electron delocalization of the difuropyridine rings <90JHC637>.

Table 23 Carbon-13 NMR chemical shift data (ppm) for furopyridines.

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-3a	C-7a	Others
(14)	144.41	105.64	129.93	118.93	143.82	—	118.93	161.72	—
2-Me-(14)	155.30	101.55	128.37	118.71	142.36	—	121.05	161.69	13.99 (Me)
2-CHO-(14)	151.50	114.59	133.09	120.66	149.06	—	118.93	162.18	180.05 (CHO)
2-CN-(14)	126.96	117.44	132.10	120.91	148.53	—	117.44	161.42	110.96 (CN)
3-Me-(14)	140.92	115.13	128.39	118.54	143.73	—	120.86	162.08	7.94 (Me)
3-CN-(14)	151.74	94.21	129.73	120.88	146.50	—	116.76	160.76	111.18 (CN)
(15)	147.60	105.60	115.66	141.99	—	133.58	133.39	151.84	—
2-Me-(15)	158.91	101.82	114.69	142.02	—	132.49	135.29	151.82	13.77 (Me)
2-CHO-(15)	153.82	114.37	117.23	143.14	—	135.90	132.36	152.16	180.10 (CHO)
2-CN-(15)	129.58	116.96	116.59	143.53	—	134.85	131.41	151.92	110.52 (CN)
3-Me-(15)	144.24	115.05	114.15	141.72	—	133.49	135.82	152.23	7.31 (Me)
3-CN-(15)	154.28	94.97	114.86	144.36	—	134.92	131.34	151.53	110.89 (CN)
(16)	148.50	107.89	—	145.70	118.56	117.88	147.31	147.41	—
2-Me-(16)	159.57	103.94	—	144.99	117.47	116.69	149.04	147.33	14.16 (Me)
2-CHO-(16)	154.45	117.22	—	148.04	122.73	119.88	145.60	149.62	179.73 (CHO)
2-CN-(16)	130.27	118.86	—	148.21	122.22	119.03	144.31	148.87	110.72 (CN)
3-Me-(16)	145.09	116.71	—	145.09	118.44	117.79	147.80	147.80	6.53 (Me)
3-CN-(16)	154.84	97.06	—	148.01	121.15	119.54	143.85	147.48	110.62 (CN)
(17)	145.19	104.52	143.97	—	144.11	106.74	124.34	158.88	—
2-Me-(17)	156.06	100.28	142.35	—	143.29	106.06	126.07	158.74	13.74 (Me)
2-CHO-(17)	152.87	114.86	147.02	—	147.94	107.89	123.90	159.94	179.22 (CHO)
2-CN-(17)	127.78	116.52	145.70	—	147.50	107.16	122.49	159.30	110.54 (CN)
3-CN-(17)	152.55	93.70	143.46	—	146.60	107.52	121.73	158.77	110.84 (CN)

Source: Shiotani and Morita <90JHC637>.

7.06.3.1.3 Nitrogen-15 NMR spectroscopy

There are few references to ¹⁵N NMR in the chemical literature for these compounds. Nitrogen-15 NMR is a very sensitive technique for studying compounds where bonding to nitrogen is of importance. A study of compound (1) was carried out and the ¹⁵N NMR data are listed in Table 24. Again, formation of a dimeric species affects the chemical shifts, with both the pyrrole and pyridine nitrogens showing significant downfield shifts from their normal positions <85MI 706-01>. Upon protonation, the pyridine nitrogen experiences a large upfield shift, while the pyrrole nitrogen is unaffected, confirming that the pyridine nitrogen is the site of protonation.

Table 24 Nitrogen-15 NMR chemical shift data (ppm) for 1H-pyrrolo[2,3-*b*]pyridine.

Solvent	N-1	N-7
CCl ₄	−237.35	−117.36
Ethanol	−239.93	−119.30
0.1 mol/L HCl	−241.68	−210.15

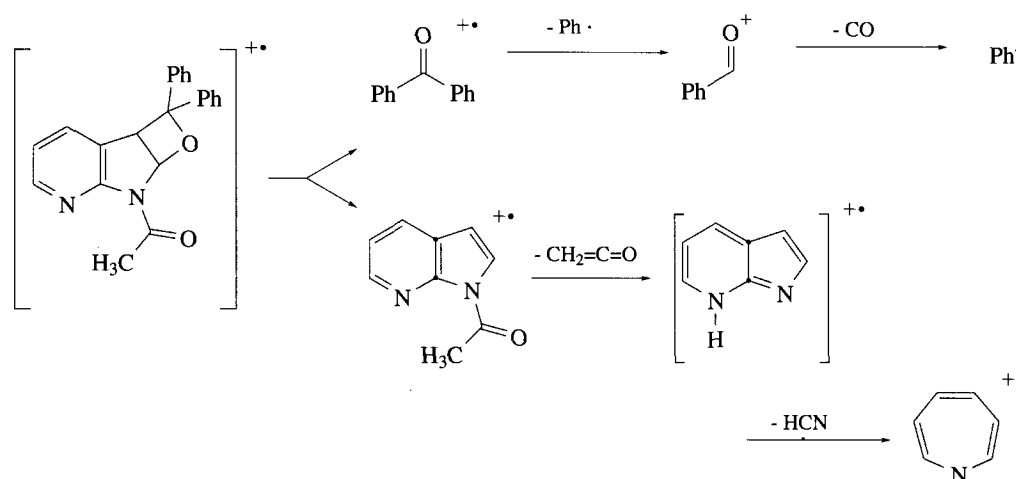
Source: Someswara Rao *et al.* <85MI 706-01>.

7.06.3.2 Mass Spectrometry

7.06.3.2.1 Pyrrolopyridines

In the mass spectral fragmentation of pyrrolopyridines both sp^2 and sp^3 nitrogen atoms are incorporated into the molecule, though each is in a different ring. It is interesting to find which dominates the fragmentation patterns. Fragmentation for metastable M^{2+} ions from compound (1) consisted only of charge separation reaction products (m/z 28 and m/z 90). Using tandem mass spectrometry techniques, the low-energy collision-induced dissociation fragmentation pattern showed loss of HCN from the M^{2+} ion as the most favored product resulting from a neutral-expulsion mechanism. In the conventional electron impact (EI) fragmentation spectrum, additional fragments were found such as m/z 63, arising from dissociative electron-capture collisions of M^{2+} . There is no evidence supporting the loss of ethyne (C_2H_2) for M^{2+} from compound (1). This type of fragmentation is characteristic of benzpyrrole cations. Based on this observation, it is reasonable to assume that radical sites located on sp^2 centers (bonding orbital of nitrogen of the pyridine ring) are more effective for initiating reactions leading to fragmentation than radicals located on sp^3 centers (nonbonding orbital of nitrogen of the pyrrole ring) <92OMS(27)89>.

Mass spectral data have been reported for an oxetane derivative of (1) formed by the reaction of benzophenone with 1-acetyl-pyrrolo[2,3-*b*]pyridine (Scheme 1). The major fragments upon electron impact result from a retro-Diels–Alder process to give the original component ions. These ions then undergo further fragmentation <76JHC585>.



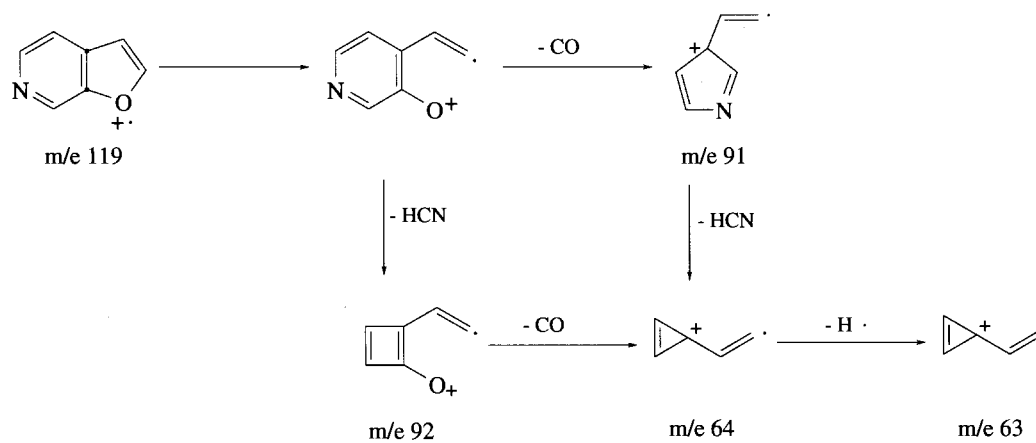
Scheme 1

7.06.3.2.2 Furopyridines

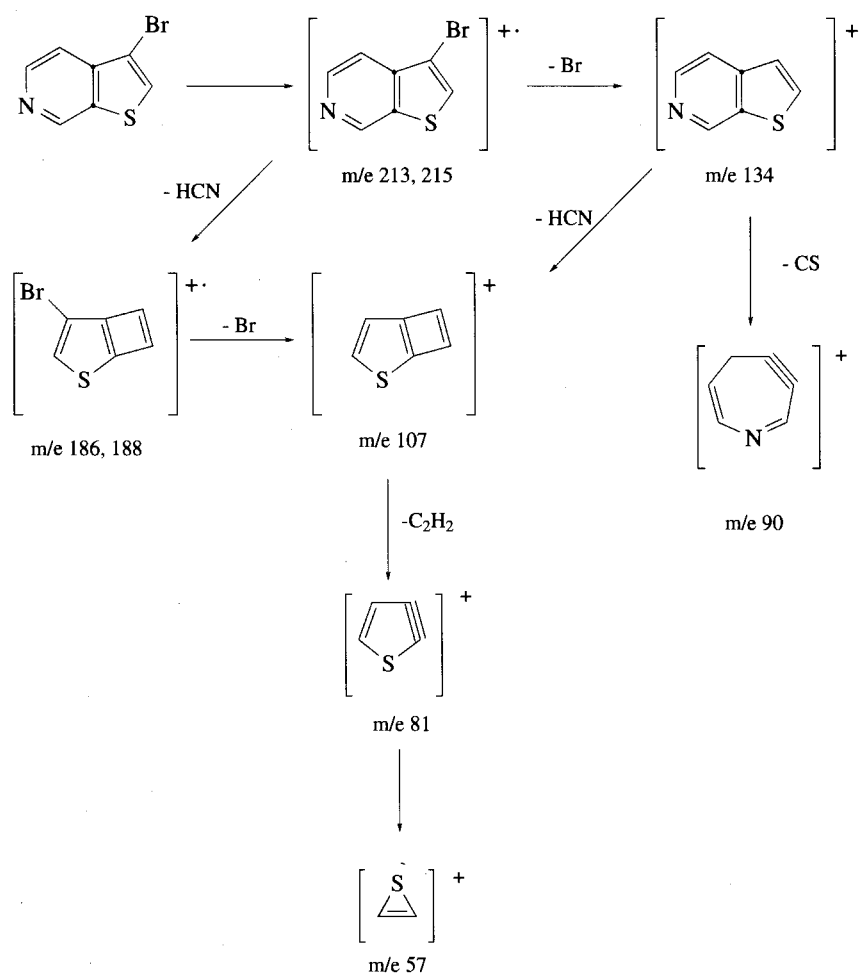
The mass spectra for compound (15) and 7-chlorofuro[2,3-*c*]pyridine showed the base peak at m/z 119, as well as intense peaks at m/z 92, 91, 64, and 63, resulting from combinations of HCN and CO loss as outlined in Scheme 2 <82JHC1207>.

7.06.3.2.3 Thienopyridines

Mass spectral data have been obtained for compounds (20), (21), (22), and (23). The data show that the most abundant peak for each is the molecular ion. Considerable amounts of $(M-1)^+$ and M^{+2} ions are also formed. Loss of HCN from the molecular ion is evidence for the pyridine ring, while loss of carbon monosulfide and/or the thioformyl radical are characteristic of the thiophene ring <75JHC865>. Mass spectral fragmentation patterns have also been reported for the halo- and halonitrothienopyridines (Scheme 3) <70AK(32)249, 74JHC205>.



Scheme 2

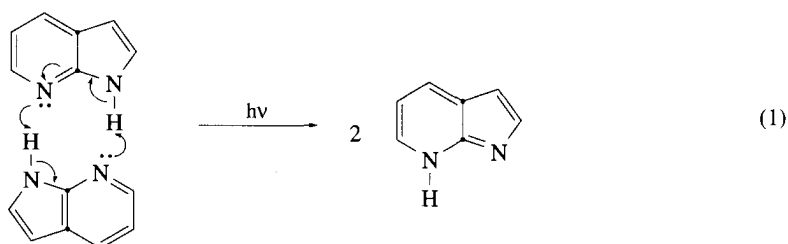


Scheme 3

7.06.3.3 UV/Fluorescence Spectroscopy

7.06.3.3.1 Pyrrolopyridines

Compound (1) has been the subject of intense investigation by fluorescence spectroscopy. At room temperature, proton transfer reactions leading to tautomers of structure (1) are so rapid that no dimeric emissions can be observed. At lower temperatures, however, emissions from the dimer appear <79CPL(66)230>. The emissions of an alcoholic solution of compound (1) (5×10^{-4} mol l⁻¹) have two noteworthy bands: a maximum in the violet region of 320–360 nm from monomer fluorescence and a maximum in the green region near 480 nm due to fluorescence of a tautomer formed by a rapid intermolecular double proton transfer reaction. Upon electronic excitation, two protons simultaneously shift from the pyrrole nitrogen toward the pyridine type nitrogen <84JPC1160>. This is a very fast reaction which continues even at temperatures as low as 4 K. The formation of the tautomer is shown in Equation (1) <74JA1674>. An analogous reaction has been observed for alcohol complexes of pyrido[2,3-*b*]indole <86JPC3868, 92JPC8430>.



The energy barriers associated with the tautomerism have been determined from quantum yields and luminescence lifetime measurements <84JST(114)329>. Table 25 lists the activation energies and solvent viscosity activation energies associated with the tautomer in a variety of alcoholic solvents. The data suggest a correlation between the energy barrier associated with proton transfer and the viscosity of the solvent.

Table 25 Tautomerization energy barriers.

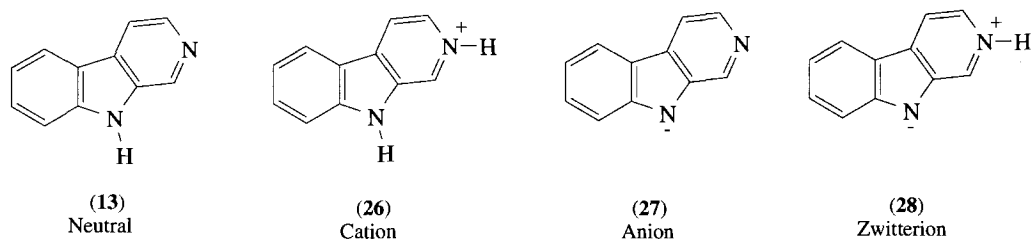
<i>Solvent</i>	<i>Tautomerism</i> E_{ACT} (kcal mol ⁻¹ (kJ mol ⁻¹))	<i>Solvent viscosity</i> E_{ACT} (kcal mol ⁻¹ (kJ mol ⁻¹))
Ethanol	4.8 (20.1)	2.7 (11.3)
Propanol	6.2 (25.9)	4.4 (18.4)
Butanol	7.5 (31.4)	4.6 (19.2)
Ethanol–ethylene glycol (1 : 1)	8.5 (35.6)	6.9 (28.9)

Source: Herbich *et al.* <84JST329>.

Further studies have shown that there is evidence for the double proton transfer reaction arising from a two-proton concerted process <93JA10158>. In addition to this excited-state double proton transfer, an excited state complex ((1)–alcohol exciplex) exists in alcohol solvents <83JPC3202>. This exciplex formation is responsible for the unusually long wavelength shift and the bandwidth of the fluorescence spectra of compound (1) in alcoholic and aqueous solvents. In aqueous solution at neutral pH, only one fluorescence is observed which corresponds to the fluorescence maximum displayed by the tautomeric species <92JA8343, 93JPC11823>.

A considerable amount of work has also been carried out on the excited-state double proton transfer phenomenon for pyrido[2,3-*b*]indole. In the solid state, this transfer appears to occur without any noted energy barrier <82CPL204, 86JPC3866>. Fluorescence spectroscopy has also been used to study compound (13) and some of its derivatives. Fluorescence measurements were carried out at pH values ranging from acidic to basic solutions. Four species, neutral (13), cation (26), anion (27), and zwitterion (28) that have been identified in the excited state are shown in Figure 3 <92JPC10290, 93JCS(P2)99, 93JPC11493>.

UV data at a given pH for some of the parent pyrrolopyridines and a few methyl derivatives are given in Table 26. In the cationic forms, the band of longest wavelength (band III) experiences a

**Figure 3** Excited-state species for 9H-pyrido[3,4-b]indole (13).

bathochromic shift in comparison to the neutral molecules <60JCS1794>. These data support mesomeric stabilization of the pyrrolopyridine cations.

Iodine complexes of several diazines including compound (1) have been studied by UV spectroscopy. The data are summarized in Table 27 <90SA(A)1107>.

Table 26 UV spectral data for pyrrolopyridines.

Compound	$\lambda_{\max}$ (nm) (H_2O)	$\log \epsilon$ (H_2O) ^b
(1)	290	3.91
(1) Cation	293	3.94
(2)	260, 291	3.59, 3.68
(2) Cation	261, 319	3.70, 3.73
(3)	265, 273 (s) ^a	3.59, 3.50 (s) ^a
(3) Cation	268, 293	3.46, 3.29
(4)	292	3.92
(4) Cation	284, 327	3.85, 3.70

Source: Adler and Albert <60JCS1794>.

^a(s) refers to shoulder peak. ^b ϵ in $L. mol^{-1} cm^{-1}$.

Table 27 UV spectral data for iodine complex of 1H-pyrrolo[2,3-b]pyridine (1).

Blue-shifted I_2 band		CT band		Shifted bands ^a (nm)	Observed absorptions ^{a,b} (nm)
$\lambda_{\max}$ (nm)	$\log \epsilon_{\max}$ ^c	$\lambda_{\max}$ (nm)	$\log \epsilon_{\max}$		
403	3.34	303	—	239	289, 295 (s)

Source: Someswara Rao *et al.* <90SA(A)1107>.

^aDonor compound (1). ^bNon-polar solvents. ^c $\epsilon_{\max}$ in $mol^{-1} cm^{-1}$.

7.06.3.3.2 Furopyridines

UV data for some parent furopyridines and methyl or chloro derivatives are listed in Table 28. UV data have been collected for a series of furodipyrindines. The data indicate that, as expected in comparison with the parent furopyridines, the entire electronic spectrum shifts toward longer wavelengths owing to the extension of the π -electron system <90JHC637>.

7.06.3.3.3 Thienopyridines

UV data for thienopyridines are summarized in Table 29.

7.06.3.4 IR Spectroscopy

7.06.3.4.1 Pyrrolopyridines

IR spectral data for pyrrolopyridines are listed in Table 30.

Table 28 UV spectral data for furopyridines.

Compound	$\lambda_{\max}$ (nm) (MeOH)	$\log \epsilon$ (MeOH) ^b
(14)	207.0, 249, 277.3, 279.7, 286.0 (s) ^a	4.10, 3.73, 3.83, 3.84, 3.72 (s) ^a
(15)	209.6, 244.5, 265.0, 272.3, 280.7	3.89, 3.90, 3.63, 3.63, 3.47
(16)	203.5, 240.5, 284.6	4.05, 3.65, 3.94
(17)	207.5, 241.0, 269.0, 276.0	4.13, 3.95, 3.30, 3.08

Source: Shiotani and Morita (90JHC637).

^a(s) refers to shoulder. ^b ϵ in L. mol⁻¹ cm⁻¹.**Table 29** UV spectral data for thienopyridines.

Compound	Solvent	$\lambda_{\max}$ (nm)	$\log \epsilon^a$	Ref.
3-Br-(20)	EtOH	235, 279, 288, 298	4.43, 3.72, 3.75, 3.70	74JHC205
3-CN-(20)	EtOH	273, 286, 297	3.90, 3.89, 3.86	74JHC205
(21)	Isooctane	223, 227, 242(s), 293, 299, 304	4.24, 4.23, 3.68, 3.88, 3.76	53JA5122
(22)	EtOH	230, 278, 285–290(s), 315	4.42, 3.71, 3.65, 2.4	60JOC1816
(23)	Isooctane	224, 238, 256, 274(s), 281, 292, 337	4.55, 3.58, 3.63, 3.45, 3.43, 3.30, 2.35	53JA5122
(24)	EtOH	224, 293, 297, 306, 343	4.27, 3.81, 3.78, 3.88, 3.45	72JHC843
(24)	EtOH/HCl	232, 303, 308, 388	4.16, 4.14, 3.41	72JHC843
(25)	EtOH	224, 270, 280, 291, 342	4.32, 3.35, 3.46, 3.31, 3.47	72JHC843
(25)	EtOH/HCl	236, 281, 290, 380	4.38, 3.69, 3.54, 3.44	72JHC843

^a ϵ in L. mol⁻¹ cm⁻¹.**Table 30** IR data for pyrrolopyridine derivatives.

Compound	Method	IR data (cm ⁻¹)	Ref.
(1)	KBr	3200 (NH); 3125; 3077; 3021; 2985; 1613; 1595; 1511; 1433; 1357; 1346	68AHC(9)27
6-Ethynyl-(1)	KBr	3296 (NH)	92BCJ2992
6-NH ₂ -(1)	KBr	3436 (NH)	92BCJ2992
(2)	KBr	3200 (NH); 3125; 3067; 3030; 2959; 1626; 1515; 1475; 1435; 1418; 1372	68AHC(9)27
1-Ac-(2)	Mineral oil	1710 (COMe); 1590 (C=C/C=N)	78CHE406
2-Me-3-Ac-(2)	Mineral oil	1640 (COMe); 1610 (C=C/C=N)	78CHE402
2-Me-3-CO ₂ Et-(2)	Mineral oil	3200 (NH); 1700 (CO ₂ Et); 1660 (C=C/C=N)	78CHE402
2-Ph-3-CO ₂ Et-(2)	Mineral oil	1700 (CO ₂ Et); 1610 (C=C/C=N)	78CHE402
3-COOH-(2)	Mineral oil	1640 (CO); 1630 (C=C/C=N)	78CHE406
(3)	KBr	3200 (NH); 3106; 3077; 3040; 2967; 1623; 1587; 1477; 1453; 1418; 1364	68AHC(9)27
(4)	KBr	3200 (NH); 3125; 3077; 3030; 2985; 1572; 1506; 1458; 1410; 1374; 1333	68AHC(9)27

7.06.3.4.2 Furopyridines

IR spectral data for furopyridine derivatives are summarized in Table 31.

7.06.3.4.3 Thienopyridines

The IR spectral data for thienopyridine derivatives are listed in Table 32.

7.06.3.5 Dipole Moments

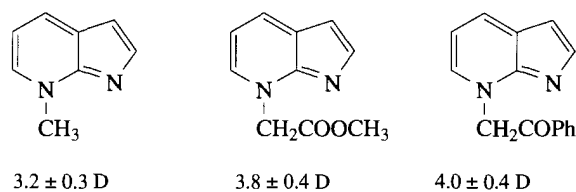
Dipole moments have been measured in the ground and excited states for three derivatives of compound (1) (83CPL58). Ground-state dipole moments are shown in Figure 4. The ground-state dipole moment of the parent structure (1) has been found experimentally to be 4.87×10^{-30} C m (1.46 D) (81JPC3181).

Table 31 IR data for furopyridine derivatives.

Compound	IR data (cm ⁻¹)	Ref.
2-CHO-(15)	1680 (CHO)	87JHC373
2-CN-(15)	2230 (CN)	87JHC373
2-CHO-(16)	1675 (CHO)	87JHC373
2-CN-(16)	2240 (CN)	87JHC373
2-CHO-(17)	1665 (CHO)	87JHC373
2-CN-(17)	2240 (CN)	87JHC373
2-NO ₂ -(17)	1520, 1350 (NO ₂)	75JHC705

Table 32 IR data for thienopyridine derivatives.

Compound	Method	IR data (cm ⁻¹)	Ref.
3-CN-(20)	CHCl ₃	2460 (CN)	74JHC205
6-CN-(20)	KBr	2220 (CN)	83JHC213
2-I-(22)	KBr	1550, 1390, 1275, 1140, 1070, 825, 780	84JHC785
2-CHO-(22)	KBr	2835&2820(ald. CH), 1680 (CO), 1550, 1520, 1240, 1155, 1145, 870, 785, 660	84JHC785
2-Ac-(22)	KBr	1655 (CO), 1550, 1515, 1260, 1195, 885, 800	84JHC785
2-CN-(22)	KBr	2225 (CN), 1545, 1395, 1150, 880, 780, 615	84JHC785
7-Cl-(22)-N-oxide	KBr	1440, 1385, 1275 (N—O), 755	85JHC1249
7-NO ₂ -(22)-N-oxide	KBr	1560, 1510, 1350, 1335 (NO ₂), 1260 (N—O), 1200, 995, 735	85JHC1249
(24)	Neat	865 ^a /800/775	72JHC843
(25)	Neat	865 ^a	72JHC843

^a Lone aromatic H.**Figure 4** Ground state dipole moments for some pyrrolo[2,3-*b*]pyridine derivatives (1D = 3.336 × 10⁻³⁰ C m).

Polarizabilities have been determined and compared for a number of azaindole compounds. The data are summarized in Table 33 <90JPC1755>. Overall, the results show that the different structural isomers have very similar values for the polarizability (α) and the second hyperpolarizability (γ) while there are dramatic differences in the first hyperpolarizability (β). This may result from the fact that α and γ are scalar properties while β is a component of a vector.

Table 33 Polarizability of parent pyrrolopyridines.

Compound	Polarizability (atomic units)
(1)	97.0
(2)	95.9
(3)	96.2
(4)	97.9
(11)	98.4
(12)	102
6H-pyrrolo[3,4- <i>c</i>]pyridine	96.8

Source: Waite and Papadopoulos <90JPC1755>.

Dipole moments have been measured for four of the parent thienopyridines. Experimentally obtained data were similar to the predictions based upon vector addition using model compounds. The data are summarized in Table 34 <75JHC615>.

Table 34 Dipole moments for parent thienopyridines.

Compound	Dipole moment (D) ^a	
	Experimental	Calculated
(20)	2.81	2.76
(21)	2.85	2.58
(22)	1.80	1.70
(23)	2.16	2.05

Source: Klemm and Jacquot <75JHC615>.

^a 1D = 3.336×10^{-30} C m.

7.06.4 THERMODYNAMIC ASPECTS

7.06.4.1 Physical Data

7.06.4.1.1 Pyrrolopyridines

Pyrrolopyridines are commonly compared to indole, but there are a number of differences in the physical properties: pyrrolopyridines are colorless and almost odorless compounds that typically have higher melting points and greater stability in acidic or basic solutions than indole <60JCS1794, 68RCR551>. Table 35 gives melting points and pK_a data for some pyrrolopyridines. From the pK_a data it is obvious that the pyrrolopyridines are also considerably stronger bases than indole. In fact, compound (3) can be considered as a derivative of 4-aminopyridine (pK_a 9.2) containing a vinyl group in position 3.

Table 35 Physical data for pyrrolopyridine derivatives.

Compound	Melting point (°C)	pK_a	Ref.
(1)	105	4.59	60JCS1794
1-Ac-(1)	62–63	—	76JHC585
2-Me-(1)	132–133	—	72CHE594
2,3-diPh-(1)	292.5–293.5	—	59JA740
3-Vinyl-(1)	112–115 (dec)	—	92BCJ2992
4-Me-(1)	—	5.23	64JCS4063
6-Me-(1)	139–140	—	63JMC480
6-Br-(1)	192–193	—	92S661
6-Ethynyl-(1)	176–177	—	92BCJ2992
(2)	137	7.95	60JCS1794
1-Ac-(2)	124–125	—	78CHE406
2-Me-(2)	183–183.5	—	77CHE1224
2-Me-3-Ac-(2)	248–249 (dec)	—	78CHE402
2-Me-3-CO ₂ Et-(2)	209–210 (dec)	—	78CHE402
2-Ph-3-CO ₂ Et-(2)	254–255 (dec)	—	78CHE402
3-CO ₂ H-(2)	194–195 (dec)	—	78CHE406
3-Br-(2)	205–206	—	78CHE406
4-Br-(2)	188–189	—	79CHE76
(3)	112	8.26	60JCS1794
3-Me-(3)	144–145	—	69CJC2061
1-Ph-(3)	58–59	—	69TL1909
(4)	127	6.94	60JCS1794
2-Me-(4)	192–193	—	48JCS198
3-Me-(4)	227–228	—	70JCS(C)303
3-Me-2-Ph-(4)	238–239	—	81H(16)1473
3-Pyr-(4)	251–252	—	81H(16)1473

7.06.4.1.2 Furopyridines

The parent furopyridines and methyl derivatives are typically recovered as oils or low-melting solids. Physical data including boiling points and pK_a values for a variety of furopyridines are given in Table 36.

Table 36 Physical data for furopyridine derivatives.

Compound	Melting point (°C)	Boiling point	pK_a (20°C)	Ref.
(14)	—	70°C/2.5 mm Hg	0.87	71JHC735, 70BSF646
2-CHO-(14)	136.5–137	—	—	86JHC1465
2-CN-(14)	204–205	—	—	86JHC1465
2-Me-(14)	—	145°C/25 mm Hg	—	86JHC1465
3-Br-(14)	93–95	—	–0.23	84JHC725
3-CHO-(14)	121–124	—	—	86JHC1465
3-CN-(14)	127–129	—	—	86JHC1465
5-NH ₂ -(14)	85.5–87	—	—	71JHC735
(15)	—	—	5.43	82JHC1207
2-CHO-(15)	120.5–121	—	—	87JHC373
2-CN-(15)	128–130	—	—	87JHC373
2-NO ₂ -(15)	99.5–101.5	—	—	75JHC705
3-Br-(15)	133–135	—	4.54	84JHC725
3-CN-(15)	121–122	—	—	87JHC373
7-Cl-(15)	—	128–138°C/20 mm Hg	—	82JHC1207
(16)	—	79–80°C/12 mm Hg	4.11	75ACS(B)233
2-CHO-(16)	141.5–142	—	—	87JHC373
2-CN-(16)	68.5–70.5	—	—	87JHC373
3-Br-(16)	53–55	—	2.38	84JHC725
3-CN-(16)	146–147	—	—	87JHC373
3-Me-(16)	—	150°C (bath)/15 mm Hg	—	86JHC665
5-Me-(16)	—	81.5–82°C/8 mm Hg	—	75ACS(B)233
5-Me-6-Ac(16)	131.5–132.5	—	—	75ACS(B)233
5-CO ₂ H-(16)	174–176	—	—	75ACS(B)233
(17)	—	85°C/15 mm H	5.79	72BSF1442, 71JHC57
2-CHO-(17)	129.5–130	—	—	87JHC373
2-CN-(17)	63.5–66	—	—	87JHC373
3-CN-(17)	129–130	—	—	87JHC373

7.06.4.1.3 Thienopyridines

Available physical data and pK_a values for parent thienopyridines are given in Table 37 <75JHC615>.

7.06.4.2 Solubility

The pyrrolopyridines exhibit a greater solubility in water than indole <60JCS1794>. Water serves as a good recrystallization solvent for 1*H*-pyrrolo[3,2-*c*]pyridine (**3**). However, some derivatives such as 1-phenylpyrrolo[3,2-*c*]pyridine are water insoluble, but are readily soluble in organic solvents such as benzene, acetone, ethyl acetate, alcohols, and chloroform <70CHE23>. 2-Methyl-1*H*-pyrrolo[2,3-*c*]pyridine is insoluble in most common organic solvents but is soluble in water and alcohols <77CHE1224>. Derivatives of pyrrolopyridines containing hydroxy, amino, or carbonyl groups tend to be soluble in polar solvents such as water and alcohols and much less soluble in typical organic solvents such as ether.

7.06.4.3 Tautomerism, Aromaticity, and Stability

7.06.4.3.1 Pyrrolopyridines

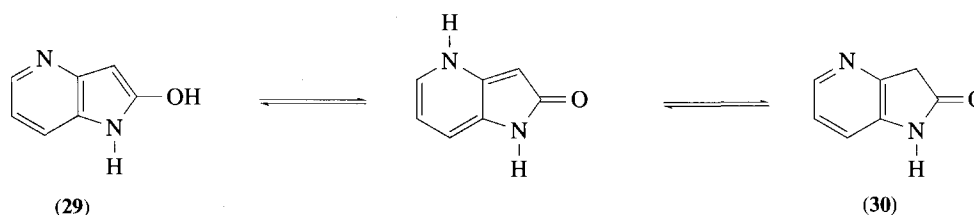
Prototropic tautomerism is observed in the pyrrolopyridines. As a consequence, the endocyclic bond angle centered on the five-membered ring nitrogen closes while the endocyclic bond angle

Table 37 Physical properties of thienopyridine derivatives.

Compound	Melting point (°C)	Boiling point	pK _a	Ref.
(20)		49–50°C/0.15 mm Hg	2.75	75JHC615
2-CO ₂ H-(20)	311–312	—	—	76JHC273
3-Br-(20)	61–62	—	—	72JHC843
3-CN-(20)	103–103.5	—	—	72JHC843
3-Ac-(20)	118–119.5	—	—	72JHC843
3-CHO-(20)	108–108.5	—	—	74JHC355
4-NH ₂ -(20)	—	—	6.41	73MI 706-01
5-NH ₂ -(20)	—	—	3.43	73MI 706-01
6-CN-(20)	116–117.5	—	—	83JHC213
(21)	—	—	5.58	75JHC615
7-CN-(21)	113–115	—	—	84JHC1119
(22)	—	107–108°C/10 mm Hg	4.35	75JHC615, 75ACS(B)233
2-CHO-(22)	134–135	—	—	84JHC785
2-CN-(22)	110–111	—	—	84JHC785
2-I-(22)	127–128	—	—	84JHC785
5-CO ₂ H-(22)	201.5–202	—	—	75ACS(B)233
5-Me-(22)	—	114.5–116.5°C/8 mm Hg	—	75ACS(B)233
(23)	—	—	5.67	75JHC615
(25) picrate	234–235 dec.	—	—	72JHC843

centered on the six-membered ring opens by approximately the same amount. Furthermore, the C—N bonds shorten for both five- and six-membered rings, while the C(8)—C(9) (ring fusion) bond lengthens. The changes in the bond angle result from the conversion of a σ -bonding orbital to a σ -lone pair orbital for the five-membered ring nitrogen, and the σ -lone pair orbital converting to a σ -bonding orbital for the six-membered ring nitrogen. As a result of the prototropic tautomerism, a significant migration of charge is observed from the six- to the five-membered ring, concentrated on N-1 and C-3 (see Figure 1, Section 7.06.2.1). The mesomeric structures, such as those shown in Figure 1 for compound (12), contribute significantly to the structures of the tautomers (see Table 14 and Section 7.06.2.1). This is confirmed by changes in the dipole moments from the parent compounds to the tautomeric forms (see Sections 7.06.2.1 and 7.06.3.6). For the unsubstituted parent pyrrolopyridines, the equilibrium lies clearly in favor of the normal form, (1), (2), (3), or (4), rather than tautomers (12), (11), (9), and (8), respectively <83T2851>.

The question of tautomerism for 2-hydroxy-1*H*-pyrrolo[3,2-*b*]pyridine (29) has been addressed. In protic solvents, (29) and the other two tautomers shown in Scheme 4 have been detected by UV spectroscopy, whereas in the crystalline form tautomer (30) predominates <72JOC51, 74JCS(P1)1531>.

**Scheme 4**

For the corresponding 1*H*-2-hydroxypyrrolo[2,3-*c*]pyridine isomer, a mixture of both lactam and lactim forms has been observed in solution as well as in the crystalline state. It is interesting to note that the lactam tautomer predominates for 1*H*-2-hydroxy-3-ethoxycarbonylpyrrolo[2,3-*c*]pyridine, whereas the lactim form is the major tautomer for the corresponding pyrrolo[3,2-*b*]pyridine derivative <74JCS(P1)1531>. Similarly, for 1*H*-6-hydroxypyrrolo[2,3-*b*]pyridine, both lactam and lactim tautomers are present in solution and the crystalline states <66T3233>. For the 2-hydroxy derivative of compound (3), both IR and ¹H NMR spectroscopy indicate that approximately equal amounts of the alcohol and carboxyl derivative are present <77CHE1224>.

7.06.4.3.2 Thienopyridines

Tautomerism for amino and hydroxy substituents of thienopyridines has been considered <77AHC(21)65>. 4-Hydroxythieno[2,3-*b*]pyridine exists in the enol form whereas the analogous 4-

hydroxyquinoline derivative predominates in the keto form. In the amino series, the tautomeric forms of derivatives of thieno[2,3-*b*]pyridine (**20**) and the analogous quinoline both exist as the amino tautomers, as opposed to the imino form. 3-Amino[2,3-*b*]thienopyridine decomposes slowly upon exposure to air <77JHC299>.

7.06.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.06.5.1 Electrophilic Attack at Nitrogen

7.06.5.1.1 Pyrrolopyridines

(i) Acylation and alkylation

Pyrrolopyridines undergo facile acylation at the pyrrole nitrogen when treated with an acid anhydride or an acid chloride in pyridine. The acylated derivatives are hydrolyzed in water or under alkaline conditions but they are more stable under acidic conditions <68AHC(9)27>.

Quaternization of pyrrolopyridines at the pyridine nitrogen center occurs readily with methyl bromide. Treatment of the methiodide derivative of compound (**1**) with sodium hydroxide gives a free base which can be further reacted with methyl iodide at the pyrrole nitrogen center <55JA6554>.

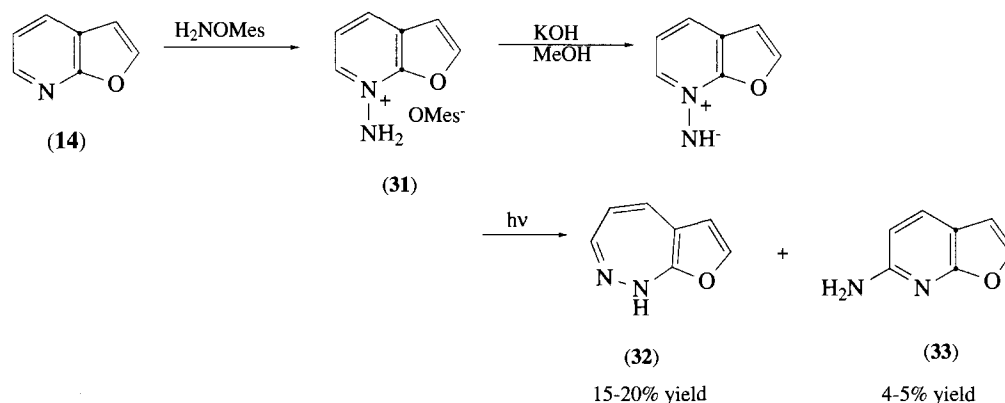
(ii) N-Amination

Treatment of 1*H*-pyrrolo[2,3-*b*]pyridine (**1**) with mesitylenesulfonylhydroxylamine resulted in *N*-amination of the pyridine nitrogen in high yields. Upon addition of a base such as potassium hydroxide the ylide which formed rapidly underwent tautomerization to give 7-amino-7*H*-pyrrolo[2,3-*b*]pyridine in nearly quantitative yields. For some substituted derivatives, which did not undergo tautomerism, diazepines were formed upon irradiation. The diazepines were too unstable to be isolated <79CPB2183> (see Section 7.06.5.1.2).

7.06.5.1.2 Furopyridines

(i) N-Amination

Furo[2,3-*b*]pyridine was aminated in good yield by treatment with *O*-mesitylenesulfonylhydroxylamine to afford furo[2,3-*b*]pyridinium mesitylenesulfonate (**31**). Treatment with methanolic potassium hydroxide forms an ylide *in situ* which, upon irradiation, generated furo[2,3-*c*]1*H*-1,2-diazepine (**32**) and a minor amount of 2-aminofuro[2,3-*b*]pyridine (**33**) (Scheme 5). This material gradually decomposes on standing <78H(9)621, 79CPB2183>.



Scheme 5

7.06.5.2 Electrophilic Attack at Carbon

7.06.5.2.1 Pyrrolopyridines

Electrophilic substitution reactions of compound (1) typically occur at the 3-position of the ring (see Section 7.06.2.1.1). A great variety of electrophilic substitution reactions have been carried out on isomers of the parent pyrrolopyridines and their derivatives. For compound (1), substituents at positions 1 and 6 influence the ease of electrophilic substitution reactions by changing the electron density at position 3 and by altering the ability to protonate at the pyridine nitrogen. When electron-withdrawing groups are placed at position 1 electrophilic substitution reactions are slowed down, whereas when electron-donating groups are placed in position 1 the electrophilic substitution reactions proceed more smoothly <68RCR551>.

(i) Nitration

Pyrrolopyridines readily undergo mononitration in excess fuming nitric acid at 0°C <55JA457, 59JA743> affording very high yields of the corresponding 3-nitro derivatives as shown in Table 38. A comparative study of the kinetics of the nitration of 4-methylpyrrolo[2,3-*b*]pyridine and compounds (2)–(4) was carried out <79CHE1195> in concentrated sulfuric acid solvent at –10 to 0°C. Results of the study indicate that the nitration proceeds most rapidly for the isomer (3) followed by 4-methylpyrrolo[2,3-*b*]pyridine. Nitration proceeds fairly slowly for compounds (2) and (4). When the 3-position of a pyrrolopyridine derivative is blocked, nitration is sometimes observed at the 2-position of the ring, as shown by 3-phenyl-4-methylpyrrolo[2,3-*b*]pyridine <69JCS(C)1505>.

Table 38 Nitration of pyrrolopyridine derivatives.

Compound	Product	Yield (%)	Ref.
(1)	3-NO ₂ -(1)	83	59JA743
(3)	3-NO ₂ -(3)	99	59JA743
(4)	3-NO ₂ -(4)	99	59JA743
<i>N</i> -Benzoyl-2,5-diMe-(4)	3-NO ₂ -2,5-diMe-(4)	51	50JCS2952

(ii) Halogenation

Unlike the violent bromination of pyrrole or indole, which leads to polybrominated products, the bromination of pyrrolopyridines proceeds readily to a monobrominated product. Table 39 lists some of the pyrrolopyridine derivatives that have been brominated. Common solvents for these bromination reactions are chloroform, dioxane, or acetic acid.

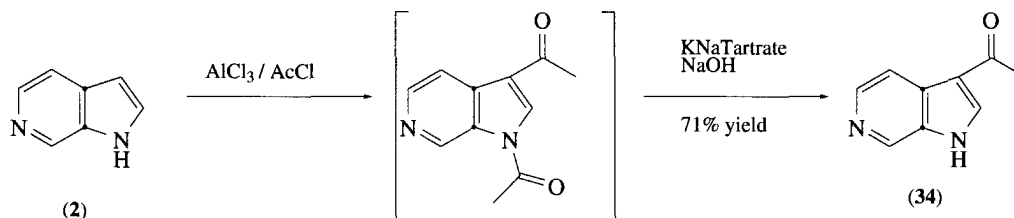
Table 39 Halogenation of 1*H*-pyrrolo[2,3-*b*]pyridines.

Compound	Product	Yield (%)	Ref.
(1)	3-Br-(1)	81	56JA1247
4-Me-(1)	3-Br-4-Me-(1)	82	65JOU2072
4-Me-6-Cl-(1)	3-Br-4-Me-6-Cl-(1)	82	65JOU2072
4-Me-6-MeO-(1)	3-Br-4-Me-6-MeO-(1)	71	65JOU2072

Bromination of pyridoindoles has been successfully carried out using an NBS and silica gel brominating system. Depending on the reaction stoichiometry, mono-, di-, or polybromination can be achieved. However, poor selectivity is observed for some of the derivatives <92T7479>.

(iii) Acylation

In spite of the fact that indoles do not undergo acylation at the pyrrole ring carbon atom under typical Friedel–Crafts acylation conditions, the pyrrolopyridines can be successfully acylated in this manner. 3-Formylation is the most useful acylation reaction of pyrrolopyridines <68AHC(9)27>. Scheme 6 shows the acylation of compound (2), which afforded 3-acetylpyrrolo[2,3-*c*]pyridine (34) in 71% yield <79CHE69>.



Scheme 6

Several different methods for the acylation of 1*H*-pyrrolo[2,3-*b*]pyridine (1) have been reported <82JHC665> and the results are summarized in Table 40. When reaction conditions which gave a 90% yield for the acylation of indole were tested on compound (1), an excellent yield (91%) of 1-acetylpyrrolo[2,3-*b*]pyridine was obtained <52JCS3592>. Other acylation methods afforded the 3-acyl derivative as the major product.

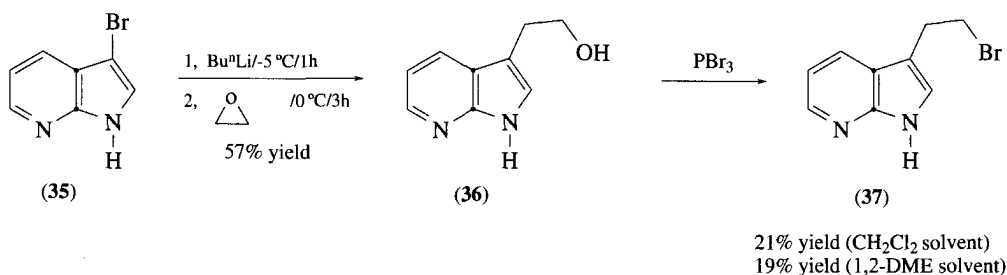
Table 40 Acylation of 1*H*-pyrrolo[2,3-*b*]pyridine (1).

Acylation reagents	Product (%)	
	1-Acetyl	3-Acetyl
<i>N,N</i> -Dimethylacetamide/ POCl_3	11	—
$\text{Ac}_2\text{O}/\text{AcOH}$	90	—
$\text{Ac}_2\text{O}/\text{AlCl}_3$	2	90
$\text{ClCH}_2\text{COCl}/\text{AlCl}_3$	—	81

Source: Galvez and Viladoms <82JHC665>.

(iv) Alkylation

Alkylation of compound (1) to give 1-(2-hydroxyethyl)pyrrolo[2,3-*b*]pyridine was achieved in 71% yield using fairly drastic conditions: heating the reactants with aluminum chloride in carbon disulfide at 50°C for 30 min. To carry out alkylation at the 3-position of the pyrrole ring, a regiospecific alkylation was done via metallation of 3-bromopyrrolo[2,3-*b*]pyridine (35), giving the 1,3-dianion <84JHC421>. In this manner, 3-(2-hydroxyethyl)pyrrolo[2,3-*b*]pyridine (36) was obtained in 57% yield. Further reaction to the bromo derivative (37) was carried out as outlined in Scheme 7.

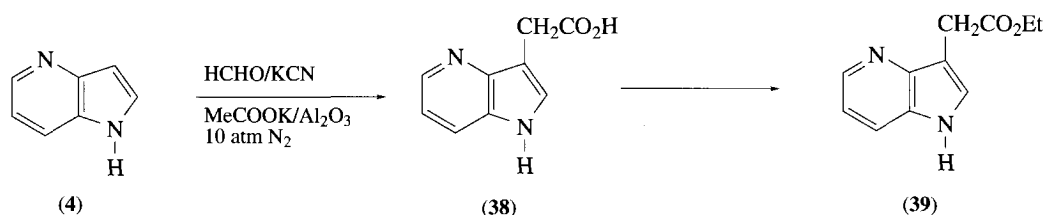


Scheme 7

An alternative route to the bromo or chloro derivative is derived from aluminum chloride–lithium aluminum hydride reduction of the corresponding 3-bromo- or 3-chloroacetylpyrrolo[2,3-*b*]pyridine (see Section 7.06.5.2.1(iii)) <82JHC665, 84JHC421>.

(v) *Cyanomethylation*

Cyanomethylation of compounds (3) and (4) was carried out using formaldehyde/potassium cyanide in aqueous ethanol at elevated pressures in the presence of potassium acetate and alumina. Under the conditions of the reaction and subsequent workup, the cyanomethylated products were converted into acetic acid derivatives (e.g., (38)) and isolated as ethyl ester derivatives (e.g., (39)) (Scheme 8) <69TL1909>. No nitrile-containing products were isolated.



Scheme 8

(vi) *Mannich reactions*

The Mannich reaction proceeded in nearly quantitative yield for the pyrrolopyridines (1) and (4). A somewhat lower yield was obtained from the isomer (3). A number of derivatives of compound (1) have also been subjected to the Mannich reaction. The typical reaction conditions include treatment with excess paraformaldehyde and dimethylamine hydrochloride in butanol. Results are summarized in Table 41 <69TL1909>.

Table 41 Mannich reactions of pyrrolopyridine derivatives.

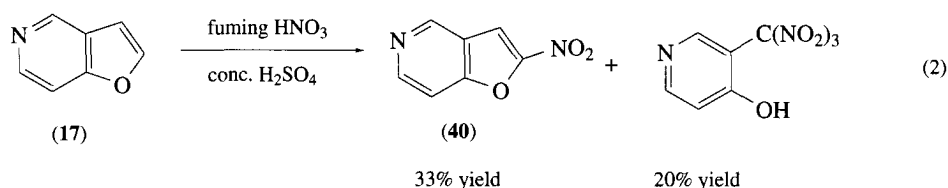
Compound	Mannich reaction product	Yield (%)	Ref.
(1)	3-Dimethylaminomethyl-(1)	99	69TL1909
1-Ph-4-Me-(1)	1-Ph-4-Me-3-Dimethylaminomethyl-(1)	72	64JGU2626
1-Bu-4-Me-(1)	1-Bu-4-Me-3-Dimethylaminomethyl-(1)	64	66KGS74
6-Cl-4-Me-(1)	6-Cl-4-Me-3-Dimethylaminomethyl-(1)	60	65JOU2072
4-Me-(1)	4-Me-3-Dimethylaminomethyl-(1)	28	65JOU2072
(3)	3-Dimethylaminomethyl-(3)	53	69TL1909
(4)	3-Dimethylaminomethyl-(4)	99	69TL1909

7.06.5.2.2 Fuopyridines

(i) *Nitration*

Nitration of fuopyridines (e.g., (17)) with fuming nitric acid and sulfuric acid led to a mixture of products as illustrated in Equation (2). The products include partially reduced products and ring-opened products as well as some aromatic derivatives <75JHC705, 84JHC725>. Nitration of compound (17) occurred in a mixture of fuming nitric and sulfuric acids below 0°C to afford the corresponding 2-nitro derivative (40) in 33% yield. Repeating the reaction in a weaker nitrating system with acetic anhydride and nitric acid resulted in recovery of starting material. Since the fuopyridine is

protonated in an acidic system, the furan ring is deactivated for further electrophilic attack and nitration does not occur in the weaker nitrating system <75JHC705>.



(ii) Halogenation

Halogenation of furopyridines using bromine affords either 2,3-dihydro-2,3-dibromofuropyridines or unstable perbromides depending on the reaction stoichiometry. Bromination with larger excesses of bromine leads to the more stable dibromo products. Dehydrobromination of the dibromo derivatives gives monobromo products. Bromination results are summarized in Table 42 <75JHC705, 84JHC725>.

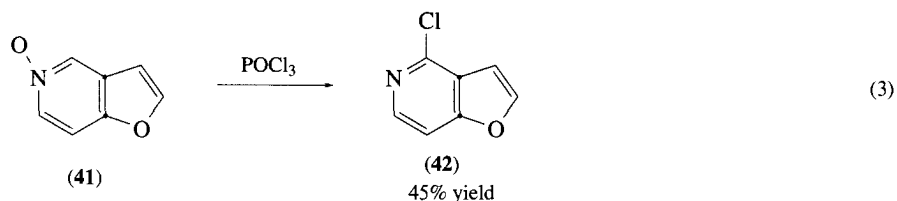
Table 42 Bromination of furopyridines.

Compound	Reagents	Product (% yield) ^a
(14)	1.2 mol Br ₂ /CCl ₄	<i>trans</i> -2,3-dibromo-2,3-dihydro-(14) (95)
(15)	1.2 mol Br ₂ /CCl ₄	(15)-perbromide
(15)	3 mol Br ₂ /CCl ₄	(15)-perbromide, <i>trans</i> -2,3-dibromo-2,3 dihydro-(15)
(16)	1.2 mol Br ₂ /CCl ₄	(16)-perbromide
(16)	3 mol Br ₂ /CCl ₄	<i>trans</i> -2,3-dibromo-2,3-dihydro-(16) (92)
(17)	1.2 mol Br ₂ /CCl ₄	(17)-perbromide
(17)	3 mol Br ₂ /CCl ₄	(17)-perbromide

Sources: McFarland *et al.* <75JHC705>, Shiotani *et al.* <84JHC725>.

^aPoor yields or unstable products (not isolable) were obtained in most reactions.

Treatment of furo[3,2-*c*]pyridine *N*-oxide (41) with phosphorus oxychloride accomplished deoxygenation along with chlorination of the ring to afford 4-chlorofuro[3,2-*c*]pyridine (42) (Equation (3)) in 45% yield <75JHC705>.



(iii) Acylation

No examples of successful acylation of furopyridine derivatives have been found in the literature. The attempted acylation of compound (17) was unsuccessful in either acetyl chloride/aluminum chloride or acetic anhydride/BF₃ etherate acylating systems <75JHC705>. Acylation via the *N*-oxide was also unsuccessful, resulting in deoxygenation to the parent furopyridine.

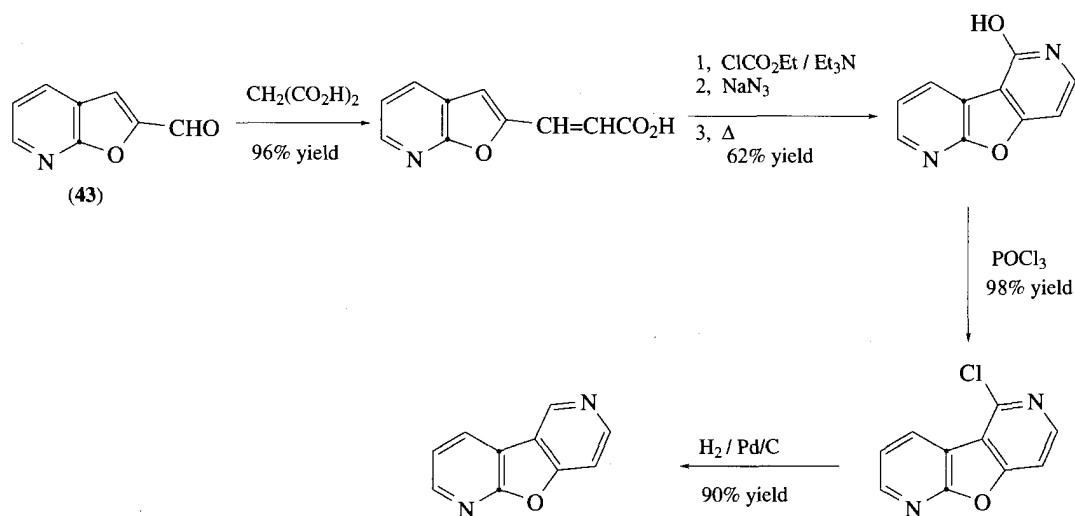
(iv) Deuteration

Compound (16) undergoes deuteration at C-3 at a fairly low reaction rate <78JCS(P2)861>. Another study examined the H-D exchange of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]-, and furo[3,2-*c*]pyridine in acidic media. After 9 h at 85°C, all compounds showed significant exchange of H-3 without noticeable changes to other hydrogen intensities. The H-D exchange of H-3 was completed to 54%,

70%, 95%, and 87% for the four isomers, respectively. The H-D exchange patterns were also examined for these compounds under conditions where proton abstraction would occur from the neutral molecule. In this system, exchange occurred at H-2. After 1.5 h, the exchange of H-2 was completed to 61%, 68%, 90%, and 68% for the four isomers, respectively, with slight exchange (5–20%) observed for H-3 <84JHC725>.

(v) *Condensation reactions*

Tricyclic derivatives of furopyridines have been prepared starting from 2-formyl derivatives of the corresponding furopyridines by the sequence shown in Scheme 9 for the furo[2,3-*b*]pyridine derivative (43) <90JHC637>.



7.06.5.2.3 Thienopyridines

(i) *Nitration*

Direct nitration of compounds (20) and (22) are straightforward reactions, with preferential electrophilic substitution occurring at C-3. The nitration proceeded in yields of approximately 50% using a mixed nitric/sulfuric acid system <70JHC373>.

(ii) *Halogenation*

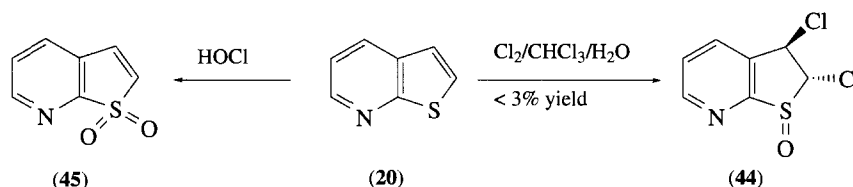
Depending on the reaction conditions, halogenation of thieno[2,3-*b*]pyridine (20) can lead to a variety of products resulting from substitution, addition, and oxidation reactions. 2,3-Dibromo-thieno[2,3-*b*]pyridine is produced by the reaction of compound (20) with bromine in an aqueous carbon tetrachloride system and the 2,3-dichloro-2,3-dihydro derivative is formed from the same starting material upon treatment with chlorine in chloroform/water or with iodobenzene dichloride in aqueous acetonitrile <70JHC81, 71JHC931>.

Monohalogenated products are obtained by treatment of this heterocycle (20) with elemental halogens (bromine, chlorine, or iodine) in concentrated sulfuric acid containing silver sulfate. This acidic reaction medium aids electrophilic attack by the positive halogen species on a protonated thienopyridine. Subsequently, nonacidic conditions have been identified for the monobromination reaction <74JHC205>. Monobromination of the isomers (21) and (23) has also been reported <70AK(32)249>.

7.06.5.3 Electrophilic Attack at Sulfur

7.06.5.3.1 Thienopyridines

In addition to chlorination, *S*-oxidation of compound (20) occurred using elemental chlorine or chlorine-bearing reagents. The oxidized products, 2,3-dichloro-2,3-dihydrothieno[2,3-*b*]pyridine 1-oxide (44) and thieno[2,3-*b*]pyridine 1,1-dioxide (45) were formed in variable yields depending on the reaction conditions (Scheme 10) <74JHC535>.



Scheme 10

7.06.5.4 Nucleophilic Attack at Carbon

7.06.5.4.1 Pyrrolopyridines

Few examples of nucleophilic substitution reactions have been reported for pyrrolopyridines. This is not unexpected since this type of reaction is also difficult for pyrroles and indoles. The pyrrole ring deactivates the pyridine ring toward attack by nucleophiles. From an analysis of the charge distribution in structure (1), nucleophilic substitution should occur most readily at either position 4 or position 6 (in the pyridine ring) <68RCR551>. Compound (1) was subjected to the conditions of the Chichibabin amination reaction: upon treatment with sodium amide in several different solvents, only starting materials or decomposition products were obtained <59JA743, 73CHE1119>.

To enhance the reactivity of the pyridine ring of the pyrrolopyridine, the 1*H*-pyrrolo[2,3-*b*]pyridine *N*-oxide (46) has been prepared. Regioselective functionalization of the 6-position of the pyrrolopyridine ring was made possible in this manner. Halogen atoms, cyano groups, and thiocyanato groups have been introduced into the 6-position of 1*H*-pyrrolo[2,3-*b*]pyridine *N*-oxide (46) via a Reissert–Henze salt. The halogenation reactions are summarized in Table 43. Under these reaction conditions acylation also occurred at the pyrrole ring nitrogen, but this substituent can easily be removed by base treatment. When trimethylsilyl cyanide (in place of hexamethyldisilazene) and benzoyl chloride were used, cyanation also occurred at C-6, along with chlorination (Equation (4)). When methyl chloroformate was used, no cyanation was observed. When trimethylsilyl isothiocyanate was used along with hexamethyldisilazene, thiocyanate substitution occurred along with chlorination at C-6 (Equation (5)). No evidence for the isothiocyanate derivative was found in the reaction <92S661>.

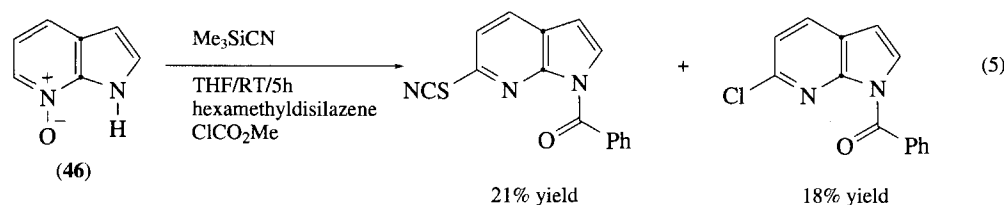
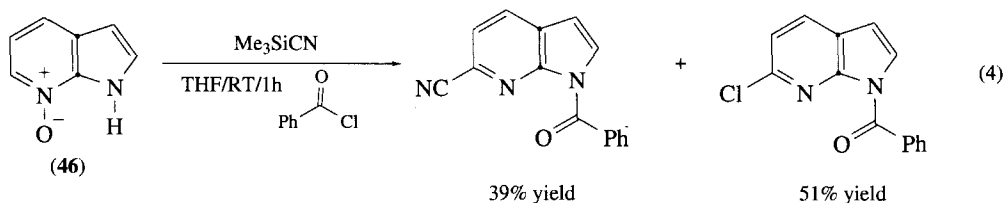
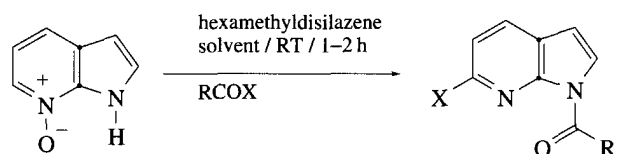
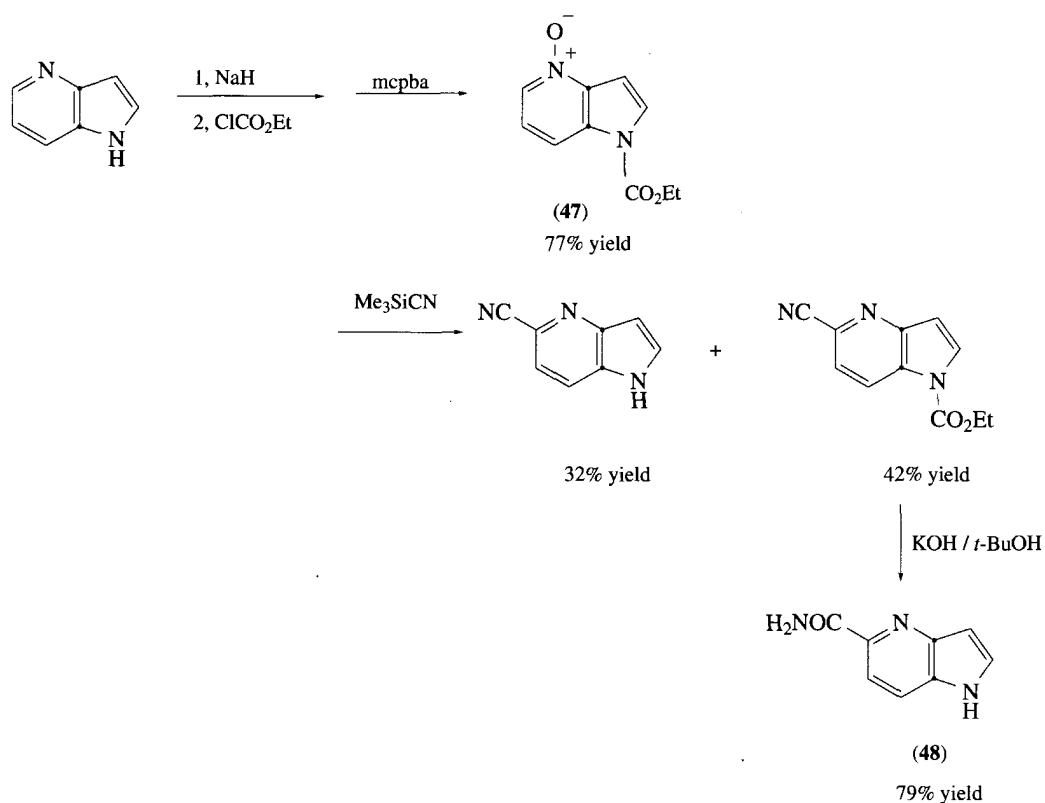


Table 43 Halogenation of 1*H*-pyrrolo[2,3-*b*]pyridine *N*-oxide.

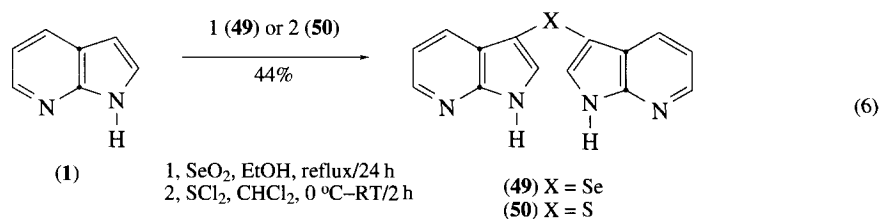
<i>X</i>	<i>R</i>	<i>Solvent</i>	<i>Yield (%)</i>
Cl	OMe	THF	66
Cl	Ph	Benzene	60
Br	Ph	Benzene	57

Source: Minakata *et al.* (92S661).

1*H*-Pyrrolo[3,2-*b*]pyridine *N*-oxide (**47**) was prepared as an intermediate in a route to the 5-carboxamido derivative (**48**) (Scheme 11) (92JHC1465).

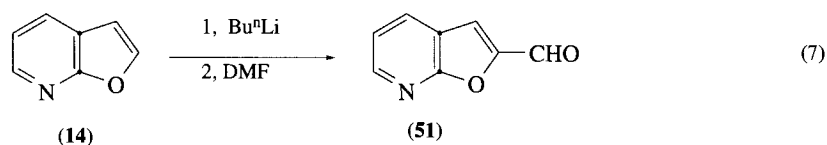
**Scheme 11**

Compound (**1**) reacted with selenium dioxide to afford the disubstituted selenium derivative (**49**). Nucleophilic attack at the pyrrolopyridine C-3 atom by diethyl selenite, generated from selenium dioxide and ethanol, afforded the product (**49**) in 44% yield (Equation 6). An analogous reaction was carried out using sulfur dichloride to give the thio derivative (**50**) (44%). Both reactions are shown in Equation (6) (92BCJ2992).



7.06.5.4.2 Furopyridines

A variety of metallation reactions have been carried out on furopyridines. Lithium derivatives are most commonly formed. Metallation of compound (14) using *n*-butyllithium followed by reaction with DMF afforded the 2-formyl derivative (51) (Equation (7)).



Metallation of furo[3,2-*c*]pyridines with *t*-butyllithium followed by treatment with DMF or DMA (dimethylacetamide) generated fair yields of the 2-carboxy derivatives. Data are summarized in Table 44 <83T1777>.

Table 44 Metallation of furo[3,2-*c*]pyridines.

Compound	Amide reagent	Product	Yield (%)
4-Cl-(17)	DMF	4-Cl-2-CHO-(17)	65
4-Cl-(17)	DMA	2-Ac-4-Cl-(17)	69

Source: Bisagni *et al.* <83T1777>.

7.06.5.4.3 Thienopyridines

Similarly to the analogous reaction with furo[2,3-*b*]pyridines, metallation of compound (20) with *n*-butyllithium in TMEDA followed by the addition of DMF afforded the 2-formyl derivative in 66% yield. Likewise, metallation of the isomer (22) under the same conditions afforded the 2-formyl derivative in comparable yield <84JHC785>. Introduction of a carbonyl group at C-3 of compound (20) was accomplished by halogen-metal exchange between 3-bromothieno[2,3-*b*]pyridine and *n*-butyllithium. Table 45 lists some of the thieno[2,3-*b*]pyridine derivatives formed by this method <74JHC355>.

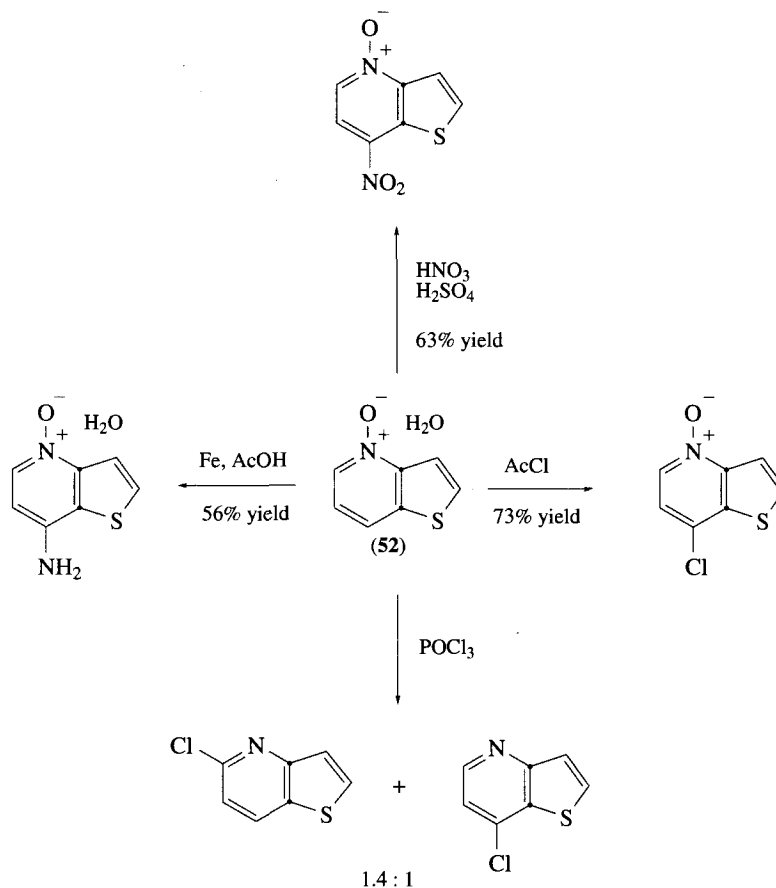
Table 45 Reactions of 3-Li-thieno[2,3-*b*]pyridine.

Reagent	Product	Yield (%)
DMF	3-CHO-(20)	77
AcCl	3-Ac-(20)	27
Ac ₂ O	3-Ac-(20)	44
ClCH ₂ COCl	3-COCH ₂ Cl-(20)	17
EtO ₂ CCl	3-CO ₂ Et-(20)	13
BzCl	3-Bz-(20)	33
PhNCO	3-CONHPh-(20)	41
Ph ₂ CO	3-C(OH)Ph ₂ -(20)	7

Source: Klemm and Merrill <74JHC355>.

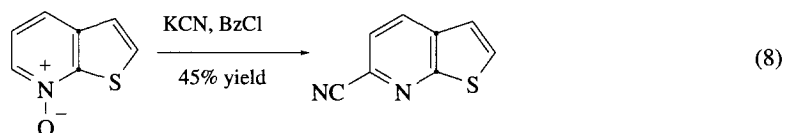
The *N*-oxidation of thieno[3,2-*b*]pyridine (22) with mcpba was carried out to afford thieno[3,2-*b*]pyridine-4-oxide. This method achieves much higher yields (83%) than the hydrogen per-

oxide/acetic acid method <71JHC931>. Nitration, halogenation, amination, and a variety of other reactions were carried out on the *N*-oxide (**52**) (Scheme 12) <85JHC1249, 90HCA763>.



Scheme 12

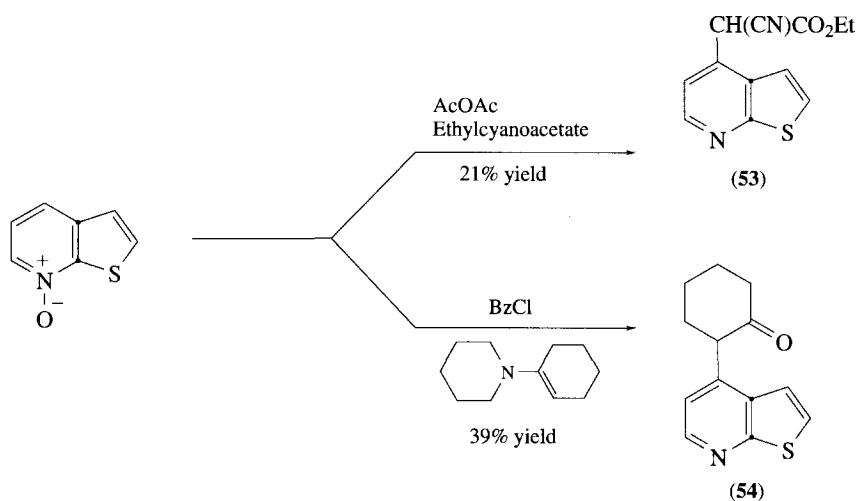
Reissert compounds have been prepared from compounds (**21**) and (**23**) using either trimethylsilyl cyanide or potassium cyanide as the cyanating agents. Yields ranged from 57% to 71% <84JHC1119, 86JHC545>. The *N*-oxides of some thieno[2,3-*b*]pyridine derivatives, as shown in Equation (8), have been used in the Reissert–Henze reaction to produce cyano-substituted products <83JHC213>.



While the Reissert reaction is a convenient method for introducing a cyano substituent into the position α to the nitrogen atom in thienopyridines, a method has been developed to introduce substituents into the position γ to the nitrogen atom. Thus, acetic anhydride/ethyl cyanoacetate or benzoyl chloride/cyclohexanone enamine reagents were useful for preparing ethyl 2-(4-thieno[2,3-*b*]pyridyl)cyanoacetate (**53**) or 2-(4-thieno[2,3-*b*]pyridyl)cyclohexanone (**54**), respectively (Scheme 13) <84JHC1135, 87JHC1467>.

7.06.5.4.4 Thienothiopyrans

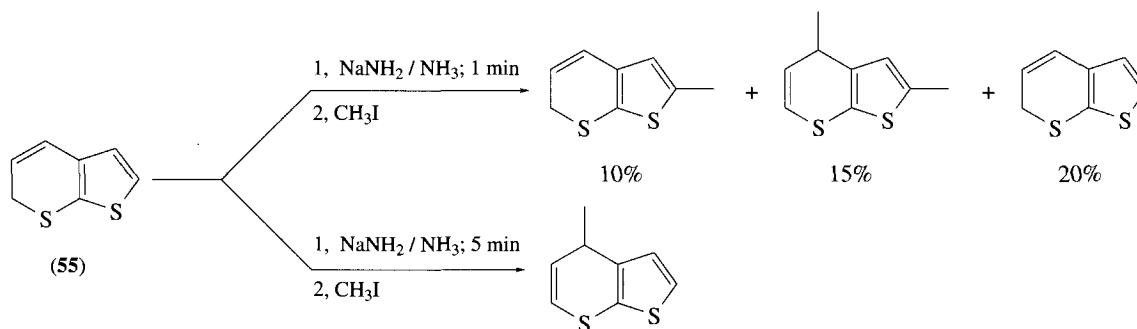
6*H*-Thieno[2,3-*b*]thiopyran (**55**) gave methylated derivatives upon treatment with sodium amide followed by methyl iodide. Depending upon reaction conditions, either a mixture of products or exclusively one isomer is formed (Scheme 14). When metallation was carried out with butyllithium,



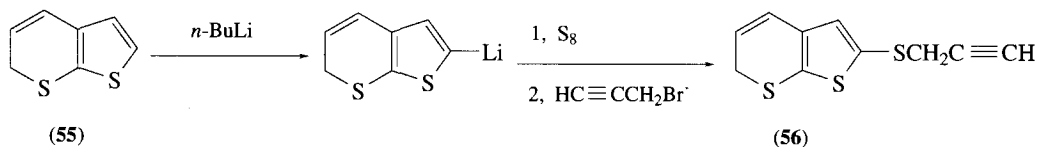
Scheme 13

the results were solvent dependent. Further methylation of the methylthienothiopyran derivatives was attempted and the results indicate that a variety of methylated or ring-opened products form, depending on reaction conditions <80RTC23>.

Compound (55) also underwent metallation with butyllithium, followed by thiolation and reaction with propynyl bromide to afford the propynyl sulfide (56) (45%) (Scheme 15) <78S578>.



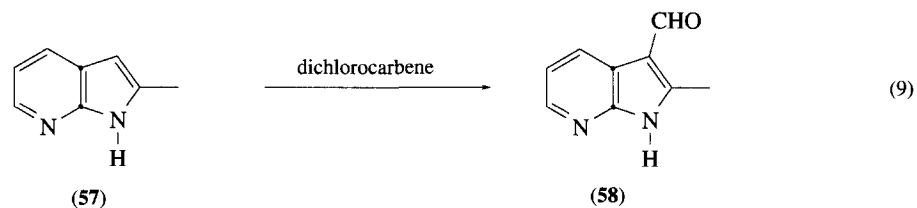
Scheme 14



Scheme 15

7.06.5.5 Reactions with Radicals and Electron-deficient Species

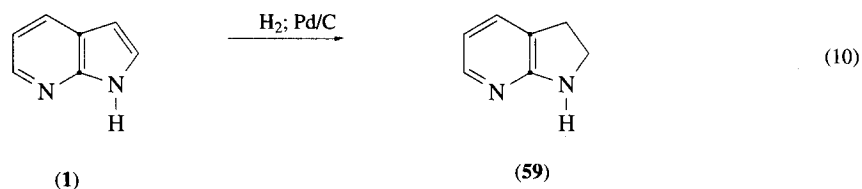
Under the conditions of the Reimer–Tiemann reaction, 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (57) gave the aldehyde (58) without any ring-expanded products (Equation (9)) <68AHC(9)27>.



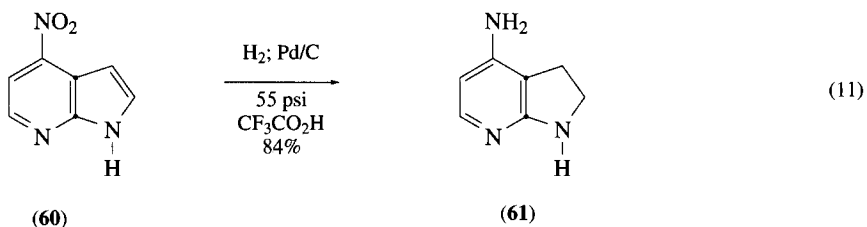
7.06.5.6 Heterogeneous Catalyzed Reactions

7.06.5.6.1 Pyrrolopyridines

Hydrogenation of compound (1) with a nickel catalyst gave the reduced pyrrolidine compound (59) <43CB128>. Partial reduction is also achieved by using a platinum catalyst under fairly mild reaction conditions (Equation (10)) <57JA2573>. Under similar conditions, compound (3) was not reduced <59JOC1008>.

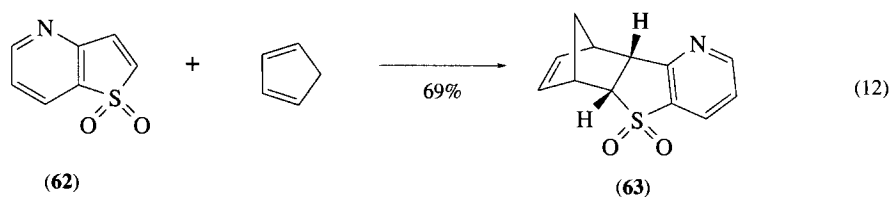


Hydrogenation of 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (60) in TFA over Pd/C resulted in reduction of the double bond at the 2,3-position in addition to conversion of the nitro group to an amine (61) (Equation (11)). This partial ring reduction occurred under fairly mild reaction conditions although earlier literature cited high pressures as being required for this transformation <82JMC1258>.

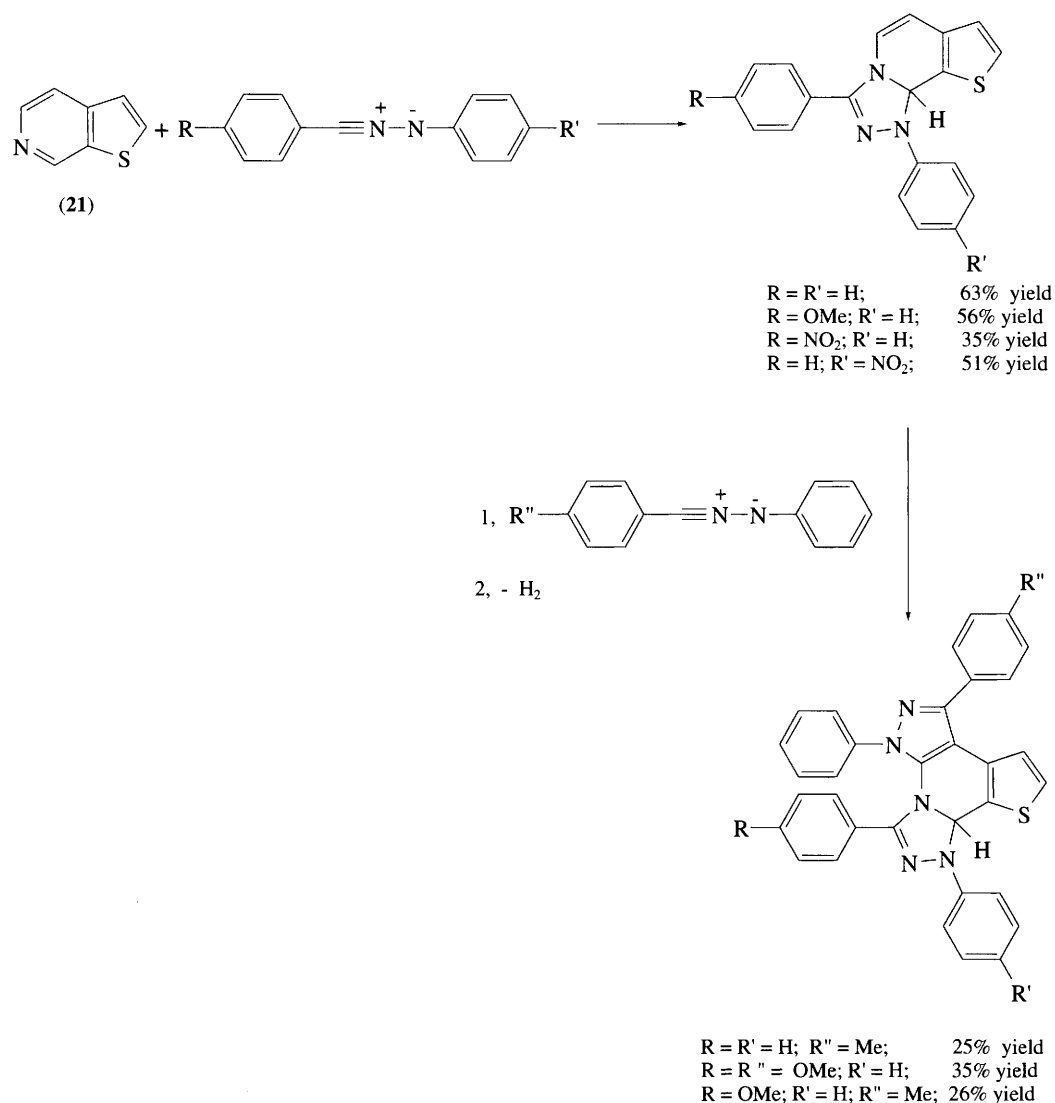


7.06.5.7 Cycloaddition Reactions

Diels–Alder reactions of thieno[2,3-*b*]- and thieno[3,2-*b*]pyridine 1,1-dioxide (62) have been carried out using cyclopentadiene, anthracene, and naphthacene as dienophiles. The *endo*-adduct (63) is produced in the reaction with cyclopentadiene (Equation (12)) <90JHC1721>.



A regiospecific cycloaddition reaction occurred between thieno[2,3-*c*]pyridine (21) and diaryl-nitrilimines as shown in Scheme 16 <87BSB145>.

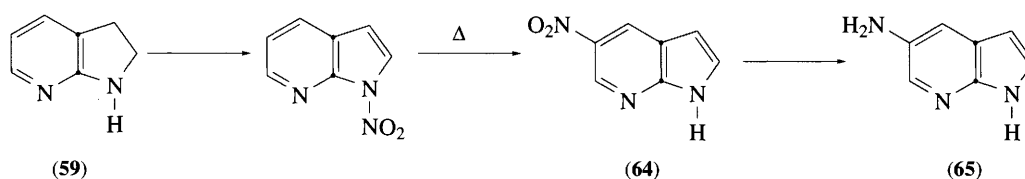


Scheme 16

7.06.6 REACTIVITY OF NONCONJUGATED RINGS

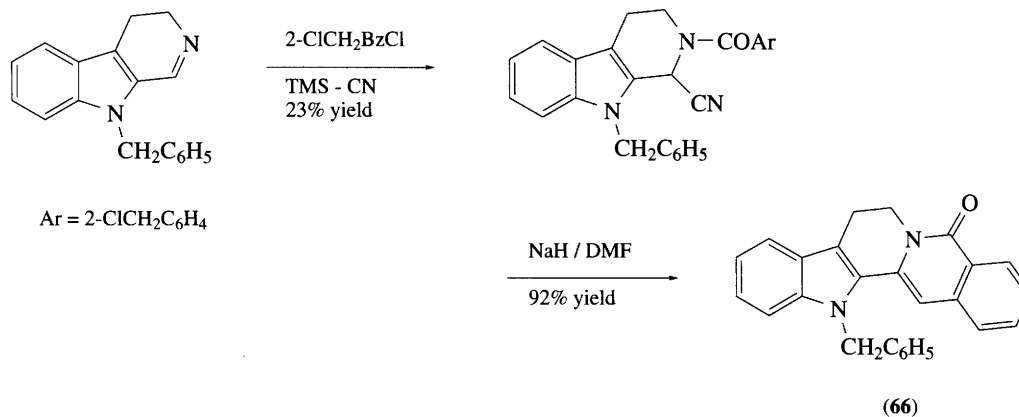
7.06.6.1 Dihydro Derivatives

Transformations involving dihydro derivatives of the pyrrolopyridines have been reported as useful methods for achieving substitution at positions of the ring that do not readily react directly. For example, substituents have been introduced into compound (59), which can be subsequently dehydrogenated to the pyrrolopyridine derivative. Scheme 17 shows that from transformations beginning with the nitration of compound (59), 5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (64) and 5-amino-1*H*-pyrrolo[2,3-*b*]pyridine (65) can be obtained <59JA743>.



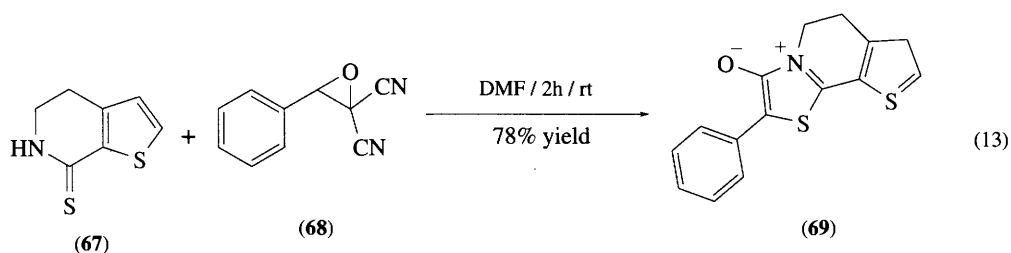
Scheme 17

Reissert compounds have been prepared from derivatives of 3,4-dihydro- β -carboline. Some of the compounds derived from these intermediates, such as the derivative (**66**), are of interest as potential intermediates in the preparation of indole alkaloid systems (Scheme 18) <81H(15)481, 81JHC909>.

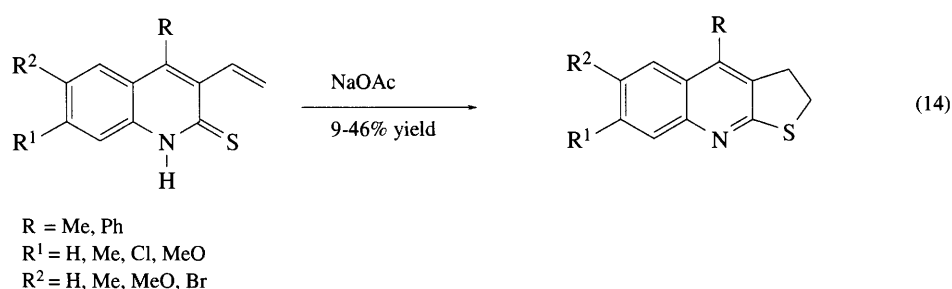


Scheme 18

Thiolactam (**67**) reacted with the epoxide (**68**) to afford the mesoionic thiazole (**69**) in 78% yield (Equation (13)) <90HCA763>.



The synthesis of dihydrothieno[2,3-*b*]quinolines has been carried out in yields ranging from 9% to 46% as shown in Equation (14) <76S595>.

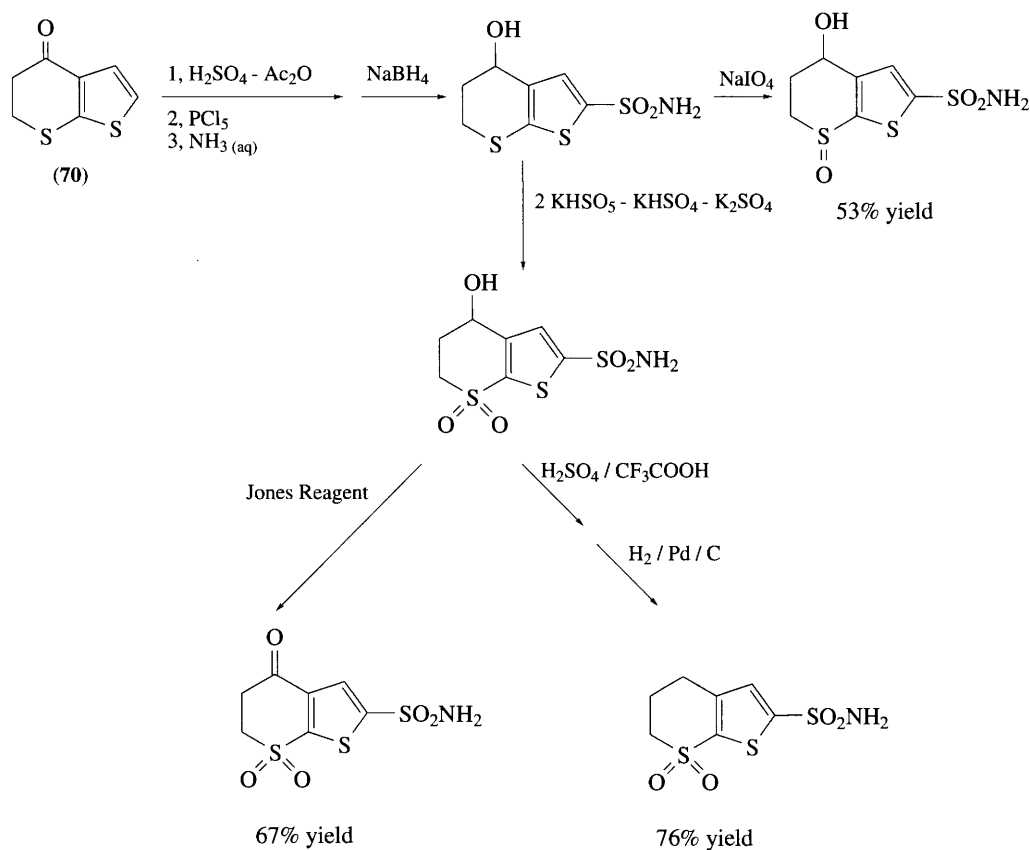


Numerous derivatives of 5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran have been prepared from the ketone (**70**) (Scheme 19). Yields ranged from 53% to 76% <87JMC591>.

7.06.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.06.7.1 Pyrrolopyridines

Some of the most useful derivatives of the pyrrolopyridines result from 3-formyl derivatives and dimethylamino products of the Mannich reaction. The carbonyl group undergoes reactions typical

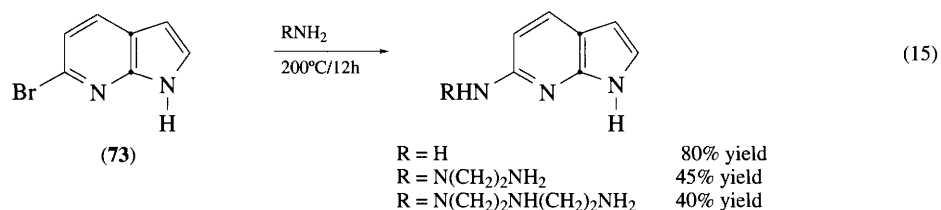


Scheme 19

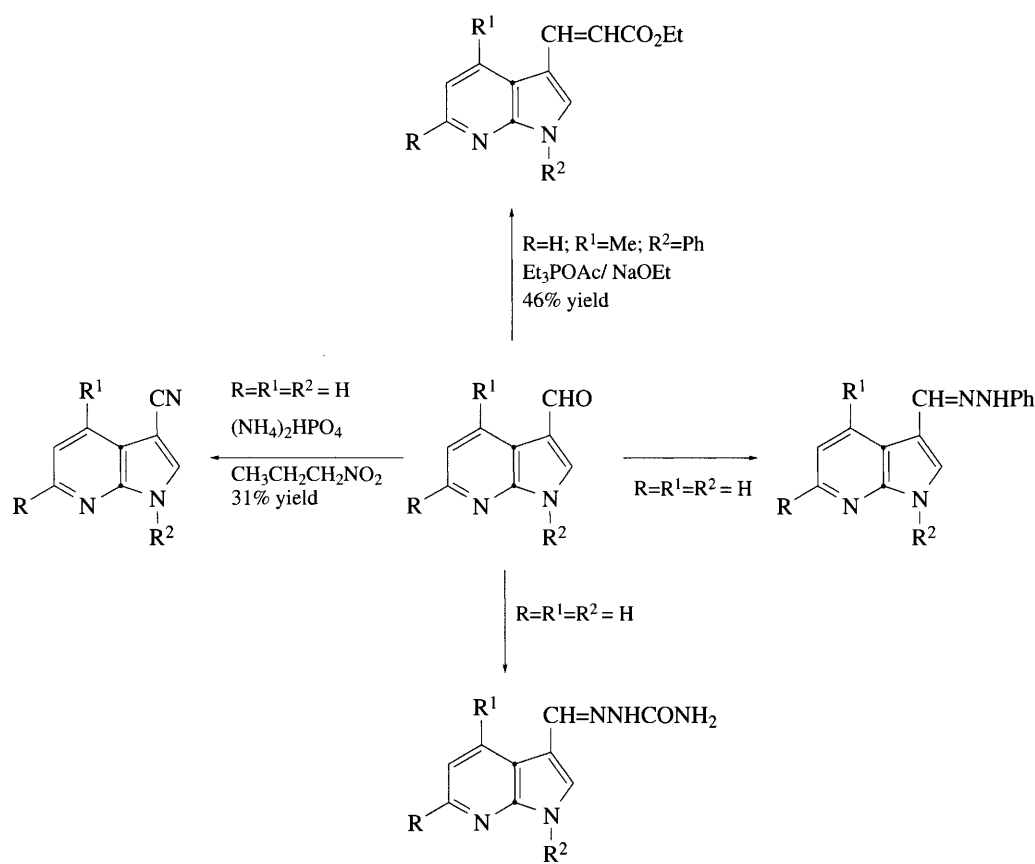
of an aldehyde such as formation of phenylhydrazones and semicarbazones $\langle 55\text{JA}457 \rangle$, reduction with sodium borohydride $\langle 64\text{JGU}2626 \rangle$, condensation with diethyl malonate $\langle 64\text{JGU}2626, 92\text{BCJ}2992 \rangle$ and the Wittig reaction $\langle 64\text{JGU}2626 \rangle$. Scheme 20 shows details of some of these reactions.

The Mannich base derived from 1*H*-pyrrolo[2,3-*b*]pyridine (71) can undergo a number of transformations and one of the most interesting is conversion to 7-azatryptophan (72) (Scheme 21), a nonnatural amino acid $\langle 68\text{AHC}(9)27 \rangle$.

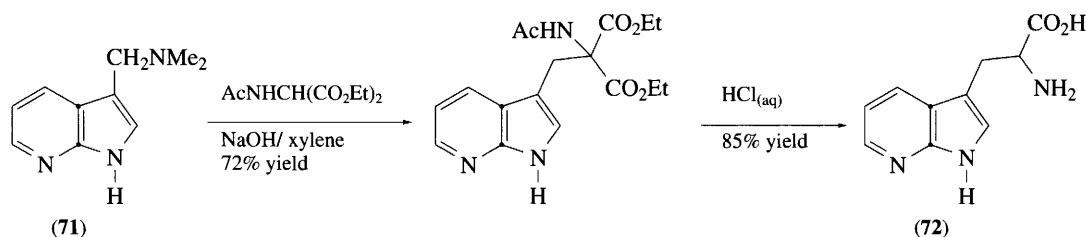
6-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (73) can be readily converted to an amino derivative in good yield using aqueous ammonia at elevated temperatures. Similarly, ethylenediamine and diethylenetriamine also reacted, though in lower yields (Equation (15)) $\langle 92\text{BCJ}2992 \rangle$. Under these conditions the 6-chloro isomer did not undergo the reaction.



Treatment of 6-chloro-4-methylpyrrolo[2,3-*b*]pyridine with methoxide ion resulted in only 39% yield of the product from chloride displacement, even under very harsh conditions (300°C). Ethynylation of the halogenated pyrrolopyridines was also carried out. The reaction was successful using compound (73), after protection of the pyrrole nitrogen, and trimethylsilylethyne. However, with unsubstituted ethyne only the iodo derivative was reactive. In this case a disubstituted ethyne derivative (74) was obtained (Scheme 22) $\langle 68\text{RCR}551 \rangle$.



Scheme 20

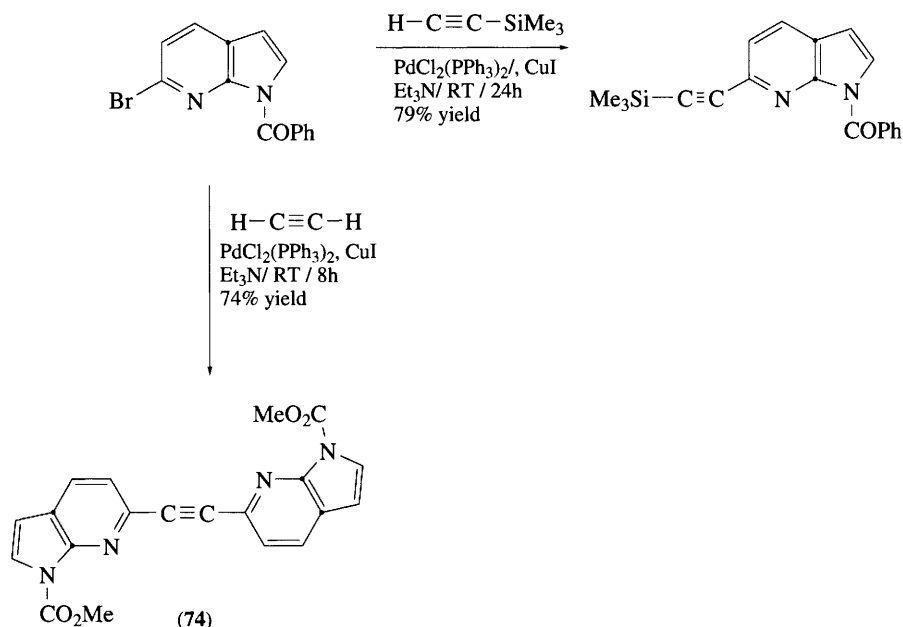


Scheme 21

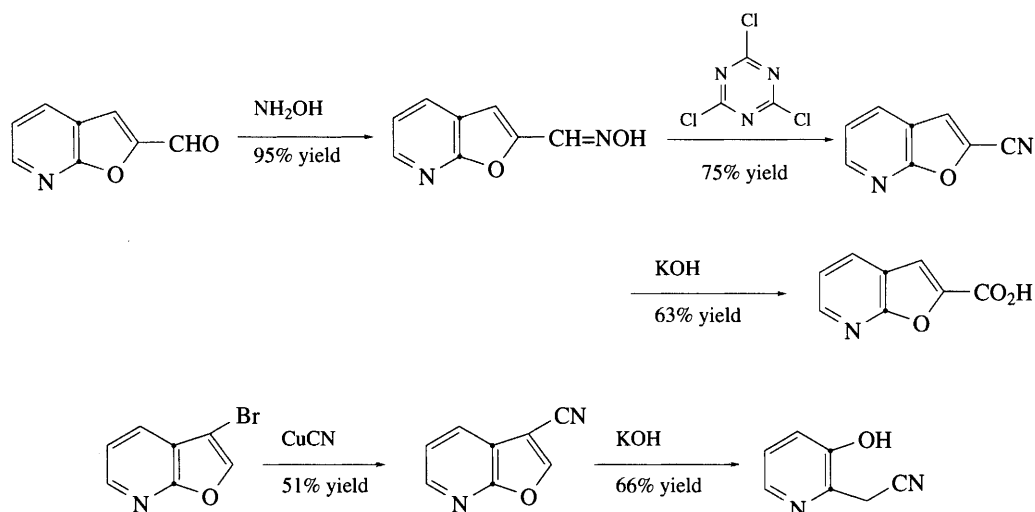
7.06.7.2 Fuopyridines

The formyl derivatives of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*], and furo[3,2-*c*]pyridines are readily converted to the 2-cyano derivatives. The 3-cyano derivatives can be prepared from the 3-bromofuopyridines by treatment with copper(I) cyanide. Because of the presence of the electron-withdrawing furan oxygen and cyano group at position C-3, the 2-position of the 3-cyano derivatives readily undergo nucleophilic attack by agents such as the hydroxide ion. The 3-cyano group is reduced to a formyl derivative by diisobutyl aluminum hydride in 82% yield. Wolff-Kishner reduction proceeded well on the 2-formyl derivatives. However, the corresponding reaction of the 3-formyl derivatives did not lead to reduction to the 3-methyl group but only to a hydrazone <86JHC1465, 87JHC373>. Alkaline hydrolysis of the 2-cyano compounds affords 2-carboxylic acids in yields ranging from 91% to 95%. Similar hydrolysis of the 3-cyanofuro[3,2-*b*]pyridine gave 2-cyanomethylpyridine-3-ol (Scheme 23); 3-cyanofuro[2,3-*c*]pyridine gave 4-cyanomethylpyridine-3-ol, and 3-cyanofuro[3,2-*c*]pyridine gave 1-[3(4-hydroxypyridyl)]-2-hydroxyacrylonitrile in much lower yields <87JHC373>.

Alkylolithium reactions of 3-bromo derivatives of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]-, and

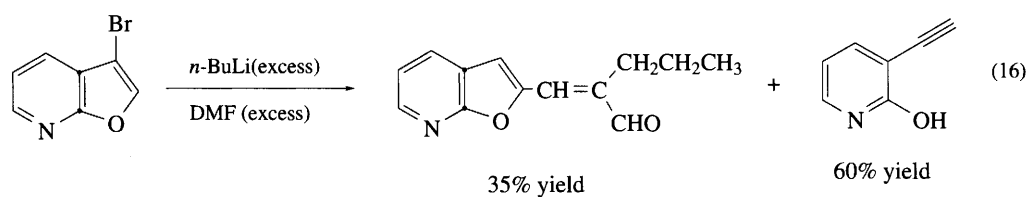


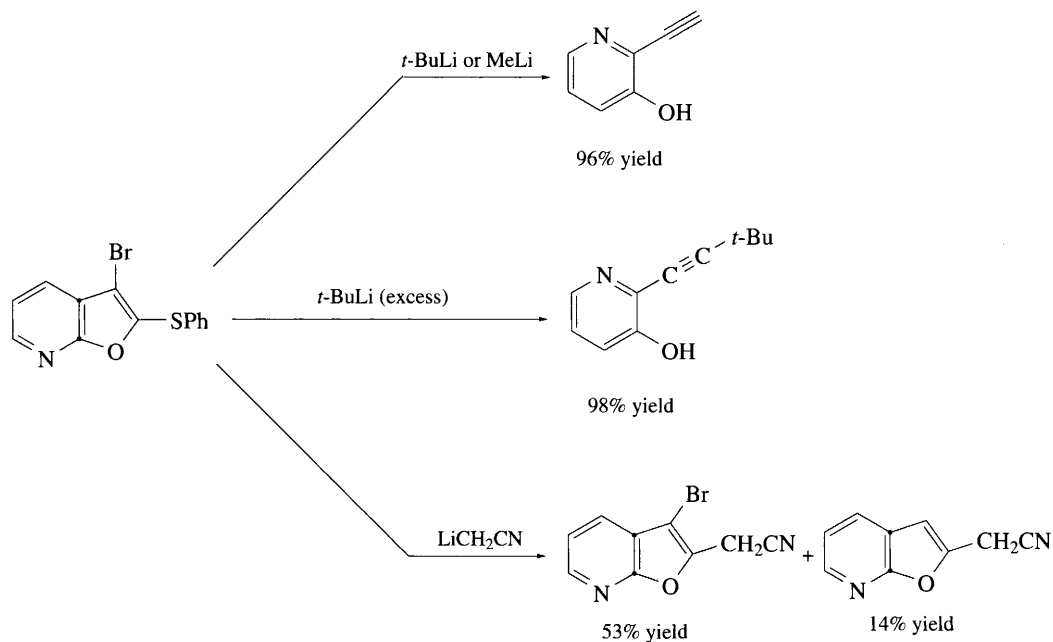
Scheme 22



Scheme 23

furo[3,2-*c*]pyridines have been investigated. Upon treatment with *n*-butyllithium or methyllithium, the parent furopyridines and *o*-ethynylpyridinols were obtained in yields of 35–58% and 36–57%, respectively. When the metallation with *n*-butyllithium was carried out in the presence of DMF, along with the *o*-ethynylpyridinols, 2-(2-formyl-1-pentenyl)furopyridines were formed in yields of 15–35% (Equation (16)). Since the α -phenylthio group is reported to activate the β -position of furan rings to electrophilic attack ^[81JOC2473], the corresponding 2-phenylthio-3-bromo derivatives of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]-, and furo[3,2-*c*]pyridines were prepared and evaluated. Depending on the alkylolithium reagent chosen for the reaction, different products were obtained. The results are summarized in Scheme 24 ^[92JHC413].



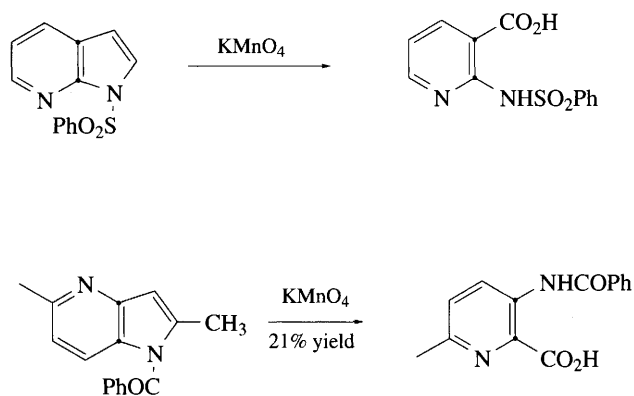


Scheme 24

7.06.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

7.06.8.1 Pyrrolopyridines

Pyrrolopyridines substituted on the pyrrole nitrogen are subject to attack by permanganate ion, resulting in ring-opened products as shown in Scheme 25 <43CB128, 50JCS2952>.



Scheme 25

7.06.8.2 Thienopyridines

Reactions of some common ring substituents on thieno[2,3-*b*]- and [3,2-*b*]pyridines are summarized in Table 46. For many of the derivatives, excellent yields were obtained for the acylation or reduction of nitro compounds.

Table 46 Substituent reactions of thieno[2,3-*b*]pyridines and thieno[3,2-*b*]pyridines.

Compound	Reagent(s)	Product(s)	Yield (%)	Ref.
3-NO ₂ -(20)	HOAc/Ac ₂ O/Fe	3-AcNH-(20)	82	75JHC1183
3-NO ₂ -(20)	conc. HCl/Sn	3-NH ₂ -(20)	39	70JHC373
3-Br-(20)	CuCN/DMF	3-CN-(20)	45	74JHC205
3-CN-(20)	MeMgI	3-Ac-(20)	18	74JHC205
2-Ac-(20)	NH ₂ OH · HCl/pyridine	2-Ac-(20)-oxime	80	70JHC373
2-Ac-(20) and 2-Ac-(22) ^a	NH ₂ NH ₂ /KOH	2-Et-(20), 2-Et-(22)	74 ^a	69JOC347
2-Ac-(22)	NH ₂ OH · HCl/NaOAc	2-Ac-(22)-oxime	96	70JHC373
3-NO ₂ -(22)	conc. HCl/Sn	3-NH ₂ -2-Cl-(22)	98	70JHC373

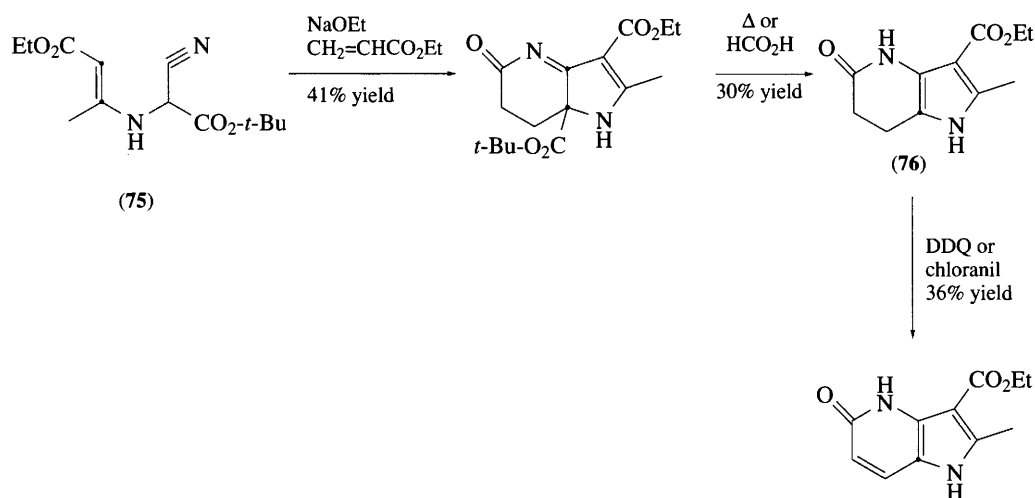
^aMixture of isomers.

7.06.9 RING SYNTHESSES

7.06.9.1 Syntheses of Pyrrolopyridines, Thienopyridines, and Furopyridines

7.06.9.1.1 Ring synthesis from acyclic precursors

There are few references to the synthesis of these ring systems from nonheterocyclic compounds. As shown in Scheme 26, reaction of the enaminone (**75**) with ethyl acrylate generated the highly functionalized pyrrolopyridine derivative (**76**) which was readily aromatized by mild oxidation <78CPB3080>.



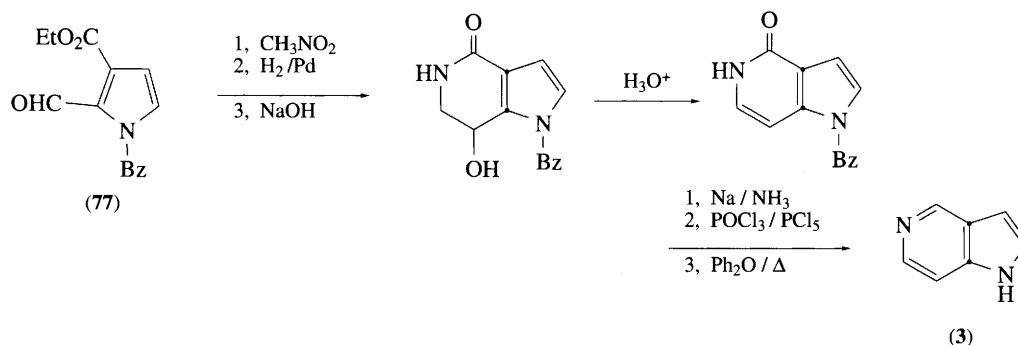
Scheme 26

7.06.9.1.2 Ring synthesis from monocyclic heterocycles

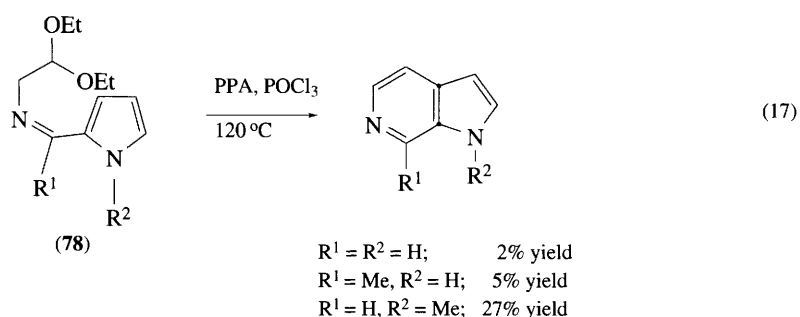
(i) Synthesis of the six-membered ring

(a) *By formation of one bond.* Compound (**3**) can be prepared from the pyrrole derivative (**77**) as shown in Scheme 27. An alternative preparation proceeded via the same pyridone intermediate but started from an acid azide which underwent a Curtius rearrangement <B-72MI 706-01>.

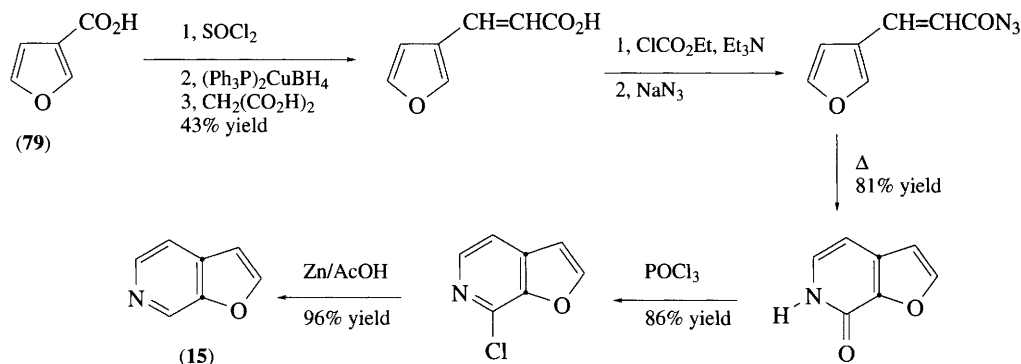
The amino acetals (**78**) afforded pyrrolo[2,3-*c*]pyridine (**2**) in very low yield when treated with POCl₃ in polyphosphoric acid (Equation (17)). A higher yield of the 1-methyl product was obtained <55JA6355>.



Scheme 27



Beginning with furoic acid (79) the synthesis of furo[2,3-*c*]pyridine (15) has been achieved in an overall yield of 29% (Scheme 28) <82JHC1207>.

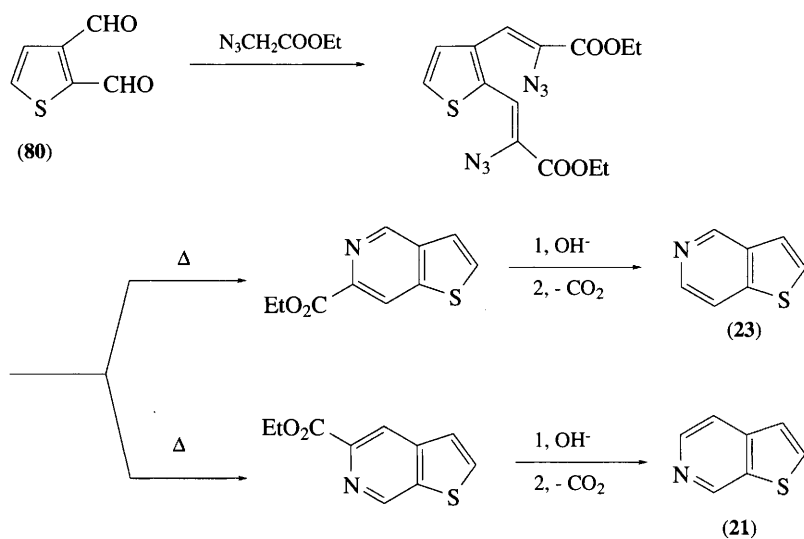


Scheme 28

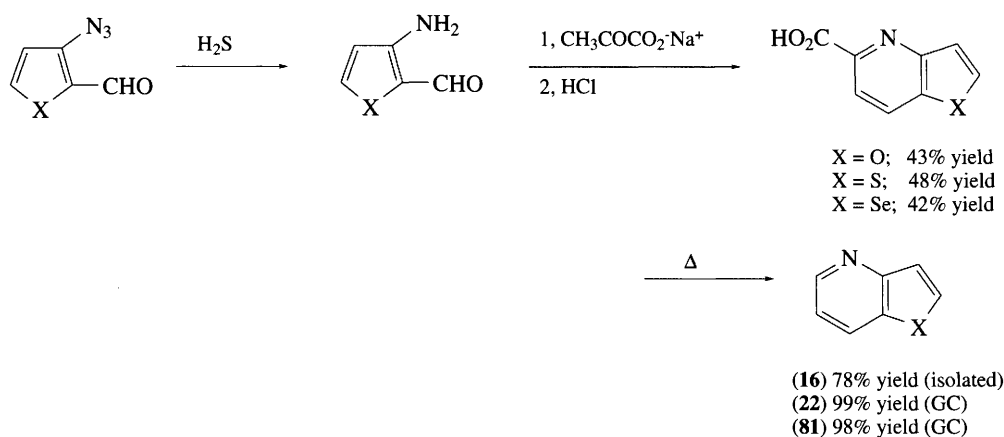
Compounds (21) and (23) have been synthesized from ethyl azidoacetate and thiophene-2,3-dialdehyde (80). Blocking one formyl group ultimately led to the corresponding pyridone derivatives. Overall yields are approximately 40% for each reaction sequence (Scheme 29) <76CJC1066>.

(b) *By formation of two bonds.* Compounds (16), (22), and seleno[3,2-*b*]pyridine (81) have been prepared by the Friedlander synthesis starting with the corresponding 3-amino-2-formyl furan, thiophene, or selenophene <75ACS(B)224>. The amino compounds were generated *in situ* from the corresponding azides. The sequence is summarized in Scheme 30. Good yields of the parent bicyclic compounds were obtained <75ACS(B)233>.

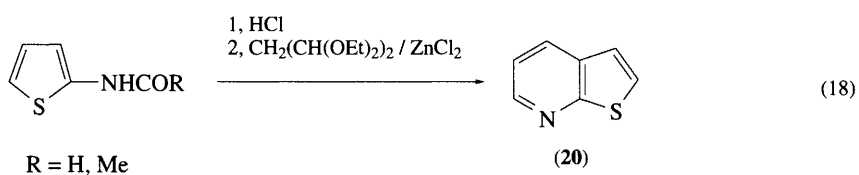
Compounds (20), (22), and their methyl derivatives can be synthesized from the appropriate thienyl formamide derivative, as illustrated in Equation (18) <76BSF883>. In analogous reactions, seleno[2,3-*b*]-, seleno[3,2-*b*]pyridine and their methyl derivatives can be prepared.



Scheme 29



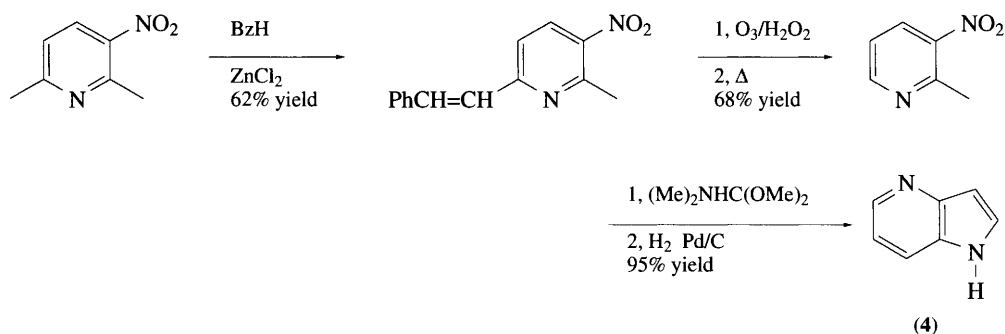
Scheme 30



(ii) Synthesis of the five-membered ring

(a) *By formation of one bond.* The majority of the literature references to the synthesis of pyrrolopyridines use pyridine derivatives as starting materials and prepare the pyrrole ring by formation of one bond. Similarly, there are numerous references to the preparation of substituted pyrrolopyridines, but few syntheses give respectable yields of the unsubstituted parent pyrrolopyridine compounds. The most common syntheses employ the Fischer, Reissert, and Madelung syntheses as routes to pyrrolopyridines $\langle 68\text{AHC}(9)27 \rangle$. Modifications to the Madelung and Reissert methods have been reported which give improved yields and reaction reproducibility for the parent compounds (1), (2), (3), and (4), as well as 7-methyl-1*H*-pyrrolo[3,2-*b*]pyridine, 7-methyl-1*H*-pyrrolo[2,3-*c*]pyridine, and 7-amino-1*H*-pyrrolo[3,2-*b*]pyridine $\langle 92\text{JHC}359 \rangle$. Details of the reactions are given in Scheme 31 for the preparation of compound (4).

A palladium-catalyzed reaction of halonitro- or nitrotriflyloxypyridines with (*Z*)-1-ethoxy-2-tributylstannylethene led to good yields of 1*H*-pyrrolopyridines $\langle 92\text{H}(34)2379 \rangle$. The reaction is shown



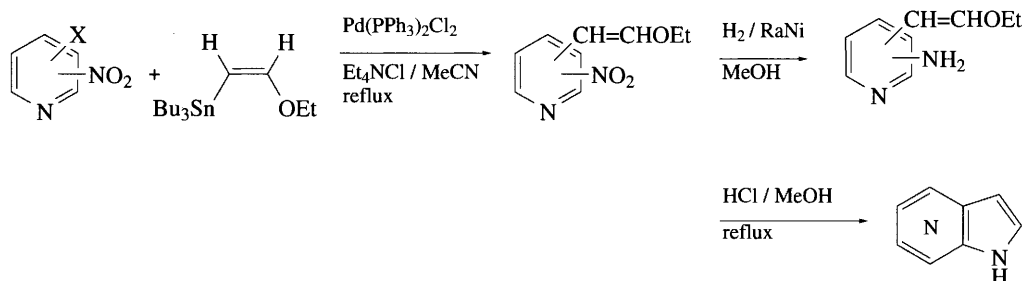
Scheme 31

in Scheme 32 and data are summarized in Table 47. It is interesting to note that 3-bromo-4-nitropyridine readily underwent the first step of the sequence shown in Scheme 32. However, it is not useful for the synthesis of compound (3) because the nitroalkene derivatives generated are unstable to the subsequent reaction conditions. An alternative route to this pyrrolopyridine (3) via the 3-bromo-4-acetylamino derivative has been successful. A less general version of this reaction sequence, applicable to the synthesis of derivatives of compounds (3) and (4), had been developed earlier <86CPB2362, 87CPB1823>.

Table 47 Preparation of 1H-pyrrolopyridines.

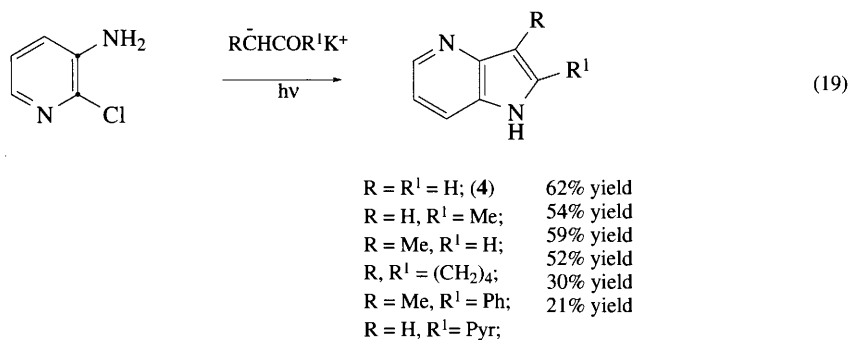
Starting material	Product	Yield (%)
3-TfO-2-NO ₂ -Pyridine	(1)	54
4-Cl-3-NO ₂ -Pyridine	(2)	36
4-AcN-3-Br-Pyridine	(3)	84
2-Cl-3-NO ₂ -Pyridine	(4)	68

Source: Sakamoto *et al.* <92H(34)2379>.

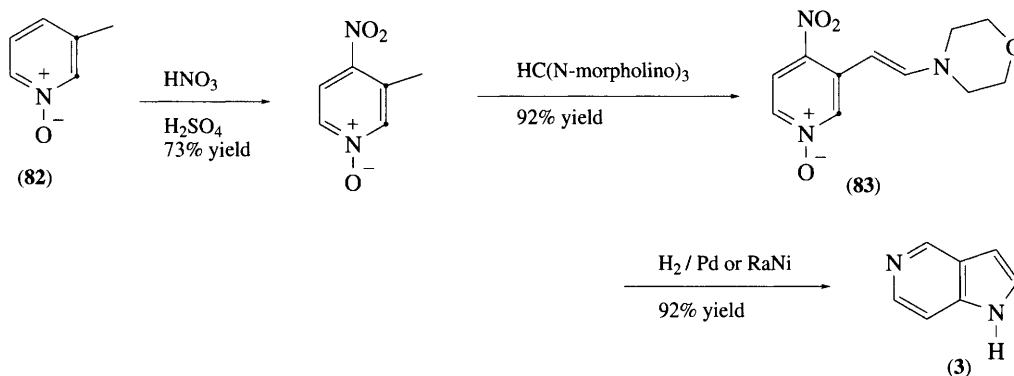


Scheme 32

A route to derivatives of compound (4) has been developed utilizing a nucleophilic heteroatom substitution reaction that proceeds via a radical intermediate <81H(16)1473>. The reaction, shown in Equation (19), gives the highest yield for the unsubstituted derivative (4) (62%) and a range of yields (21–59%) for substituted derivatives.

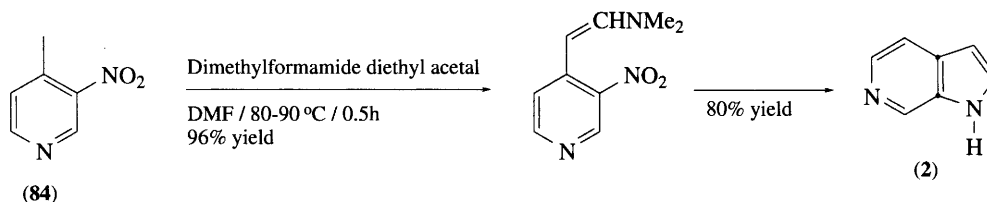


A synthesis of compound (3) has been developed that is useful for large-scale preparations. This method, outlined in Scheme 33, proceeds via the *N*-oxide of 3-methylpyridine (82) <93T2885>. The authors note that use of the *N*-oxide enhanced reactivity in the formation of the enamine (83).



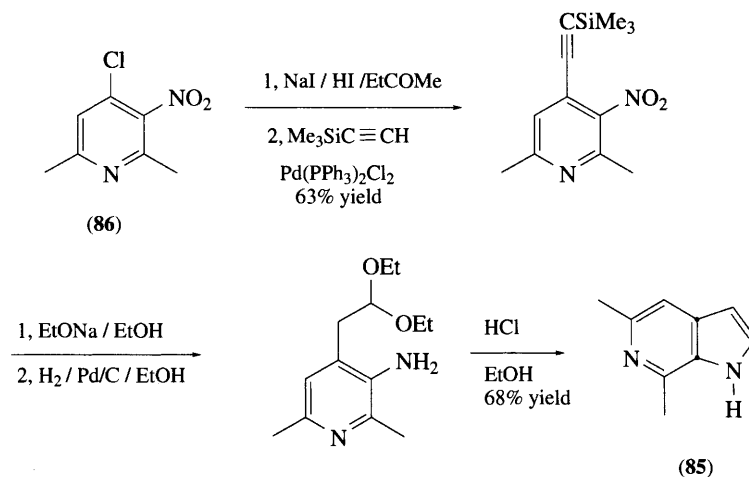
Scheme 33

Good yields of compound (2) have been obtained by condensation of dimethylformamide diethyl acetal with 3-nitro-4-methylpyridine (84) followed by hydrogenation (Scheme 34) <78CHE919>. By similar reactions, 2-substituted-1*H*-pyrrolo[2,3-*c*]pyridines (from 3-nitro-4-chloropyridine), 3-substituted-1*H*-pyrrolo[2,3-*c*]pyridines (from 3-nitro-4-pyridylacetone), 2,3-disubstituted-1*H*-pyrrolo[2,3-*c*]pyridines (from 3-nitro-4-chloropyridine), and 4-bromo-1*H*-pyrrolo[2,3-*c*]pyridine (from 3-bromo-4-chloro-5-nitropyridine) can be prepared in yields ranging from 40% to 80% <77CHE1224, 78CHE402, 78CHE406, 79CHE76>. The same methodology is useful for preparing compound (4) in nearly quantitative yield (from 2-methyl-3-nitropyridine) and 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine (from 2-methyl-3-nitro-6-chloropyridine) <77CHE1145>.



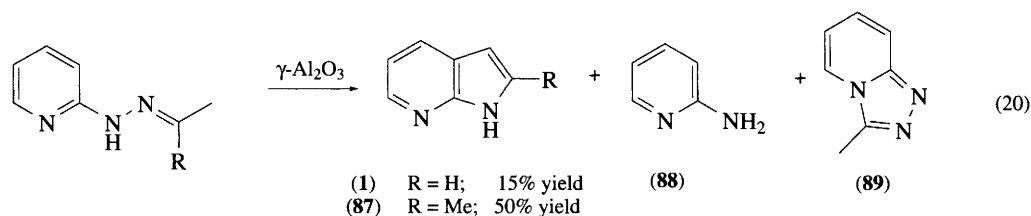
Scheme 34

The synthesis of 5,7-dimethyl-1*H*-pyrrolo[2,3-*c*]pyridine (85) has been carried out starting with 4-chloro-2,6-dimethyl-3-nitropyridine (86) according to Scheme 35 <84H(22)1347>.

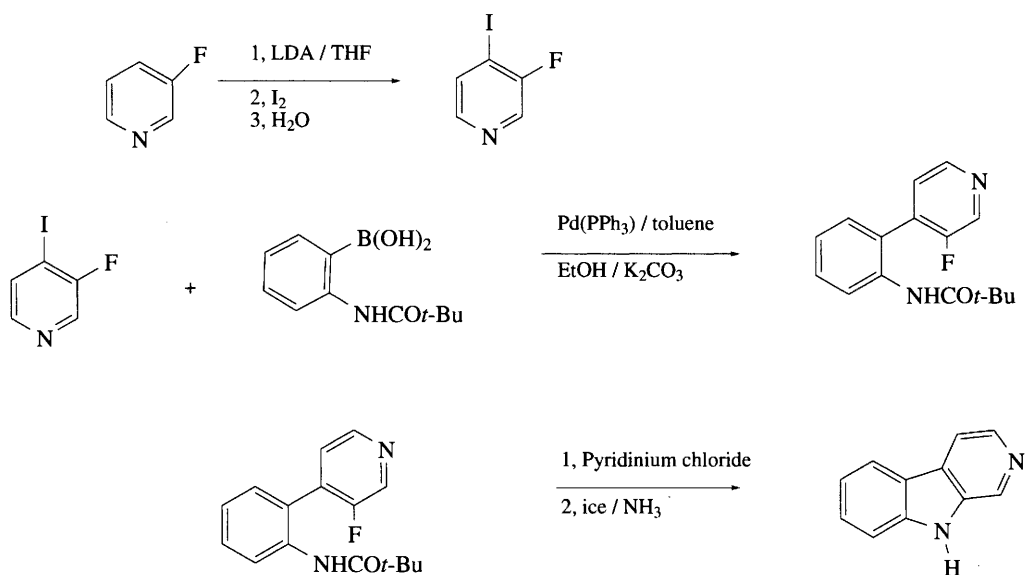


Scheme 35

Compound (1) and 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (87) have been prepared by a heterogeneous catalyzed Fischer reaction. A cyclization reaction occurred with acetaldehyde and acetone 2-pyridylhydrazones in the presence of γ -alumina and fluorinated aluminum oxide (Equation (20)). In addition to the desired pyrrolopyridine products, 2-aminopyridine (88) and a triazine derivative (89) were also formed. Use of the fluorinated aluminum oxide maximized formation of the desired products <72CHE594, 72CHE1037>.



Most syntheses of the β -carboline alkaloids employ indole or indole derivatives as starting materials <89TL3605, 90JOC3666>. A new convergent and regioselective synthesis of azacarbolines has been developed which incorporates metallation, cross-coupling, and intramolecular substitution reactions starting from (2-aminobenzene)boronic acid and *o*-fluoroiodopyridines. Through a three-step sequence the parent carbolines, α -, β -, γ -, and δ -carbolines have been prepared in overall yields of 72%, 79%, 49%, and 26%, respectively. The method is outlined in Scheme 36 <93T49>. Most commonly, the preparation of these compounds is carried out via the Fischer reaction.

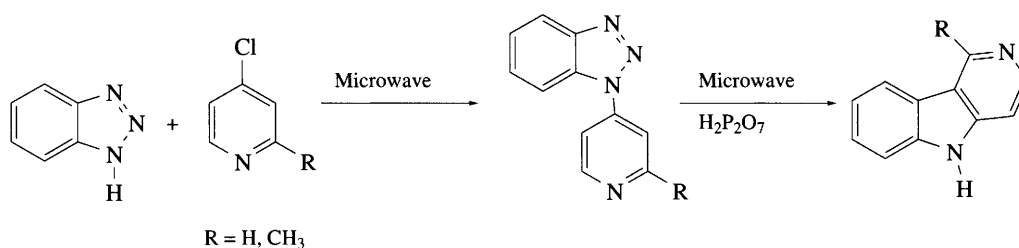


Scheme 36

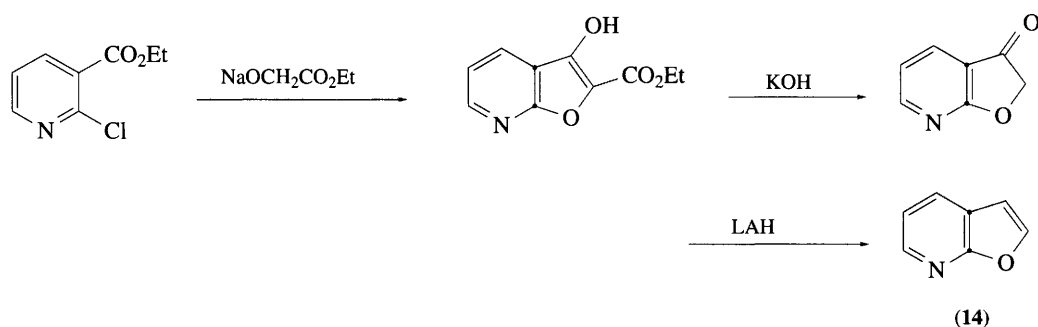
As a recent modification, the Graebe-Ullmann synthesis of γ -carbolines under microwave irradiation has been conducted (Scheme 37). Yields of the reaction were comparable to those obtained by conventional heating at 150–210°C (30–81% yield), but the reaction times were significantly reduced <93TL2673>. Similarly, using flash vacuum pyrolysis techniques, nitroarylbenzotriazoles have been converted to pyridoindoles <88BSB245>.

Compound (14) has been prepared from ethyl 5-aminofuro[2,3-*b*]pyridine-2-carboxylate which originated from 2-furoic acid in an overall yield of less than 3% <66JHC202, 71JHC735>. Another synthesis began with 2-hydroxynicotinic acid and proceeded via furo[2,3-*b*]pyridine-3(2*H*)-one in 14% yield <70BSF646>. An alternative synthesis beginning with 2-hydroxynicotinic acid has been reported and gave an overall 28% yield of compound (14) in a six-step reaction sequence outlined in Scheme 38 <86JHC1465, 88JHC1205>.

The parent compound (15) and 2- and 3-methylfuro[2,3-*c*]pyridine derivatives have been synthesized from ethyl 3-hydroxyisonicotinate (90) as shown in Scheme 39 <86JHC549>. The parent compound (15) has been prepared using an alternative method starting with 3-furaldehyde

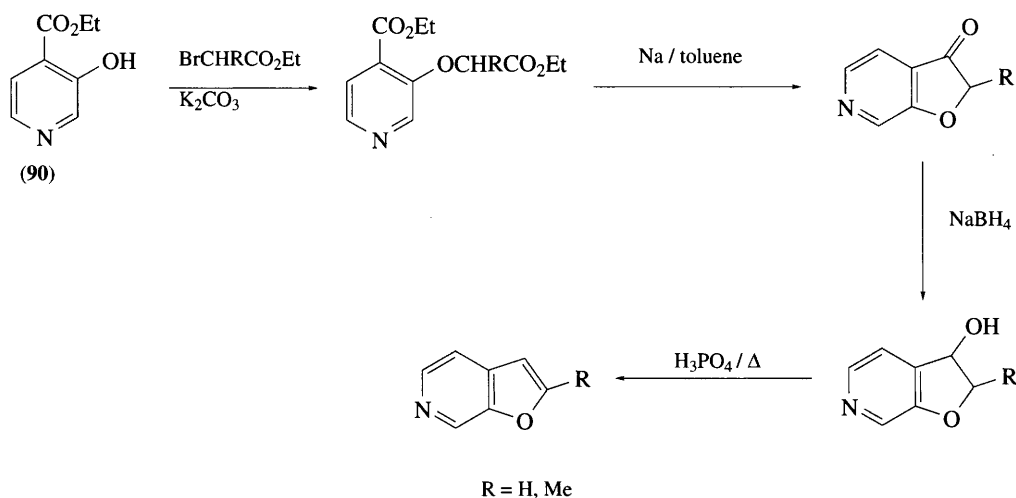


Scheme 37



Scheme 38

<82JHC1207>, but this route is not attractive for the preparation of methyl derivatives owing to the difficulty of preparing the appropriately substituted methylfuraldehyde starting materials.



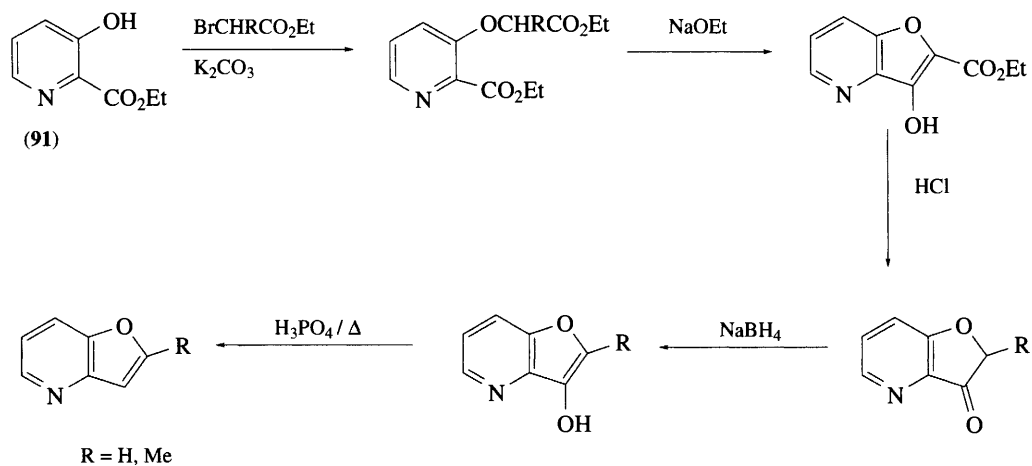
Scheme 39

The parent compound (16) and 2- and 3-methyl derivatives have been prepared from ethyl 3-hydroxypicolinate (91) in a five-step synthesis that gave an overall yield of 60% (Scheme 40) <86JHC665>. Earlier synthetic routes to the parent compound have been developed starting from 2-furoic acid (see Section 7.06.9.1.3) <75ACS(B)233> or furfural <81S464>, but the overall yields are low (3% and 10%, respectively), making these routes impractical for preparation of large quantities of material.

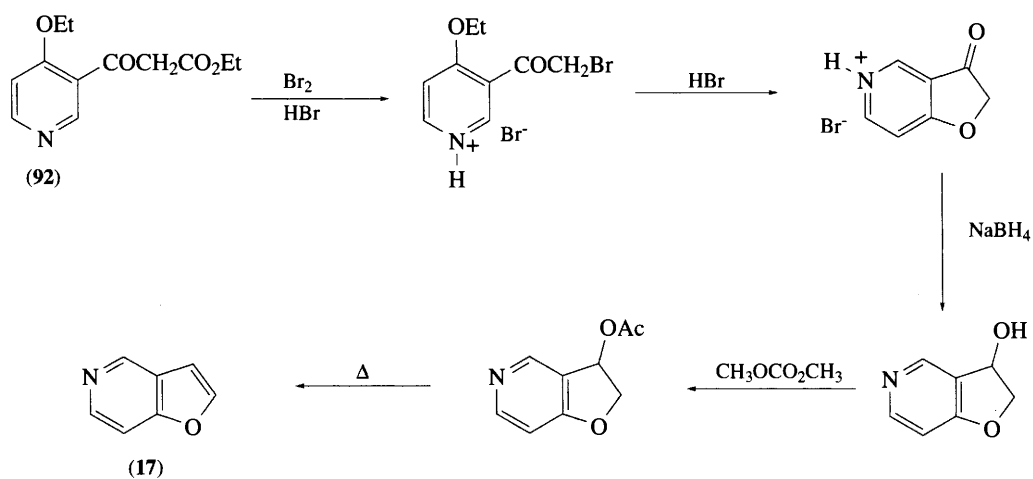
Compound (17) has been synthesized in 12% overall yield from the pyridine derivative (92) according to the sequence in Scheme 41 <72BSF1442>.

Compound (19) and its dimethyl derivative have been prepared *in situ* and trapped by 1-bromo-2-chlorocyclopropene according to the sequence outlined in Scheme 42 <89HCA1608>.

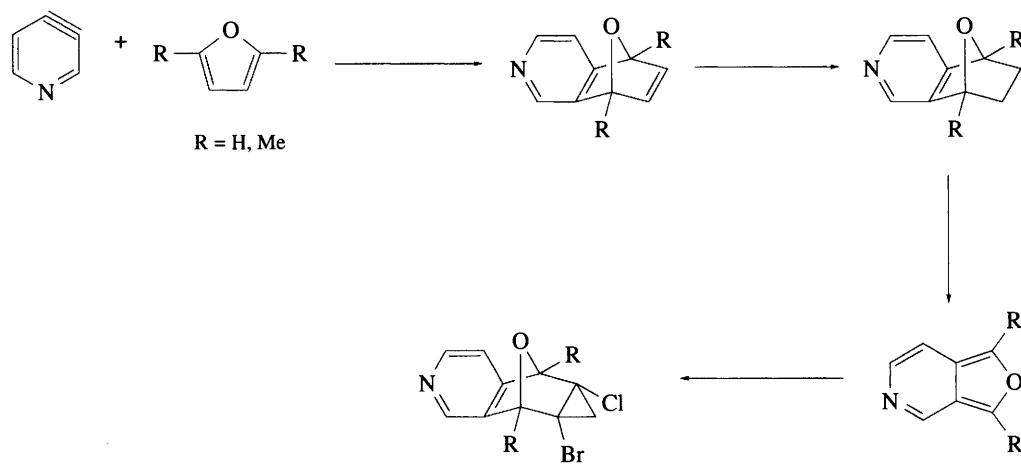
Furo[2,3-*c*]quinolines have been synthesized by a coupling reaction of furanboronic acid with haloarenes. The reaction of 2-bromonitrobenzene (93) with 2-formylboronic acid (94) afforded



Scheme 40

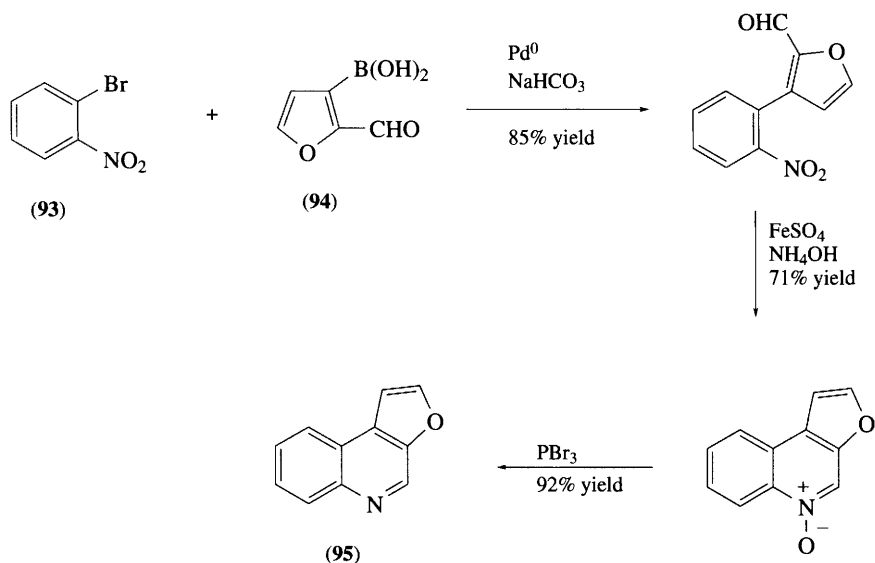


Scheme 41



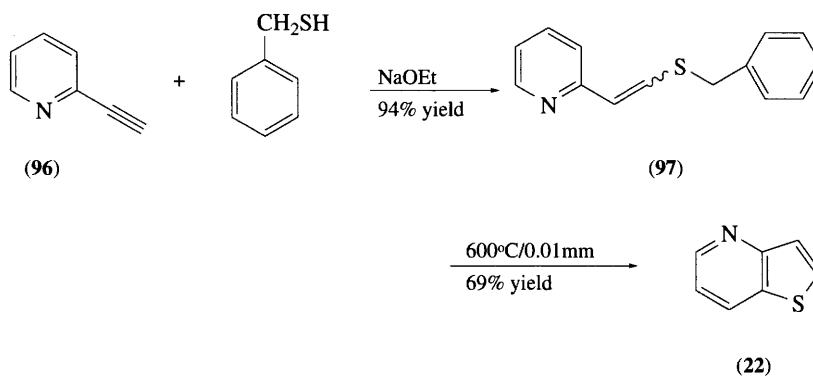
Scheme 42

furo[2,3-*c*]quinoline (**95**), after deoxygenation of the *N*-oxide, in excellent yield according to Scheme 43 <89SC1001>.



Scheme 43

Compound (**22**) can be synthesized in good yield in a two-step reaction starting from 2-ethynylpyridine (**96**). The second step employs vacuum pyrolysis of the intermediate vinyl sulfide (**97**) (Scheme 44) <84JHC785>.



Scheme 44

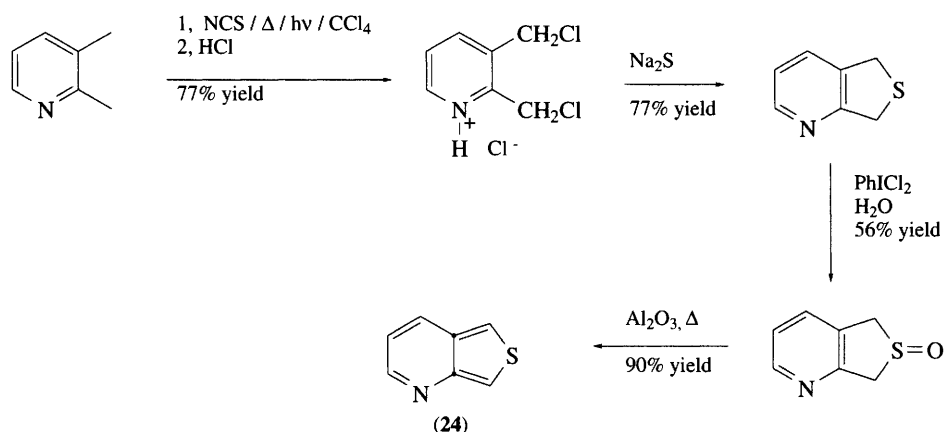
Compounds (**24**) and (**25**) have been prepared in a sequence of four steps beginning with 2,3-dimethylpyridine and 3,4-dimethylpyridine, respectively. Both compounds are fairly unstable, darkening within hours and turning into resinous materials: they can be stored as crystalline picrates. Scheme 45 gives details of the reaction for the [3,4-*b*] isomer (**24**) <72JHC843>.

(*b*) *By formation of two bonds.* No pertinent information was found for synthesis of the five-membered ring system by formation of two bonds.

7.06.9.2 Syntheses of Fuopyrans, Thienopyrans, Furothiopyrans, and Thienothiopyrans

7.06.9.2.1 Ring synthesis from acyclic precursors

No information is available on the formation of these ring systems from acyclic precursors.



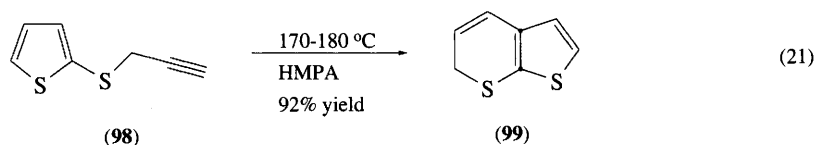
Scheme 45

7.06.9.2.2 Ring synthesis from monocyclic heterocycles

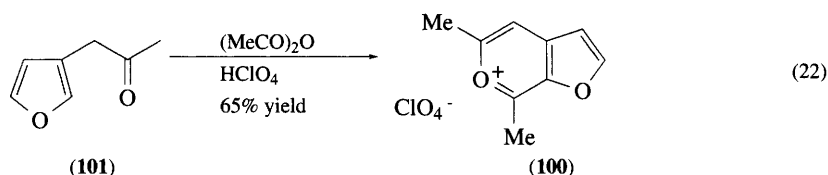
(i) Synthesis of the six-membered ring

(a) *By formation of one bond.* A series of dithiainones has been synthesized from halo-substituted thiophene derivatives. These ketones were subsequently reduced to generate dithiaindenes (Scheme 46) <73T1829>.

Reaction of 2-thienyl propargyl sulfide (**98**) in HMPA led to 2*H*-thieno[2,3-*b*]thiopyran (**99**) (Equation (21)). Claisen type rearrangements are involved in the reaction, which proceeded in excellent yields. The reaction is also a useful method for the preparation of 5*H*-thieno[3,2-*b*]thiopyran and methyl derivatives of these compounds <69RTC732, 72RTC785>.

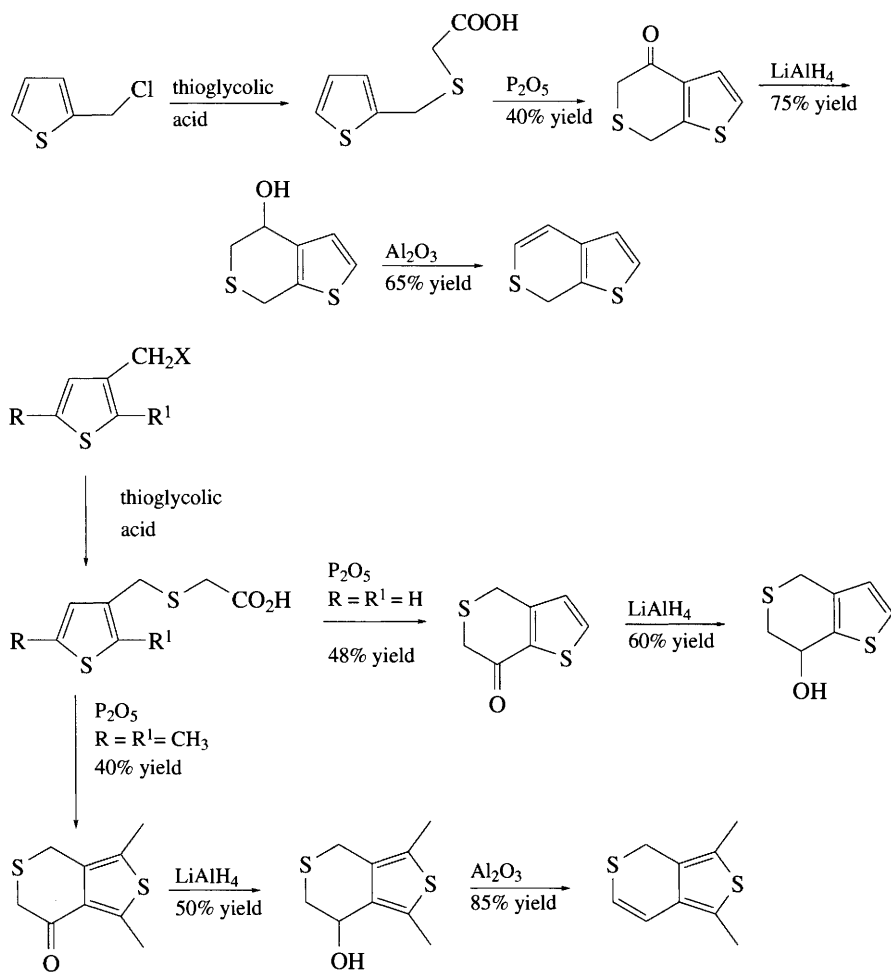


(b) *By formation of two bonds.* The furo[2,3-*c*]pyrylium perchlorate (**100**) can be prepared by acylation of 3-acetylthiophene (**101**) with an acetic anhydride–perchloric acid mixture (Equation (22)) <86CHE677>. Furo[2,3-*b*]- and furo[3,2-*c*]pyrylium salts are also known <69CHE313, 71BSF3343>.

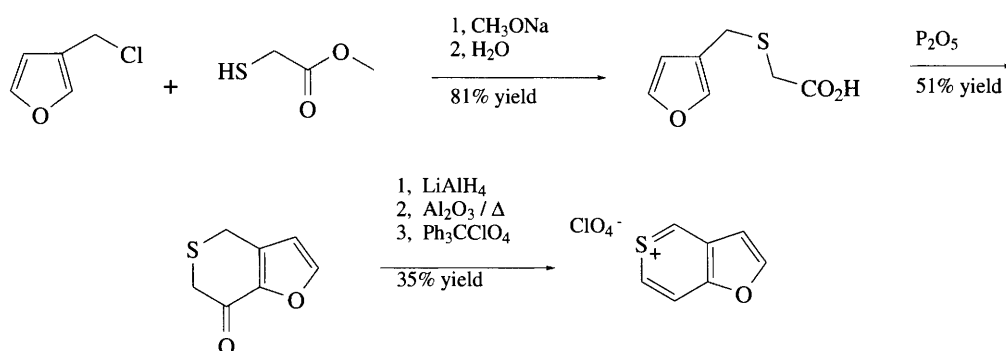


Furo[2,3-*c*]- and furo[3,2-*c*]thiapyrylium perchlorate salts have been prepared as illustrated in Scheme 47 <76JHC365>. This synthetic sequence is very similar to that used for the preparation of thienothiopyrylium salts <74G671>.

Thienoisquinolines can be prepared in high yields by the palladium cross-coupling reaction of *o*-formylarylboronic acids with aryl halides. By this method, thieno[3,2-*c*]- (**102**), thieno[3,4-*c*]- (**103**), and thieno[2,3-*c*]isoquinolines (**104**) have been prepared in yields of 90%, 52%, and 75%, respectively (Scheme 48) <86CS311, 89JHC865>. This method was unsuccessful for the preparation of thieno[3,2-*c*]quinoline *N*-oxide and thieno[3,2-*c*]isoquinoline *N*-oxide. The former compounds were readily prepared via a modification of the reaction using a palladium-catalyzed coupling reaction between 2-tributylstannyl-3-thiophenecarboxaldehyde and *o*-bromonitrobenzene, while the isoquinoline *N*-oxide was prepared by mcpba oxidation of the parent compound <90JHC1127>.



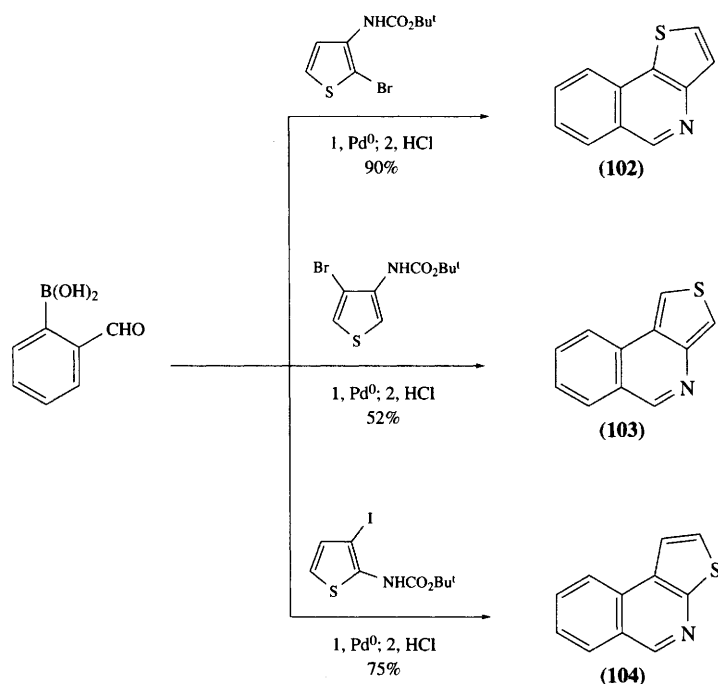
Scheme 46



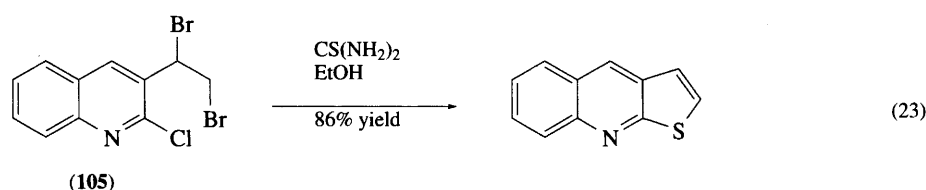
Scheme 47

(ii) Formation of the five-membered ring

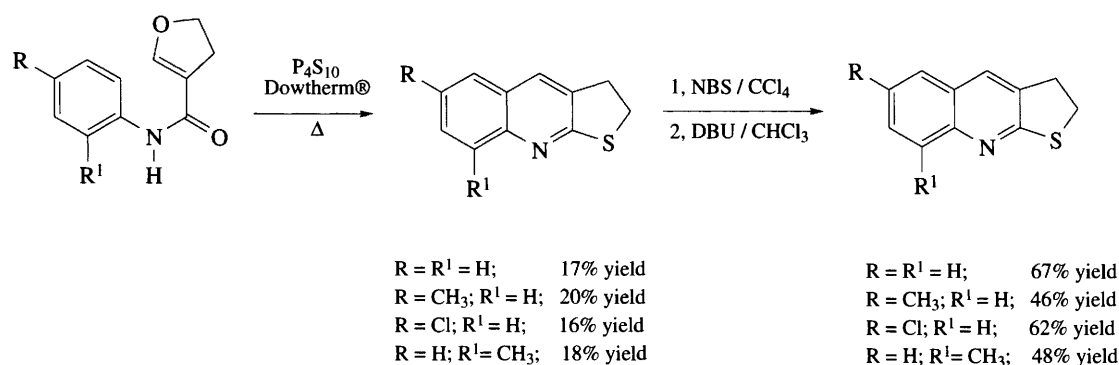
(a) *By formation of one bond.* Thieno[2,3-*b*]quinolines can be conveniently prepared in high yields by the reaction of 2-chloro-3-(1,2-dibromoethyl)quinolines (**105**) with thiourea (Equation (23)) <77JCS(P1)2024>.



Scheme 48

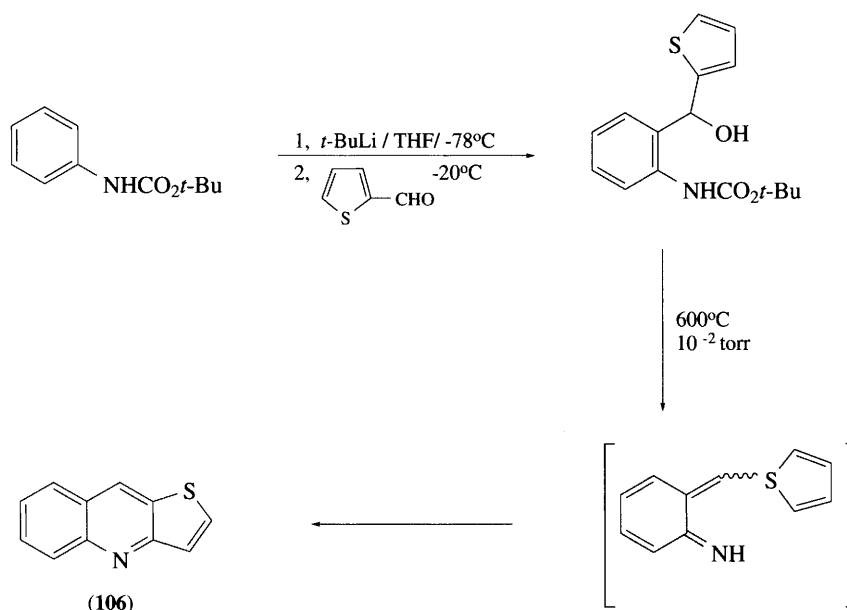


Another route to thieno[2,3-*b*]quinolines is a three-step sequence starting with anilines. The reaction proceeds via conversion of the aniline derivative to an amide, which is then followed by treatment with tetraphosphorus decasulfide to generate dihydrothienoquinolines which are dehydrogenated to the thienoquinolines in fair to good yields (Scheme 49) <77S612>.



Scheme 49

(b) *By formation of two bonds.* Flash vacuum pyrolysis is a useful method for the preparation of thienoquinoline (106) as shown in Scheme 50 <84CC1304>.



Scheme 50

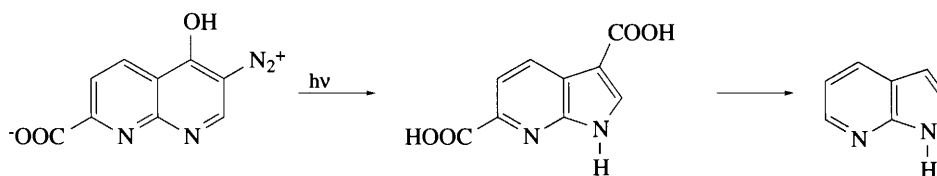
7.06.9.3 Syntheses of Pyranopyrroles and Thiopyranopyrroles

No pertinent references were found to the syntheses of these compounds from either acyclic or heterocyclic precursors.

7.06.10 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROBICYCLIC SYSTEMS

7.06.10.1 Pyrrolopyridines

Early literature references cite the photochemical contraction of naphthyridine rings to generate all four pyrrolopyridine isomers (e.g., Scheme 51) <58LA(612)153>. This method involves a multistep reaction sequence which can only be carried out on a very small scale.

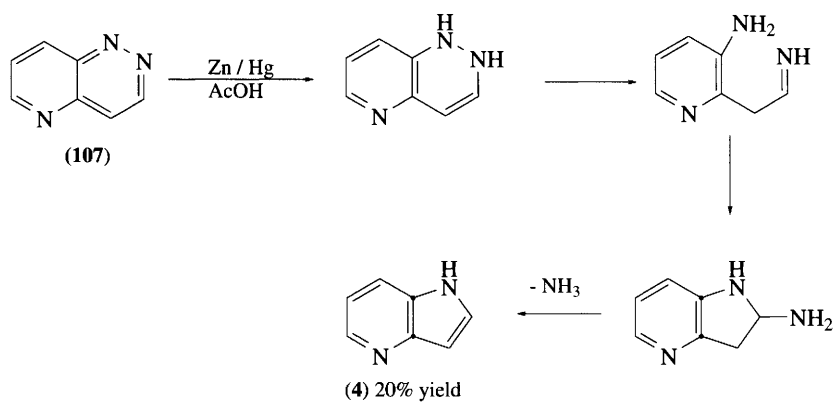


Scheme 51

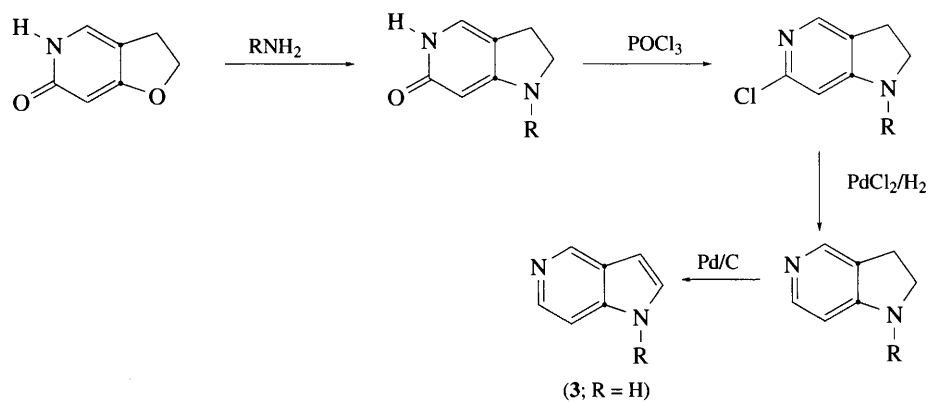
The reduction of 5-azacinnoline (**107**) with zinc amalgam in 30% acetic acid resulted in a rearrangement with ring contraction to generate compound (**4**) (Scheme 52) <75CHE1222>.

A route to compound (**3**) and its derivatives has been developed based on the reaction of 5-azabenzofurans with amines (Scheme 53). The ease of replacement of oxygen by nitrogen is very dependent on the nucleophilicity of the amine. For example, amines such as *p*-toluidine with an electron-donating group in the *para* position react much more readily than aniline <70CHE23>.

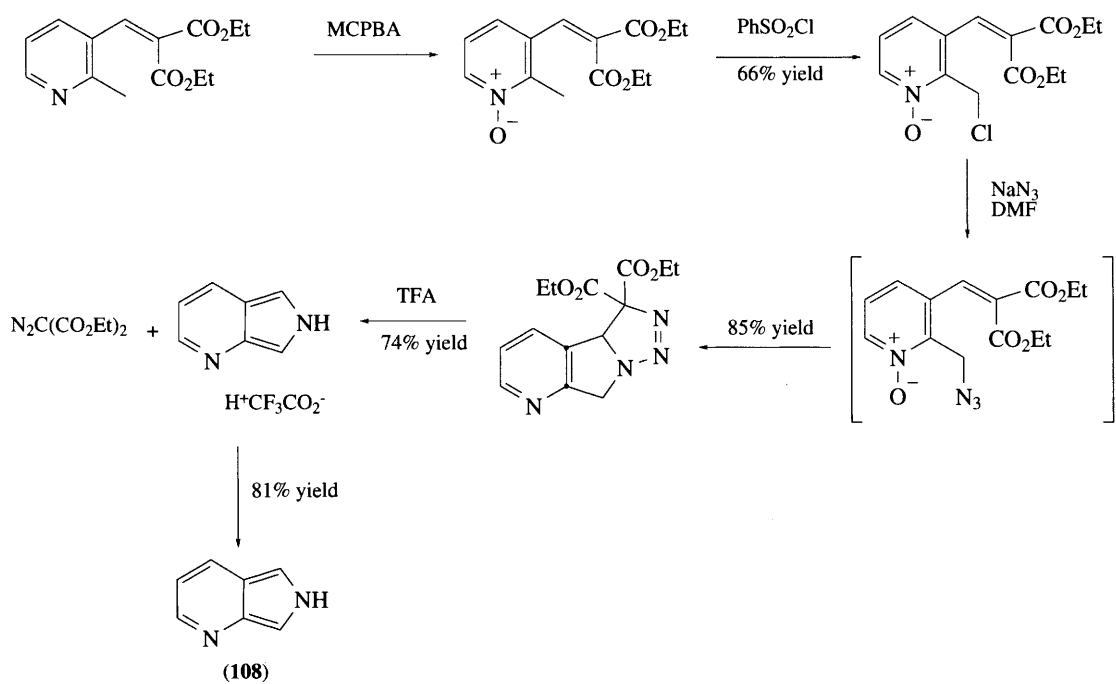
2*H*-Pyrrolo[3,4-*b*]pyridine (**108**) and 2*H*-pyrrolo[3,4-*c*]pyridine (**7**) have been prepared for the first time according to the reaction sequence outlined for compound (**108**) in Scheme 54 <87TL1419>.



Scheme 52



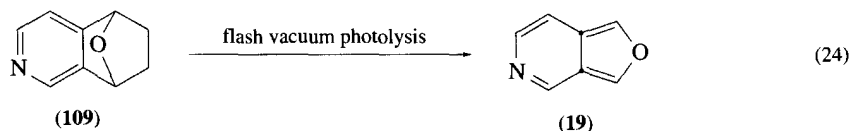
Scheme 53



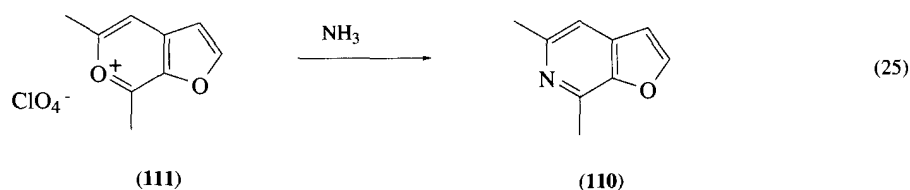
Scheme 54

7.06.10.2 Furopyridines

A retro-Diels-Alder reaction achieved by flash vacuum photolysis of 5,8-epoxy-5,6,7,8-tetrahydroisoquinoline (**109**) has been used to prepare furo[3,4-*c*]pyridine (**19**) in quantitative yield (Equation (24)). The material discolors upon contact with air and melts below room temperature, but it is somewhat more stable in chloroform solution with a half-life of 50 h at 4 °C <77TL1741>.

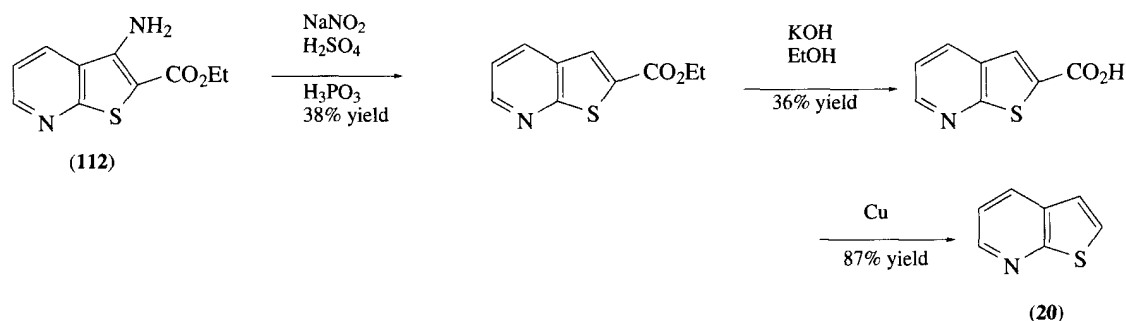


5,7-Dimethylfuro[2,3-*c*]pyridine (**110**) can be prepared by the treatment of furo[2,3-*c*]pyrylium perchlorate (**111**) with ammonia (Equation (25)) <86CHE677>.



7.06.10.3 Thienopyridines

Compound (**20**) can be prepared in a facile synthesis (Scheme 55) involving the conversion of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate (**112**), which is a readily available thieno[2,3-*b*]pyridine derivative <74JHC975, 76JHC273>.



Scheme 55

7.06.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND A CRITICAL COMPARISON OF AVAILABLE ROUTES

Most of the compounds discussed are materials that are obtained synthetically. Syntheses for some of the derivatives were only discovered in the 1970s and 1980s. In the pyrrolopyridine family of compounds, the pyrrolo[2,3-*c*]pyridine parent structure is found in a variety of naturally occurring compounds including yohimbine, harmine, and canthine <68AHC(9)27>. The furopyridines and thienopyridines are of interest because, again, they are analogous to a variety of heterocycles found in naturally occurring products such as furoquinolines. As noted above (see Section 7.06.9), there are few routes to any of these compounds starting from nonheterocyclic materials. The most common routes typically begin with a pyridine derivative.

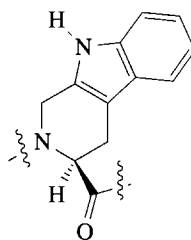
For many of the compounds described in this chapter, there is not sufficient commercial interest in the materials for the development of reasonable synthetic routes. Exceptions are the pyrrolopyridines, furopyridines, and thienopyridines. Even for these compounds, most of the classical literature routes (Madelung and Fischer methods, for example, for the pyrrolopyridines) lead to

poor yields of products. For some of the derivatives, excellent yields of functionalized products are possible, but high-yielding routes to the parent molecules are lacking.

7.06.12 APPLICATIONS

7.06.12.1 Pyrrolopyridines, Furopyridines, and Thienopyridines

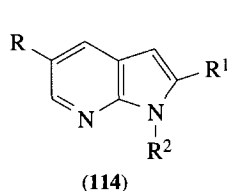
Derivatives of compound (1) are of interest because they are aza analogues of indoles which are commonly found in natural alkaloids and synthetic pharmaceutical preparations <90MI 706-01>. Compound (1) has been used as a chromophoric moiety in 7-azatryptophan, an optical probe useful in the study of protein structure and dynamics <92JA8343>. Benzo derivatives such as the partial structure (113) have been used as tryptophan mimics <B-89MI 706-01>.



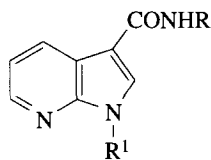
(113)

Another use of compound (1) involves synthesis of NADH models incorporating chiral and nonchiral 1*H*-pyrrolo[2,3-*b*]pyridine derivatives. In this latter application, the products derived from compound (1) have been useful for the study of systems that were unreactive with similar reagents. By the appropriate manipulation of reaction conditions, products derived from compound (1) selectively form either (but only one) enantiomer in reduction of a prochiral ketone. Finally, the products derived from compound (1) are useful reagents in the preparation of chiral precursors of target molecules <91T429>.

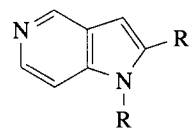
Pyrrolopyridine derivatives have been used in the preparation of nasal decongestants and anti-hypertensives such as the derivatives (114) <73GEP2427207, 75SAP7402787>, for anti-AIDS compounds <91MIP9109849>, as 5-hydroxytryptamine antagonists (115) <92JAP9221681>, as intermediates for anthelmintics (116) <86FRP2574406>, as angiotensin II antagonists useful for treatment of hypertension and congestive heart failure <92USP5124335>, for use in nucleic acid sequence analysis and antiviral activity (117) <88EUP286028>, for platelet-activating factor antagonists <92USP5120749>, as amino acid analogues useful for CCK antagonists <92MIP9204025>, and for renin inhibitory activity <92MIP9216497>. Pyrrolo[3,4-*c*]pyridines have been synthesized for use as potential antineoplastic agents <80DIS(B)5279>. The benzo derivative intolpicin (118) was put into use in clinical trials in the late 1980s for use in cancer treatment <90JMC1519>.



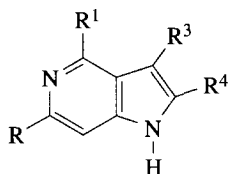
(114)



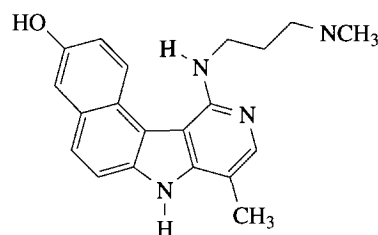
(115)



(116)

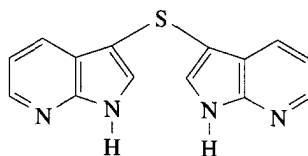


(117)



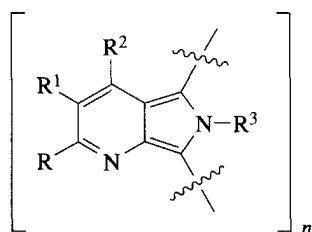
(118) intolpicin

The fungicidal activity of 1*H*-pyrrolo[2,3-*b*]pyridine derivatives has been tested. The 3,3'-bis sulfide derivative (**119**) shows medium to high fungicidal activity, especially against rice blast and rice leaf spot damage <92BCJ2992>.

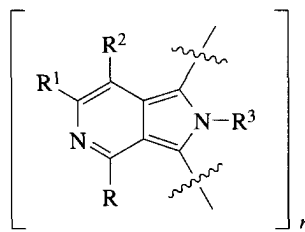


(119)

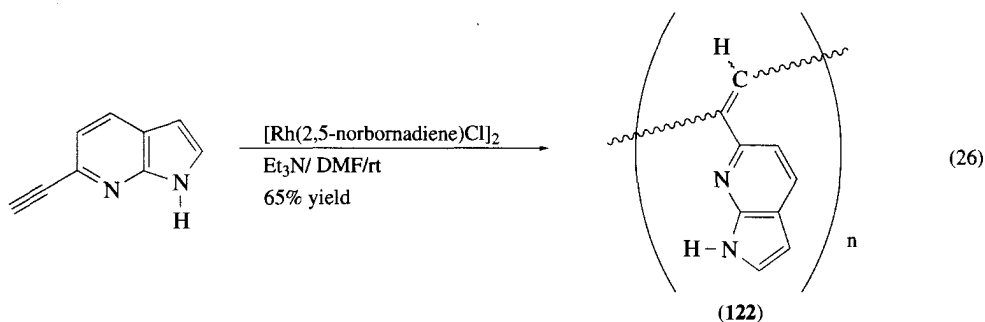
Doped conductive polymers useful for applications such as electrodes, displays, and electromagnetic shields, have been prepared from pyrrolo, furo, thieno, seleno, and telluropyridines ((**120**) and (**121**)) <90JAP90170823>. Cation doping of the electrically conducting polymers such as the polymer derived from compounds (**5**) and (**6**) with potassium ions leads to highly conductive polymers <91JAP91166225>. Polyacetylene polymers containing a 1*H*-pyrrolo[2,3-*b*]pyridine substituent (**122**) have been prepared according to Equation (26) <92BCJ2992>.



(120)



(121)



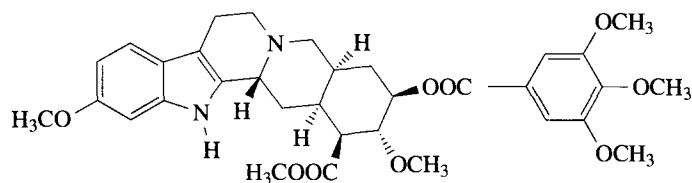
(122)

Photoresist compositions based on compound (**4**) have shown excellent adhesion on copper-laminated resin plates <81JAP8167844>.

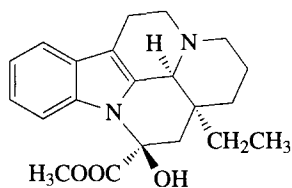
In general, alkaloids containing the pyridoindole structure are found widely in nature in both plants and animals. Reserpine (**123**) has antihypertensive activity. Total syntheses as well as a stereoselective synthesis have been reported in the literature <79JA6404, 80JA6157, 89PAC439>. Vincamine (**124**) <81MI 706-01, 82H(18)255, 83JJC(B)531> and eburnamonine (**125**) <82CPB1521> are both useful as vasodilators. Yohimbine (**126**) has been used as an α -adrenergic blocking agent <80H(14)631, 82JA2244>.

Some of these compounds have been detected upon thermal decomposition of certain foods, amino acids, and proteins. Significant amounts of compound (**13**), known as norharman, and its 9-methyl derivative, commonly called harman, have been found in tryptophan pyrolyzates. Similarly, cigarette smoke condensate has been found to contain significant amounts of both of these compounds <82JC331>.

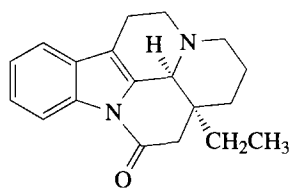
The 6-bromo and 7-bromo derivatives of norharman (**13**), known as eudistomin N and O, respectively, have been shown to have both antiviral and antimicrobial activity <87JA3378>. Compound (**13**) and some of its derivatives, including tetrahydro derivatives, were investigated for their ability to bind to benzodiazepine receptors in the brain. Trends showed that fully aromatic deriva-



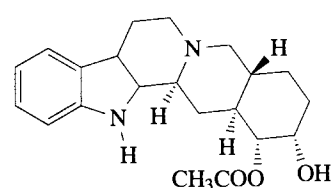
Reserpine (123)



Vincamine (124)



Eburnamonine (125)

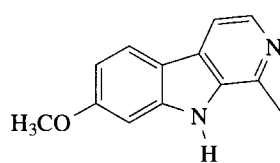
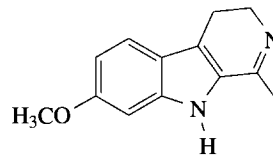
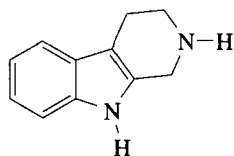


Yohimbine (126)

tives containing a carbonyl-containing substituent at C-3 showed an enhanced *in vitro* activity. 3-(Hydroxymethyl)-, 3-formyl-, and 3-acetyl-9*H*-pyrido[3,4-*b*]indole were found to be *in vivo* benzodiazepine antagonists (82JMC1081). Additional investigations have been carried out on the effects of derivatives of 9*H*-pyrido[3,4-*b*]indole as neurotoxicants present in the brain (93MI 706-01, 93MI 706-02, 93MI 706-03, 94MI 706-01).

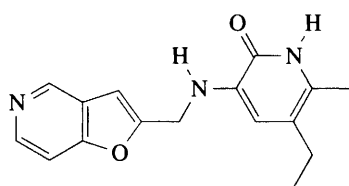
Both 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole and 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole were found to possess potent convulsant activity (90MI 706-01).

Compound (13) and the derivatives (127)–(129) have been useful as a vital stain to serve as a physiological probe for specific neurotransmitter pools. Inhibition of the binding of radiolabeled serotonin, choline, γ -aminobutyric acid, noradrenaline, and dopamine was observed (91MIP9114184).

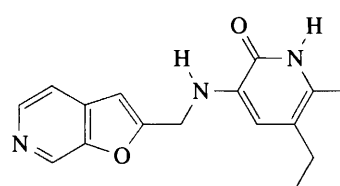
(127)
Harmine(128)
Harmaline(129)
Tetrahydronorharman

Fuopyridine derivatives (130) and (131) were tested for HIV-1 reverse transcriptase activity but proved to be much less potent than the corresponding benzo analogues (92JMC3792).

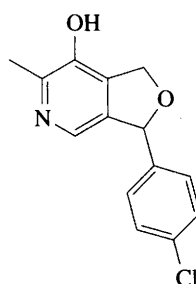
The antihypertensive diuretic drug cicletanine (132) is a fuopyridine derivative. The fuopyridine skeleton from which this compound is derived is not associated with any known pharmacological classes (85MI 706-02).



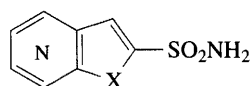
(130)



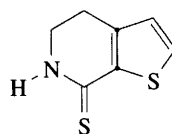
(131)

(132)
Cicletanine

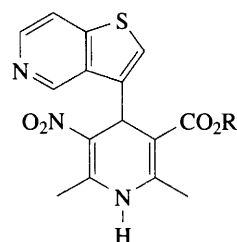
Cephalosporin derivatives incorporating furopyridine and thienopyridine moieties have been prepared <83EUP74268, 83USP4406898, 87FRP2586019, 87FRP2586020, 88FRP2610629, 91EUP462009>. Sulfonamide derivatives useful as antiglaucoma agents have been prepared from furo- and thienopyridines (133) <89USP4808595, 88EUP271273>.

X = O, S
(133)

Thienopyridine derivatives have been prepared for use as anticonvulsants (134) <86EUP183994>, and for use as calcium channel modulators (135) <90USP4902694>.

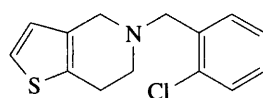


(134)

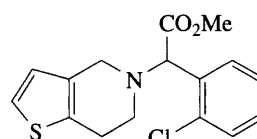


(135)

Ticlopidine (136), a thienopyridine derivative, and related compounds such as the ester (137) are being tested for use in the chronic therapy of arterial thrombotic disorders <92MI 706-01>.



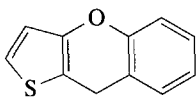
(136) Ticlopidine



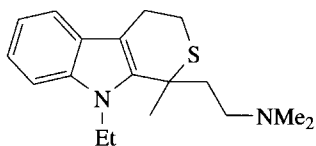
(137)

7.06.12.2 Thienopyrans and Thiopyranopyrroles

Thienobenzopyran derivatives based on structure (138) were synthesized and found to possess anti-inflammatory activity <84JAP8427894>.

**(138)**

Tandamine (139) is a thiopyranopyrrole derivative and has been tested as an antidepressant <83MI 706-01>.

**(139)**

7.07

Bicyclic 5-6 Systems: Three Heteroatoms 1 : 2

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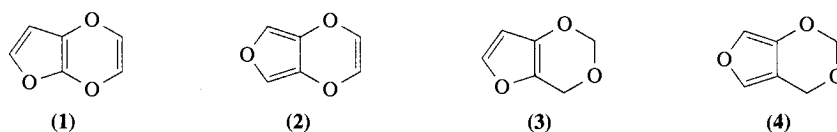
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7.07.1 INTRODUCTION

The subject matter of this chapter was mainly covered in two chapters in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(4)97, 84CHEC-I(4)973>. There are also occasional references to some compounds in other chapters, for example in chapters on benzofurans and benzothiophenes. In most cases the ring systems have not been studied in a systematic way, although many examples have been prepared. The systems which have attracted the most attention are the fused diazines, and these systems are covered in the greatest detail in this chapter. Some ring systems are not covered, either because there is little data on them or because they are more logically covered under other headings. Examples of these are the furodioxins. The furo[2,3-*b*]-1,4- (**1**), furo[3,4-*b*]-1,4- (**2**), 4*H*-furo[3,2-*d*]-1,3- (**3**), and 4*H*-furo[3,4-*d*]-1,3-dioxin (**4**) have all been described in the literature. However, all of the systems which have been described are nonaromatic and are essentially carbohydrate derivatives. Several hundred references have appeared since 1982, most of which are in the journals devoted to carbohydrate chemistry. There was only one mention of a furodioxin and one mention of a thienodioxin in CHEC-I. Therefore the systems are not covered in this chapter, and the reader is directed to the carbohydrate literature for data on them <84CHEC-I(4)973>.

The interest in, and importance of, the compounds which are the subject of this chapter is indicated by the very large number of references (several thousand) which have been published since 1982. A survey of the literature in which the two heteroatoms in the six-membered ring are nitrogen reveals a considerable variety of interest. The fused diazines were covered to some extent in CHEC-I and the pyrrolopyrimidines had been the subject of a previous review <74S837>. Not surprisingly, the pyrrolo[2,3-*d*]pyrimidines and pyrrolo[3,2-*d*]pyrimidines, also known as 7- and 9-deazapurines, respectively, have commanded the most interest in laboratories around the world. Pyrrolopyridazines, although a much less studied subject, have also been reviewed <B-73MI 707-01>.



The oxygen and sulfur analogues, the furodiazines and thienodiazines, have attracted less interest. A brief review of the furo- and thieno[2,3-*d*]pyrimidines, which also included the pyrrolo[2,3-*d*]pyrimidines, has been published <85RCR262>. The other six-membered ring, two heteroatom, fused systems have been grouped together in this chapter as miscellaneous fused pyrrolo, furo, and thieno systems (Sections 7.07.5.10 to 7.07.5.12). Apart from a few cases, there are relatively few examples of them. All of the ring systems which are considered in this chapter are illustrated in Figures 1–5.

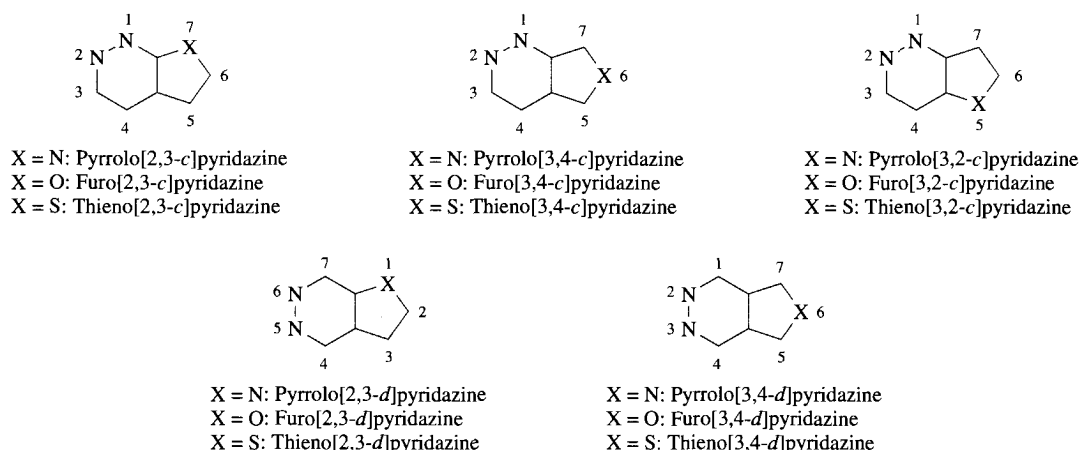


Figure 1 Fused pyridazines.

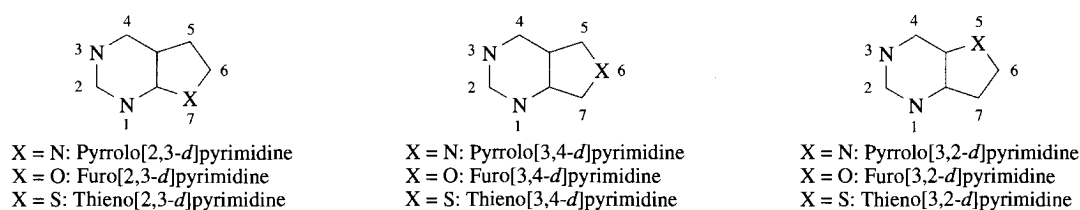


Figure 2 Fused pyrimidines.

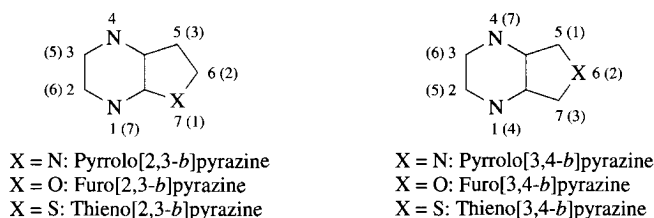


Figure 3 Fused pyrazines.

7.07.2 THEORETICAL METHODS

Although there is a large body of literature associated with these ring systems, very little of it is related to fundamental properties or to structural considerations of the rings themselves. Much of the literature describes synthetic methods designed to create new functionality on existing ring systems. There was no data on theoretical methods for these ring systems in CHEC-I. However

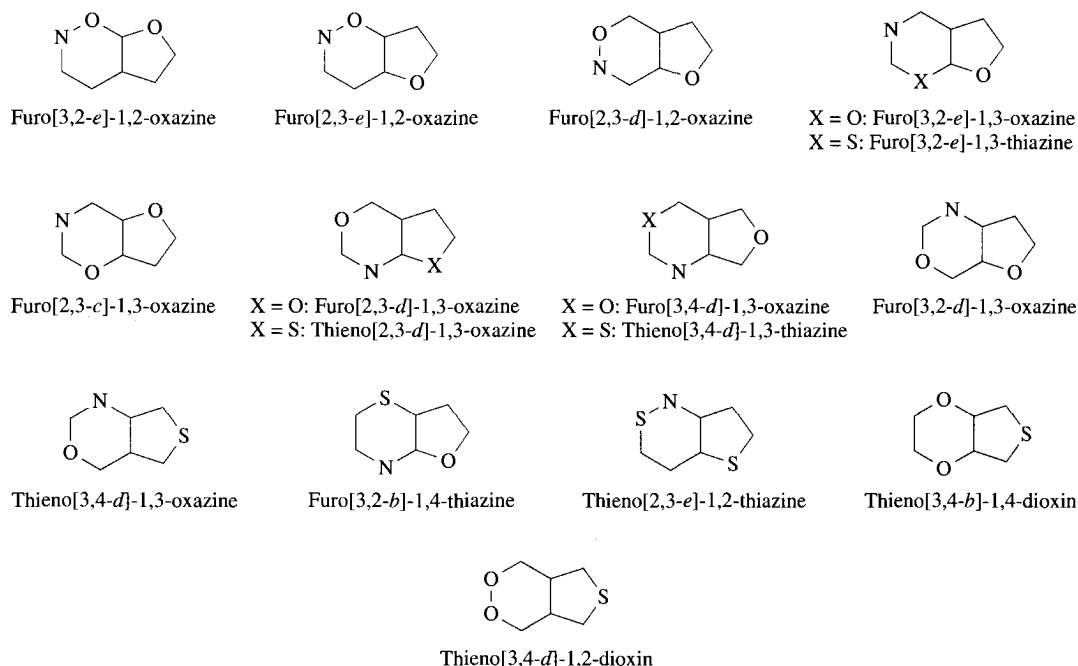


Figure 4 Fused oxazines and thiazines.

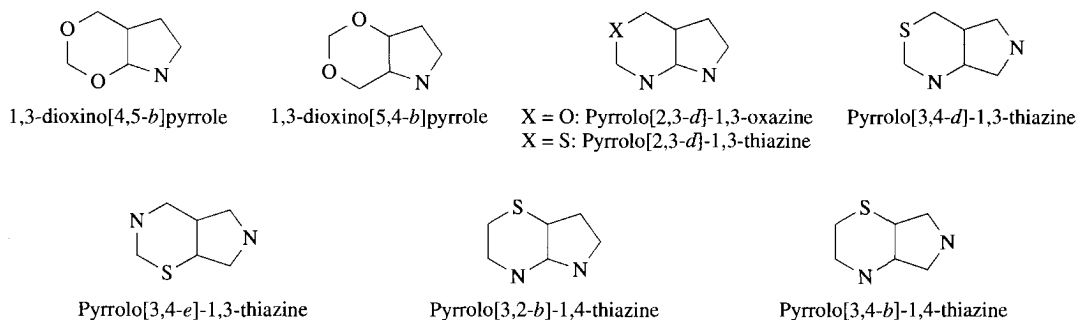


Figure 5 Pyrrolo fused systems.

there have been some reports of the use of molecular modeling and x-ray crystallographic data to predict types of molecules as targets for synthesis (93JMC55, 93JMC1847). Structures of substrates complexed with enzymes, such as purine nucleoside phosphorylase, have been examined by these techniques, and have been found to be useful.

7.07.3 EXPERIMENTAL STRUCTURAL METHODS

Much of the structural information relating to these compounds has been obtained by standard methods, and is included in the references to their synthesis. There is nothing to merit special discussion, and the more extensive reviews on the ring systems cited here, and in CHEC-I, cover this material. The NMR spectral data of the parent ring systems, where they have been measured, are given in Table 1.

Many complex derivatives of these rings, however, particularly natural products and nucleoside derivatives, have been isolated, and their structures have been determined by a combination of functional group manipulations, spectroscopic methods, and synthesis. Such compounds include the nucleosides dapiramicin A (83TL495), mycalisine A (88TL4073), kanagawamicin (83H(20)27), 2¹-C-, 3¹-C- and 5¹-C-methylsangavamicins (92H(33)391). Other nucleosides which have been isolated,

Table 1 Proton NMR chemical shifts for parent ring systems.

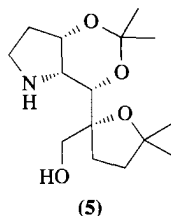
Compound	Solvent	Pos. 1	2	3	4	5	6	7
Pyrrolo[2,3- <i>b</i>]pyrazine	d ₆ DMSO		7.95	6.77		8.43 ^a	8.30 ^a	
Pyrrolo[2,3- <i>b</i>]pyrimidine	d ₆ DMSO		8.82		9.04	6.57	7.57	
Furo[2,3- <i>d</i>]pyridazine	CDCl ₃		8.04	7.06	9.65			9.57
Thieno[2,3- <i>d</i>]pyridazine	d ₆ DMSO		7.93	7.56	9.59			9.71
Thieno[3,2- <i>c</i>]pyridazine	CDCl ₃			9.14	8.04		7.85	
Thieno[3,4- <i>d</i>]pyridazine	d ₆ DMSO	9.16			9.16	8.53		8.53
Thieno[2,3- <i>d</i>]pyrimidine	d ₆ DMSO		9.12		9.36	7.61	8.02	
Thieno[2,3- <i>d</i>]pyrimidine	CDCl ₃		9.01		9.18	7.31	7.58	
Thieno[3,2- <i>d</i>]pyrimidine	d ₆ DMSO		9.22		9.59		8.55	7.68
Thieno[2,3- <i>b</i>]pyrazine	CDCl ₃		7.83	7.46		8.63	8.46	

^aUnconfirmed assignment.

and whose structures have been confirmed, are those from the marine organism *Echinodictyum hypnea* <83AJC165, 83BP347>, the cyanobacterium *Anabaena affinis* strain VS-1 <93JA2504>, *Streptomyces mirabilis* <87MI 707-01>, and *Jaspis johnstoni* <89MI 707-02>.

Nonnucleoside compounds which have been fully characterized include rigidin, from the marine tunicate *Eudistoma* cf. *rigida* <90TL4617> and echiguanines A and B from *Streptomyces* sp. <91MI 707-03>.

The complexity of many of these molecules contributes to errors in assignment of their structure. The crystal structure of an inhibitor of starfish embryonic development led to a revision of its structural assignment. Instead of a 4-oxo compound, the correct structure is 4-amino-7-(β-D-ribofuranosyl)-3*H*-furo[3,2-*d*]pyrimidine <92MI 707-02>. The crystal structure of compound (5), an intermediate in the enantioselective synthesis of 8-epicastanospermine has also been reported <93AX(C)40>.



There is some interest in the spectral properties of copper complexes of thieno[2,3-*d*]pyrimidines <88ICA165>, and of polymers of thieno[2,3-*b*]pyrazines <92CC1672, 93SM960>. The latter have been investigated as low band-gap polymers.

7.07.4 THERMODYNAMIC ASPECTS

Interest in the thermodynamic properties of these heterocycles is focused on their biological attributes. Typical of this activity is a study of the conformational restrictions of sangivamicin, and its analogues, and their correlation with inhibitory activity of protein kinase C <93CPB775>.

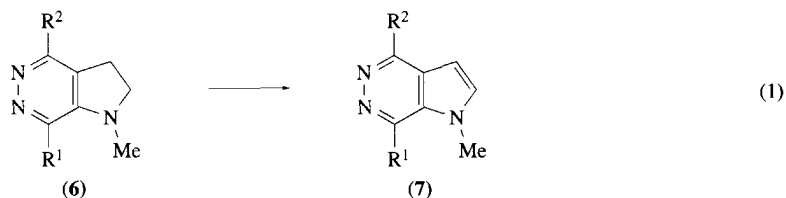
Measurements of the equilibrium binding of 7-deazaguanine analogues have also been reported <93BI1374>.

7.07.5 REACTIVITY OF THE BICYCLIC RINGS AND RING SUBSTITUENTS

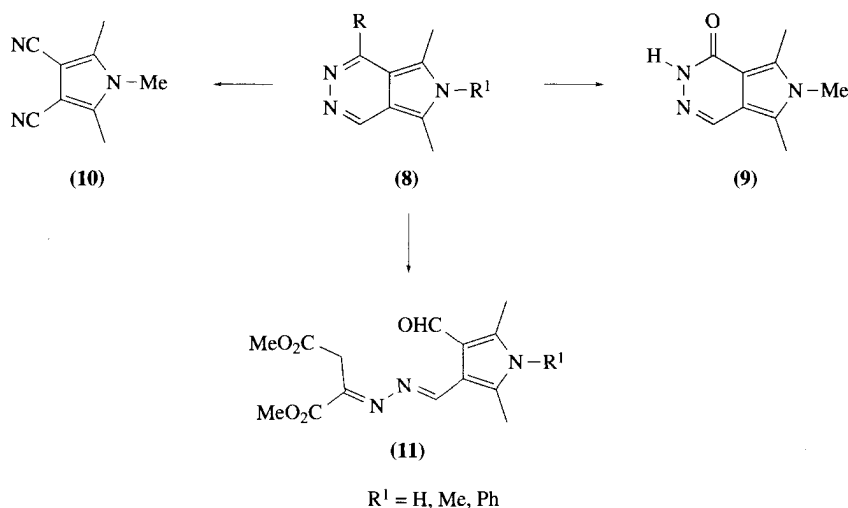
Relatively few fundamental reactions of these ring systems have been described and, rather than subdivide this section into reaction types, they have been divided into sections devoted to the different ring systems.

7.07.5.1 Pyrrolopyridazines

There have been few studies of the reactions of these ring systems. For example only one case of oxidation of a partially reduced ring system to form an aromatic ring is reported. The *N*-methylpyrrolo[2,3-*d*]pyridazine (6) is converted to the aromatic compound (7) on treatment with potassium permanganate (Equation (1)) <87JHC545>.



The reactions of pyrrolo[3,4-*d*]pyridazines are dominated by cleavage of the pyridazine ring. Treatment of 1-chloro-5,6,7-trimethylpyrrolo[3,4-*d*]pyridazine (8; R = Cl; R¹ = Me) with aqueous or alcoholic bases provides a good yield of the oxo product (9) (Scheme 1). On the other hand, similar bases in DMF give the pyrrole product (10) in addition to compound (9) <84CI(L)270>.



Scheme 1

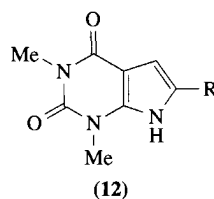
As part of a study to explore the Diels-Alder reactions of this ring system, compound (8; R = R¹ = H) was reacted with DMAD to give the pyrrole derivative (11) <85JCS(P1)899>. It appears that this ring cleavage is initiated by nucleophilic ring reaction with DMAD. Methyl propiolate behaves similarly, whilst DEAD reacts with the pyrrole ring instead <87JCR(S)356>.

7.07.5.2 Pyrrolopyrimidines

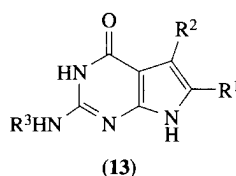
Considerably more attention has been paid to reactions of pyrrolopyrimidines than to any other ring system covered in this chapter. Clearly, their similarity to natural purines, as they are deazapurines, has been the cause of this interest. The discussion here will focus on the introduction of substituents at carbon and at nitrogen.

Almost without exception, the introduction of new substituents into aromatic pyrrolopyrimidines

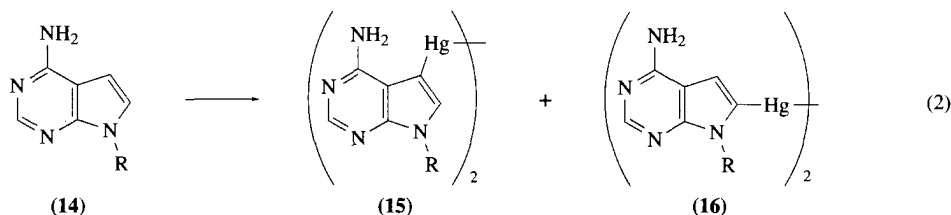
occurs in the pyrrole portion of the system. Acylation of the dioxo compound (**12**; R = H) with a variety of anhydrides provides a series of 6-acyl derivatives (**12**; R = acyl) <88JHC1443>.



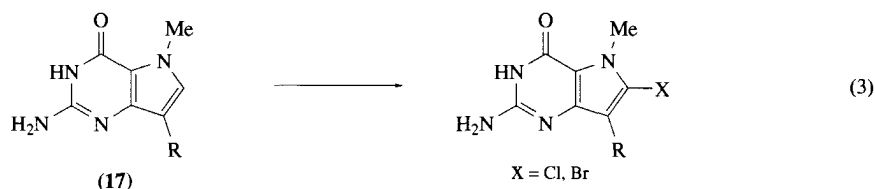
Alkylation, via the Mannich reaction, affords a mixture of 5- and 6-substituted products. Treatment of compound (**13**; R¹ = R² = R³ = H) with dimethylamine and formaldehyde leads to a mixture in which product (**13**; R³ = CH₂NMe₂, R² = H) is favored over product (**13**; R³ = H, R² = CH₂NMe₂) by 2 : 1 <83JHC1023, 88JCS(P1)1637>. The 4-thio analogue behaves similarly <86JMC1749>.



The great interest in palladium-catalyzed coupling reactions prompted the reaction between the 7-deazaadenine derivative (**14**) and mercury(II) acetate (Equation (2)). A mixture of the 5- and 6-substituted mercury compounds, (**15**) and (**16**) respectively, was obtained <91JOC5598>.



A similar reaction occurs with 2-pivaloylamino-4-oxopyrrolo[2,3-*d*]pyrimidine. In this case the ratio of the 6-mercuri derivative to the 5-mercuri derivative was 10 : 1 <93H(36)1897>. Subsequent conversion of the mercuri compounds to the corresponding iodo derivatives provides the actual substrates for the palladium-catalyzed coupling reactions. Direct halogenation of the pyrrole ring has also been effected. In the only position available both chlorination (sulfuryl chloride) and bromination (NBS) have been achieved on the C-nucleoside (**17**; R = benzoyletated ribose) (Equation (3)) <90JMC2750>.

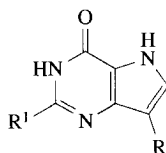


However, bromination has also been reported to occur at C-2 of the derivative (**18**; R¹ = H) as well as replacing a formyl group in the pyrrole ring of the aldehyde (**18**; R¹ = CHO). The resulting dibromo compound (**18**; R¹ = R = Br) can be dehydrogenated to give the deazahypoxanthine (**18**; R² = R¹ = H) <88KFZ860>.

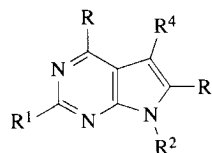
Many of the standard functional group interconversions are described in synthetic schemes involving the pyrrolopyrimidines. In order to conserve space, only a few illustrative examples are shown here. The references cited in Section 7.07.6.2 on synthesis should be consulted for further examples.

Replacement of chlorine by amines has been accomplished on a variety of structures resulting in 4-amino derivatives (**19**; R = Cl → **19**; R = amine) <83JHC295, 84LA1972, 89MI 707-01, 90ZC248>. The 4-

chloro group is less reactive than a 6-bromo substituent in the derivative (**19**; $R = \text{Cl}$, $R^4 = \text{Br}$) towards displacement by ammonia <90MI 707-03>. Displacement of a 2-chloro substituent is considerably more difficult. Nevertheless, hydrolysis of a 4-amino-2-chloropyrrolo[2,3-*d*]pyrimidine nucleoside is accomplished photochemically in the presence of water <91HCA1742>.



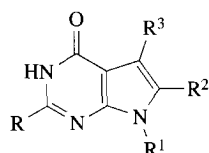
(18)



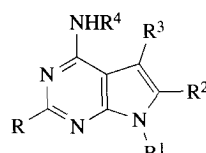
(19)

More common is the replacement of chloro groups by a variety of amines. This can occur at various sites on simple pyrrolopyrimidines (**19**) where chlorine has been located <82KFZ1338, 88KFZ185>, or on ring-chlorinated nucleosides (**19**; $R^2 = \text{carbohydrate}$) to obtain analogues of purine nucleosides <87JHC821, 90JHC171>. Likewise, sulfur has been introduced by replacement of chlorine using thiourea <84KFZ958>.

An alternative pathway to 4-aminopyrrolopyrimidines involves the one-pot conversion of 4-oxo compounds (**20**) into the desired amines (**21**). Primary alkyl- or aryl-amines, phosphorus pentoxide and an organic base lead to the expected products (Equation (4)) <85LA142, 85JHC859, 88CS201, 88CS427>.



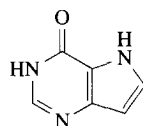
(20)



(21)

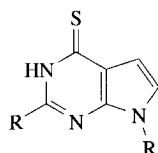
(4)

Alkoxy groups are convenient substituents in the primary synthesis of fused pyrimidines. These allow the formation of oxo derivatives to proceed smoothly. One example of this is the hydrolysis of the 4-methoxy derivative by hot aqueous hydrochloric acid to give the 3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**22**) which is a deazahypoxanthine <92JCS(P1)1883>.



(22)

The use of sulfur substituents at C-4 has seen limited use in preparing other derivatives. One unusual reaction involves treatment of a 4-thio group, as in compound (**23**), with chloramine to give the *S*-aminated product (**24**), which is subsequently oxidized, selectively, to the sulfinamides or sulfonamides (Equation (5)) <90JMC1220>.



(23)



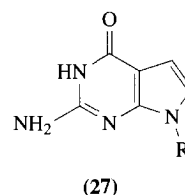
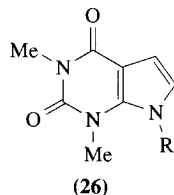
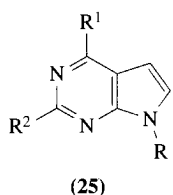
(24)

(5)

Whilst not strictly a functional group interconversion, the palladium-catalyzed coupling reaction is becoming more commonplace in synthesis involving halogenated rings. Thus, 5-iodopyrrolo[2,3-*d*]pyrimidines serve as good substrates for this process <90TL3731>.

Clearly, the most widespread nucleophilic reaction by heteroatoms is alkylation at ring nitrogen atoms. It is unsurprising that the very great interest in nucleosides of pyrrolo[2,3-*d*]pyrimidines, as deaza analogues of purine nucleosides, dominates this field. Selected examples of this chemistry

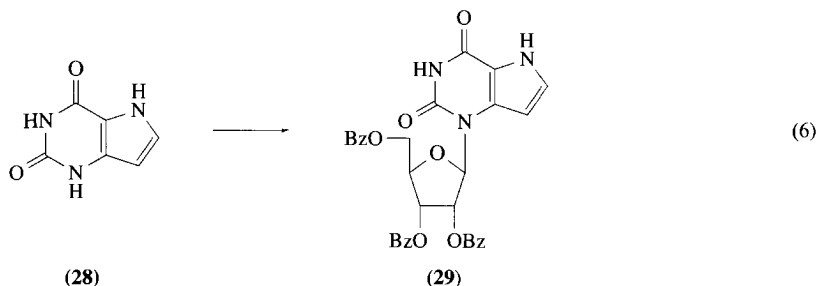
include those types of substituted compounds (25)–(27) where R = H is converted into R = carbohydrate.



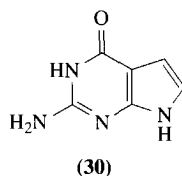
In the derivatives (25), for example, R¹ and R² may be H, Cl, MeO, NH₂ in any combination deemed essential to allow conversion to functionality consistent with natural purine nucleosides. The use of a stereospecific sodium salt glycosylation procedure developed by Robins and co-workers accounts for much of this synthetic activity <84JA6379, 85JMC1461, 88JHC1893>.

Phase-transfer-mediated glycosylation accounts for the development of the majority of nucleosides in this area. This technique has been exploited by Seela and co-workers <83LA876, 83JOC3119, 84LA273, 85LA1360, 87LA15, 88JCS(P1)697, 89H(29)2193>. Other workers have utilized more conventional methods for the synthesis of similar nucleosides <85S926, 86BCJ1915, 86T199, 88TL4061>.

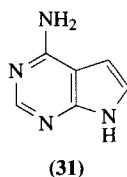
Alkylation on ring nitrogen remains the most frequently cited reaction of a heteroatom. Due to the considerable interest in nucleosides for their biological importance, this will be dealt with further. Standard treatment of the dioxo compound (28) with hexamethyldisilazane, followed by 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose gives the protected nucleoside (29) (Equation (6)), which can be converted into the free nucleoside with methanolic ammonia <92JHC343>.



The antiviral activity of acyclovir, with that of other similar compounds, has created significant interest in the synthesis of acyclic sugar analogue derivatives of pyrrolo[2,3-*d*]pyrimidines as 5-deaza analogues. Generally, these compounds are prepared from the heterocycle via alkylation at N-7 in a manner analogous to nucleoside formation. Thus, the derivatives (25–27; R = H) are readily converted to the derivatives (25–27; R = (substituted)alkyl). Typically, the heterocycle is treated with sodium hydride to generate the nitrogen anion which then reacts with an appropriate alkyl halide to give the desired product. In this way hydroxyethoxymethyl <83LA137, 88JMC1501, 88JMC2086, 89JMC1420>, 1,3-dihydroxy-2-propoxymethyl <85JHC1137, 89JMC402, 90JMC1984>, propanoic acid <85HCA2165>, 2,3-dihydroxypropyl <82LA1940>, and phosphonomethoxypropyl <93CCC1403, 93CCC1419> analogues have been described. The isomeric *N*-methyl derivatives of 7-deazaguanine (30) have been obtained in an unequivocal manner. Excess dimethyl sulfate affords the 3-methyl derivative whilst the 7-methyl isomer is obtained by using phase-transfer-catalyzed methylation of 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine with methyl iodide. Hydrolysis of the chloro group leads to the guanine analogue. The 1-methyl isomer is derived by cyclization of the appropriate *N*-methylated pyrimidine <84JMC981>.

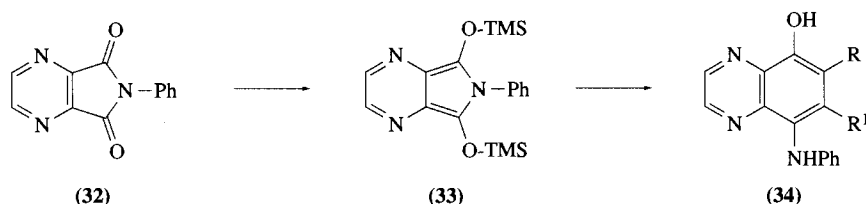


Alkylation of 7-deazaadenine (31) affords mixtures of products arising from reaction at N-1 and N-3 as well as the exocyclic amino group <84MI 707-02>.



7.07.5.3 Pyrrolopyrazines

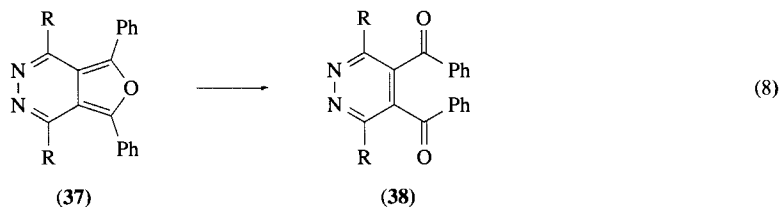
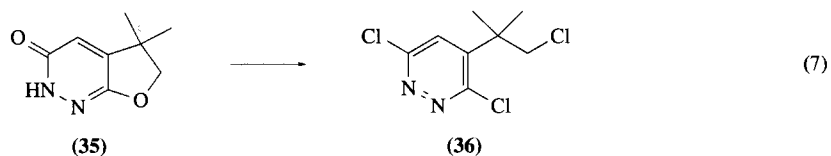
There is a paucity of functional group reactions associated with the pyrrolopyrazines. A few examples may be found within the references describing their syntheses. However, a reaction has been reported which describes the [4 + 2] cycloaddition of pyrrolopyrazines. Ring expansion of 2-phenyl-2*H*-pyrrolo[3,4-*b*]pyrazine (32) occurs through cyclocondensation of the trimethylsilyl ether (33) with, amongst other dienophiles, methyl acrylate, and a mixture of quinoxalines (34) is obtained in 38% yield (Scheme 2) <86JHC1641>.



Scheme 2

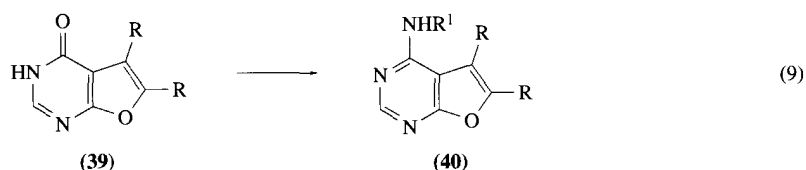
7.07.5.4 Furopyridazines

The major reaction described for furopyridazines is ring opening. The furo[2,3-*c*]pyridazine (35) is converted, in 50% yield, to the chloropyridazine (36) on treatment with phosphoryl chloride in chlorobenzene with DMF as catalyst <88JOC5704>. The symmetric furo[3,4-*d*]pyridazine (37; R = H, Ph) is oxidatively cleaved with ceric ammonium nitrate to give the pyridazine (38) (Equations (7) and (8)) <83S1018>.

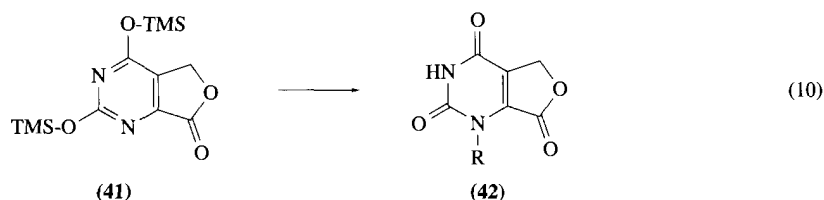


7.07.5.5 Fuopyrimidines

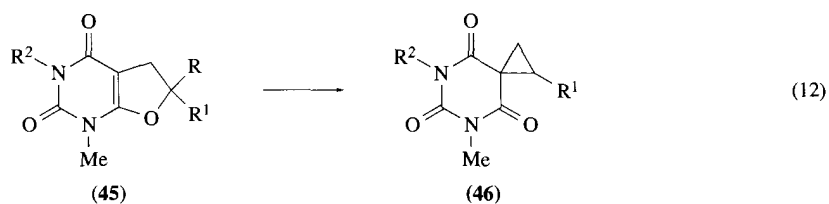
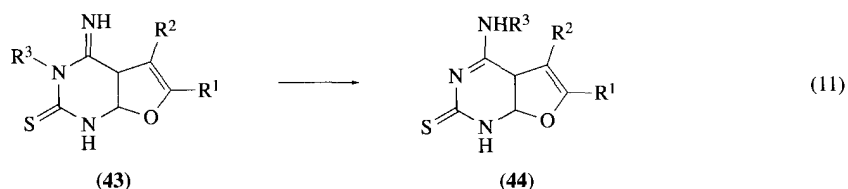
Fuopyrimidines undergo many of the reactions that the pyrrolopyrimidines do, although there are fewer examples. The conversion of the oxofuro[2,3-*d*]pyrimidine (39) to the (substituted)amino compound (40) with phosphorus pentoxide and a primary amine exemplifies the type of functional group interconversion which is possible (Equation (9)) <86CS337>.



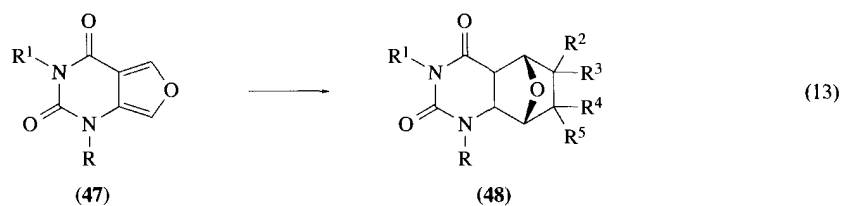
As with other nitrogen-containing heterocycles, *N*-alkylation is a reaction of some interest. This is particularly true when the products are nucleosides. One interesting example of nucleoside formation arises from reaction of a suitable furo[3,4-*d*]pyrimidine (**41**) and 1-*O*-acetyl-2,3,5-tribenzoyl- β -D-ribose: the product formed seems to be solvent dependent. The *N*-1 substituted nucleoside (**42**; R = tribenzoylribose) is formed in 81% yield when the heterocycle and the protected sugar are treated with tin(IV) chloride in acetonitrile. However, use of 1,2-dichloroethane as solvent affords only 17% of this product together with 81% of the *N*-1,*N*-3 disubstituted product (Equation (10)) <83CPB3074>.



Two examples of ring opening, followed by a recyclization step, have been reported. The Dimroth reaction of the furo[2,3-*d*]pyrimidine (**43**) has been shown to yield the product (**44**) <91JIC660>. The photochemical ring opening of the furo[2,3-*d*]pyrimidine (**45**) and subsequent cyclization to the spiropyrimidine (**46**) is an interesting reaction (Equations (11) and (12)) <87CB1433>.

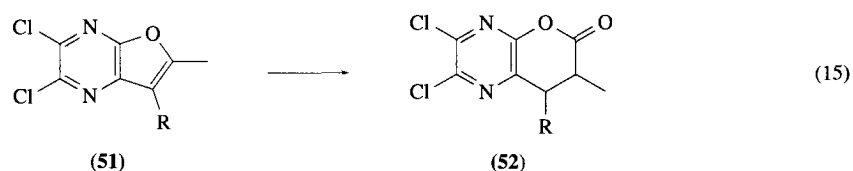
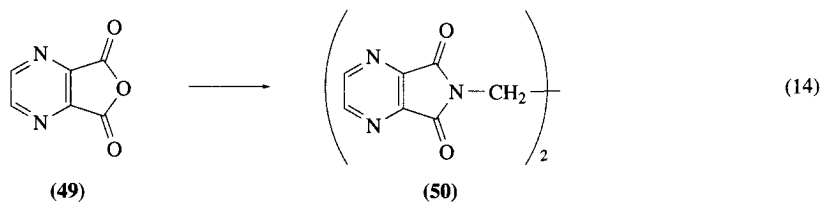


Furo[3,4-*d*]pyrimidines are ideally suited for participation in Diels-Alder reactions. The reaction of the derivatives (**47**) with dienophiles leads to tricyclic compounds of the type (**48**) <91JOC245>. There is some selectivity, since methyl acrylate forms only two regioisomeric *endo* products whilst other dienophiles yield both *endo* and *exo* adducts (Equation (13)).



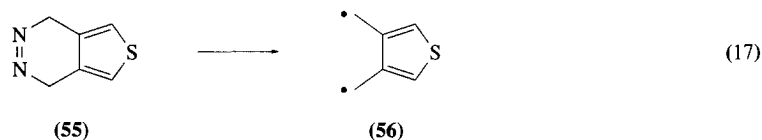
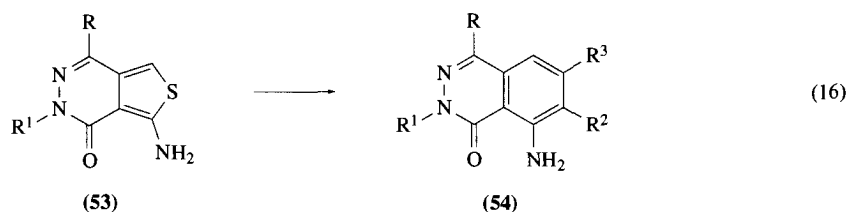
7.07.5.6 Furopyrazines

Two reactions of note involve ring opening, followed by cyclization to a new bicyclic system. In a classic reaction the dioxofuro[3,4-*d*]pyrazine (**49**) undergoes reaction with 1,2-diaminoethane to give the bispyrrolopyrazine (**50**). Presumably other primary amines would react in a similar manner <91AP(324)185>. A less obvious process is observed in the reaction of the furo[2,3-*b*]pyrazine (**51**; R = CO₂Et, CONEt₂) with potassium cyanide. The product (**52**) probably results from cyclization of a carboxylic acid group producing the lactone ring. The acid may be derived from initial addition of the cyanide ion to the C—C bond of the furan portion of the molecule, followed by ring opening and subsequent hydrolysis of the cyano group (Equations (14) and (15)) <83JHC365>.



7.07.5.7 Thienopyridazines

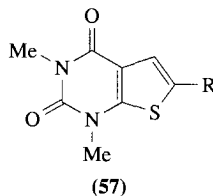
Although there is very little reported on the reactions of thienopyridazines, thieno[3,4-*d*]pyridazines (**53**; R = CO₂Et or CSNH₂, R¹ = Ph or 4-ClC₆H₄), like the comparable oxygen system, undergo Diels–Alder reactions quite readily. Dienophiles such as phenylvinyl ketone, chalcone, and β-nitrostyrene, lead to the appropriate benzenoid compounds (**54**) upon loss of sulfur <93JCR(S)130>. In another reaction, without apparent synthetic value, the dihydrothienopyridazine (**55**) undergoes a photochemical cleavage to form the diradical (**56**). This reactive intermediate is of theoretical interest <87TTL4263>.



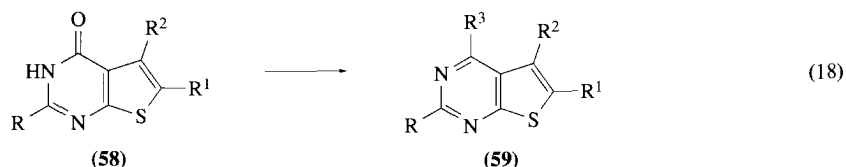
7.07.5.8 Thienopyrimidines

The direct introduction of functional groups into the thienopyrimidine ring has been accomplished in some cases. The 6-substituted-thieno[2,3-*d*]pyrimidine (**57**; R = CHO) has been formed, using

phosphoryl chloride-DMF, from the precursor (**57**; R = H). Similarly, bromine leads to compound (**57**; R = Br) and nitric acid produces compound (**57**; R = NO₂) <90JHC717>.

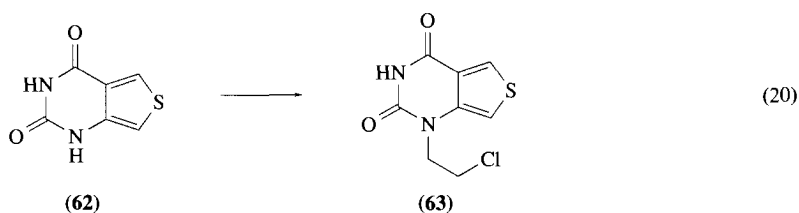
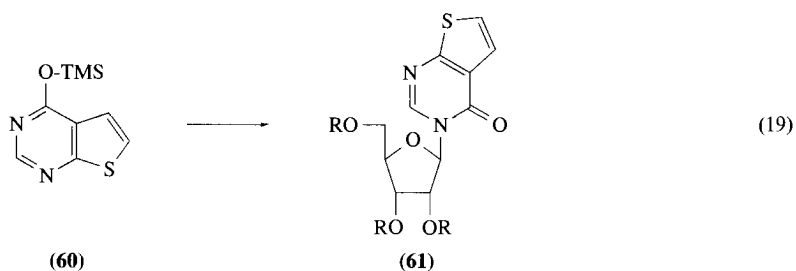


Halogenation of groups attached to the ring system has also been described. Bromination of methyl groups at the 5- or 6-positions of a series of thieno[2,3-*d*]pyrimidines has been accomplished using NBS <87KFZ197>. Exocyclic double bonds can also be halogenated using either bromine or iodine <89KGS413>. There is greater interest in producing halogenated ring systems which can undergo nucleophilic displacements. 4-Oxothieno[2,3-*d*]pyrimidines (**58**) are treated with phosphoryl chloride to give first the chloro compound (**59**; R³ = Cl) which is then substituted by a variety of nucleophiles <85KGS925, 86PHA23, 92PHA20, 93PHA192>.



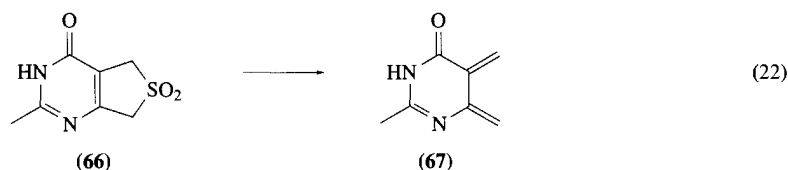
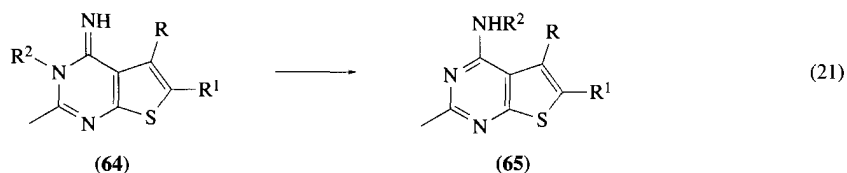
Substitutions can also occur at the 2-position of similar thienopyrimidines <86PHA23, 91IJC(B)618>. 2-Methylthiothieno[2,3-*d*]pyrimidines undergo reaction with hydrazine in an analogous manner <87KGS1131>.

Condensation between aromatic aldehydes and either 2-methyl- <87PHA131> or 4-methyl- <89YZ642> thieno[2,3-*d*]pyrimidines provides the corresponding vinyl-substituted derivatives. Alkylation reactions have been described at both nitrogen and sulfur sites. Nucleoside (**61**) formation results from the reaction of the ether (**60**) (Equation (19)) with an appropriately substituted ribose derivative. However, location of the carbohydrate did not occur at the desired nitrogen <85JMC423>. Reactions of other 4-oxothieno[2,3-*d*]pyrimidines also favor N-3 substitution <86PHA661>. Similar results occur with 2,4-dioxo compounds <86PHA661> and disubstitution is also observed when phase-transfer catalysis is used <83PHA135>. However, N-1 substitution (**63**) is reported when 2,4-dioxothieno[3,4-*d*]pyrimidine (**62**) is alkylated with 1-bromo-2-chloroethane (Equation (20)) <92SC3221>.



2-Thiolthieno[2,3-*d*]pyrimidines can be alkylated with simple alkyl derivatives <90PHA493> or with complex alkyl moieties <87PHA160>.

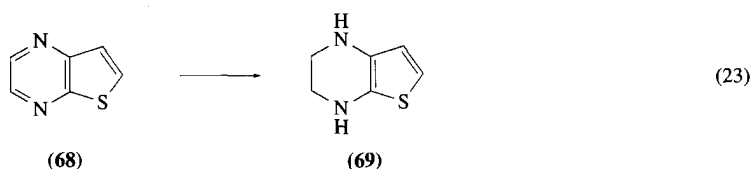
Several reactions involving ring opening should be noted. As expected the derivatives **(64)** undergo Dimroth rearrangement to form the isomers **(65)** (Equation (21)) <88CS195>. Loss of sulfur dioxide from compound **(66)** on heating leads to 2-methyl-5,6-dimethylenepyrimidin-4-one **(67)** (Equation (22)). This reactive species **(67)** has been trapped by dienophiles and by nucleophiles <93SL347, 93SL397>.



7.07.5.9 Thienopyrazines

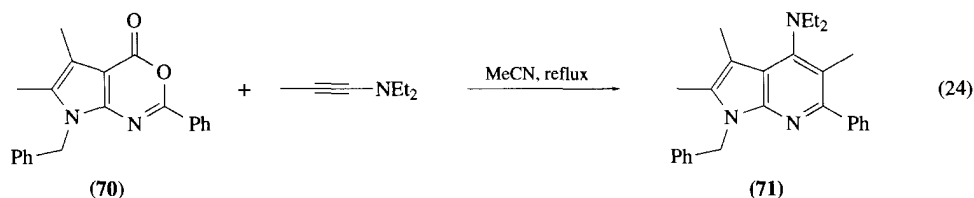
Consistent with a sparse literature for the synthesis of thienopyrazines, there is very little of note that can be recorded for reactions of these ring systems.

One study that could have synthetic utility is the electrochemical reduction of thieno[2,3-*b*]pyrazines, such as the parent molecule **(68)** to the corresponding tetrahydro compound **(69)** (Equation (23)) <91JOC4840>. Thieno[3,4-*b*]pyrazine, as well as the oxygen analogues of both compounds, behave similarly.

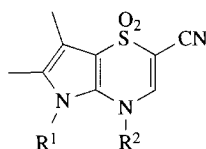


7.07.5.10 Miscellaneous Fused Pyrrole Systems

The pyrrolooxazines **(70)** undergo Diels–Alder cycloadditions with *N,N*-diethyl-1-propynylamine, followed by carbon dioxide extrusion to yield pyrrolopyridines **(71)** <87CB1427>. The furooxazines react similarly (Equation (24)).

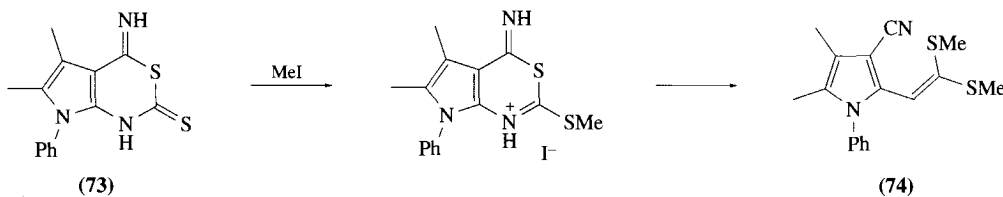


The pyrrolothiazine dioxides **(72)**, some of which show muscle relaxant properties, can be ethylated (NaH/THF, reflux) to give the *N*-ethyl derivatives, but all attempts to hydrolyze the nitrile to the corresponding acid have failed <88PJS242>. The compound **(73)** was first reported in 1966 <66AG333>. Its methylation has been shown to give the *S*-methyl product but prolonged reaction leads to the pyrrole **(74)** (Scheme 3) <87JHC425>.



(72)

$R^1 = \text{PhCH}_2, \text{PhCH}_2\text{CH}_2, \text{cyclohexyl}, \text{Bu}$ and others
 $R^2 = \text{H}, \text{Et}$

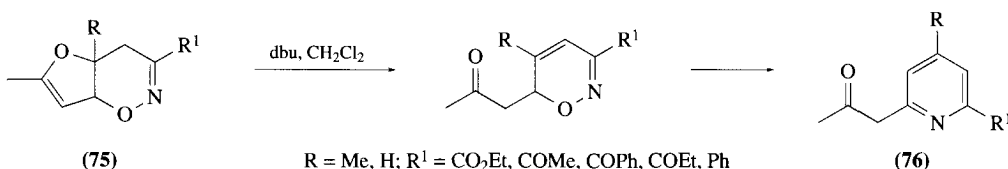


Scheme 3

7.07.5.11 Miscellaneous Fused Furo Systems

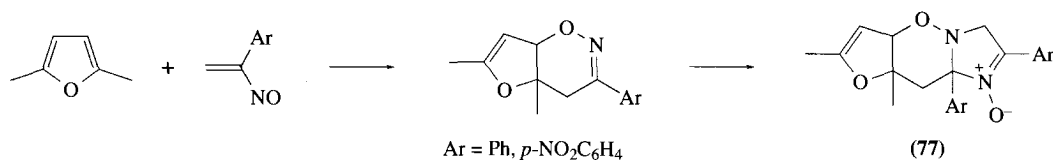
The coverage of hetero-fused furo systems in CHEC-I was sparse, and there were few references. However, it was recorded that 4*H*-furo[3,4-*d*][1,3]oxazine-2(1*H*),4-dione can be synthesized from diethyl 3,4-furandicarboxylate, and that it reacts with N or O nucleophiles exclusively at the *N*-carbonyl to give ureido or carbamato acids <81JOC3853>. The preparation and reactions of furo-oxazines have been extensively studied in particular by Gilchrist and co-workers <79CC1089, 79JCS(P1)249, 79JCS(P1)258, 81JOC3853>.

The furooxazines (75) react with DBU to form oxazines which can react further under the conditions of the reaction to yield pyridines (76). The compound (75; $R = \text{H}, R^1 = \text{Ph}$) rearranges under acid catalysis to yield α -(2-furyl)acetophenone oxime (Scheme 4) <79JCS(P1)249, 83JCS(P1)1283, 87JCS(P1)2505>.



Scheme 4

The furooxazines obtained from the cycloaddition of α -nitrostyrene, generated *in situ* from chloroacetophenone oxime, to 2,5-dimethylfuran react further with nitrostyrene, or with other nitrosoalkenes, to yield the tricyclic nitrones (77) (Scheme 5) <90JCS(P1)1497>.



Scheme 5

The tricyclic compound (79), obtained from 5-hydroxy-2-pentenolide (78), undergoes ring opening on treatment with hydrazoic acid/sodium azide to give a mixture of the two furooxazine stereoisomers (80) and (81). These undergo the series of reactions shown in Scheme 6 <86HCA1442>.



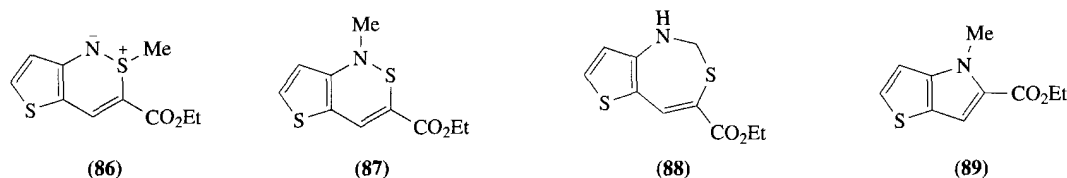
7.07.5.12 Miscellaneous Fused Thieno Systems

$$\begin{array}{ccc}
 \text{p-MeOC}_6\text{H}_4 & \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{PhCH}_2\text{NH}_2} & \text{p-MeOC}_6\text{H}_4 \\
 \text{O} & & \text{O} \\
 \text{N} & & \text{N} \\
 \text{Ph} & & \text{Ph} \\
 \text{(82)} & & \text{(83)}
 \end{array}$$

(25)

$$\begin{array}{ccc}
 \text{Thienothiopyran derivative (84)} & \xrightarrow[\text{>120 } ^\circ\text{C}]{\text{heat}} & \text{Thienothiopyran derivative (85)} \\
 \text{(84)} & & \text{(85)}
 \end{array}
 \quad (26)$$

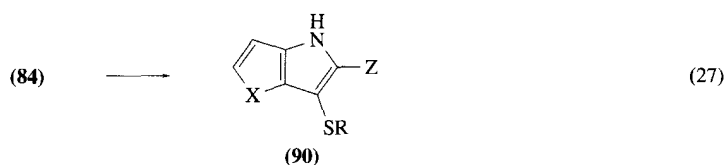
On thermolysis the *S*-methyl-thienothiazine (**86**) gives, in addition to the expected product (**87**), the thieno-1,3-azepine (**88**). When the reaction is carried out in boiling bromobenzene, the *N*-methylthienopyrrole (**89**) (9%) is also obtained <86JCS(P1)491>. The formation of the thiazepine can be explained by tautomerism of compound (**86**) into the isomeric sulfonium ylide followed by a [1,2] nitrogen shift to the carbanionic centre in a Stevens-type rearrangement. A possible mechanism for the formation of the *N*-methylthienopyrrole is a [1,2] methyl shift from S to N followed by extrusion of sulfur <86JCS(P1)491>.



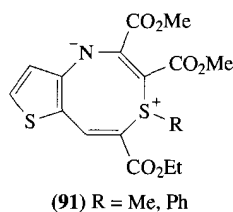
The fused thiazines (**84**) have been shown to be photo-labile and they decompose in acetonitrile at 300 or 350 nm to yield fused pyrroles (**90**) (Table 2) suggesting that the RS group undergoes a very rapid [1,5] sigmatropic shift (Equation (27)) <86JCS(P1)497>.

Table 2 Photo-decomposition of thieno[3,2-*c*][1,4,2]thiazines (**84**) and related species <86JCS(P1)497>.

<i>X</i>	<i>R</i>	<i>Z</i>	Yield (%)
S	Me	CO ₂ Et	50
S	Ph	CO ₂ Et	83
S	Ph	COMe	77
S	Ph	CHO	75
O	Ph	CO ₂ Et	32
CH:CH	Ph	CO ₂ Et	75



The thienothiazines (**86**) react with DMAD in aprotic solvents at room temperature to yield 1,4-thiazocines (**91**) but in protic solvents 2:1 adducts are also observed <82CC1060>.



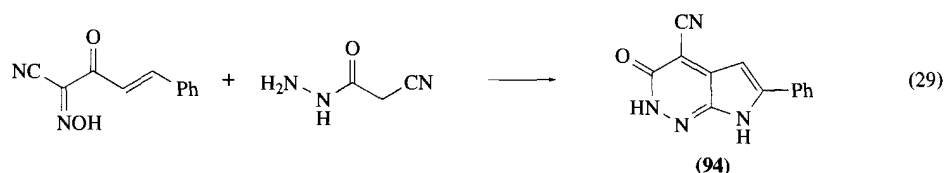
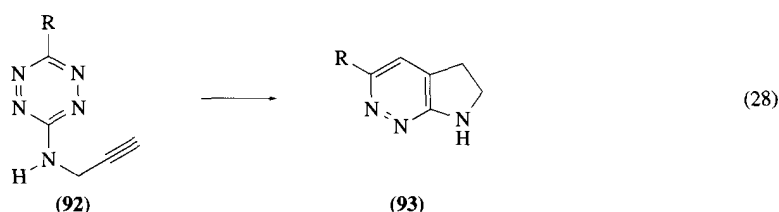
7.07.6 RING SYNTHESSES

7.07.6.1 Pyrrolopyridazines

7.07.6.1.1 Pyrrolo[2,3-*c*]pyridazines

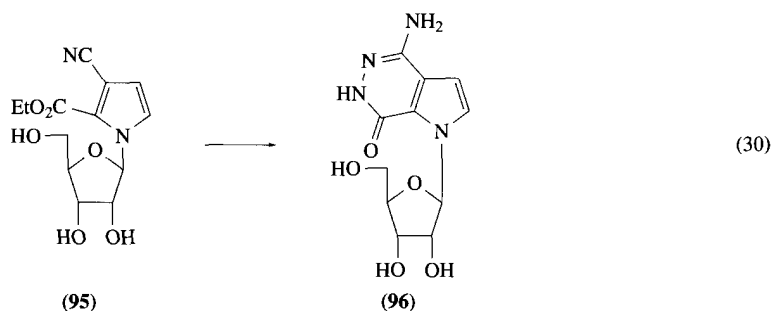
A common method of synthesizing heterocyclic rings is intramolecular cycloaddition. This approach has been successfully used with the tetrazine (**92**) to yield the reduced pyrrolo[2,3-*c*]-

pyridazine (**93**) (Equation (28)) <84CZ331>. One example of the synthesis of a pyrrolo[2,3-*c*]pyridazine, without the isolation of a monocyclic intermediate, has been reported when cinnamoyl-acetonitrile oxime and cyanoacetic acid hydrazide react together to give the derivative (**94**) (Equation (29)) <91MI 707-02>.

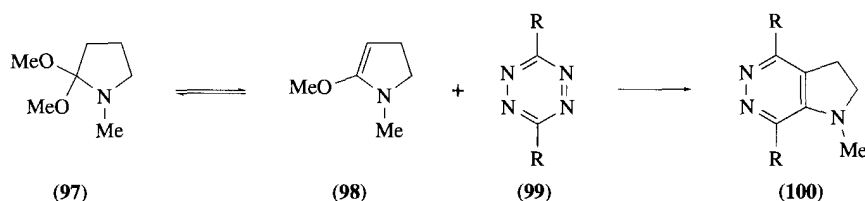


7.07.6.1.2 Pyrrolo[2,3-*d*]pyridazines

Formation of the pyridazine ring occurs in a straightforward way from a suitably substituted pyrrole. Thus the pyrrole nucleoside (**95**) forms the pyrrolo[2,3-*d*]pyridazine (**96**) on treatment with hydrazine <93JMC3834>. Another report describes the preparation of 4-amino-1-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyridazine (Equation (30)) <91BMC111>. Similar pyrrole nucleosides, with an ester function at position 3 and an aldehyde at position 2, lead to 4-oxo derivatives upon treatment with hydrazine <90JHC1989>, or 4-amino derivatives with a cyano group at position 3 <92JMC526>.

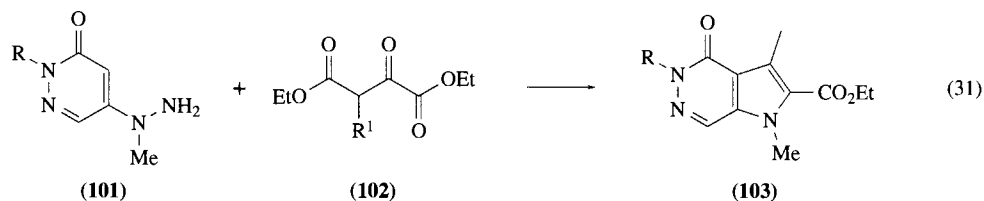


Diels–Alder cycloaddition reactions with tetrazines provide a useful approach to the preparation of pyrrolo[2,3-*d*]pyridazines. Thus, the lactam acetal (**97**), which is in equilibrium with the cyclic ketene *N,O*-acetal (**98**), reacts with tetrazines (**99**) to give the partially reduced product (**100**) <86CB3600>. The methylthio analogue of the acetal (**97**) also reacts similarly with tetrazines (Scheme 7) <87JHC545>.

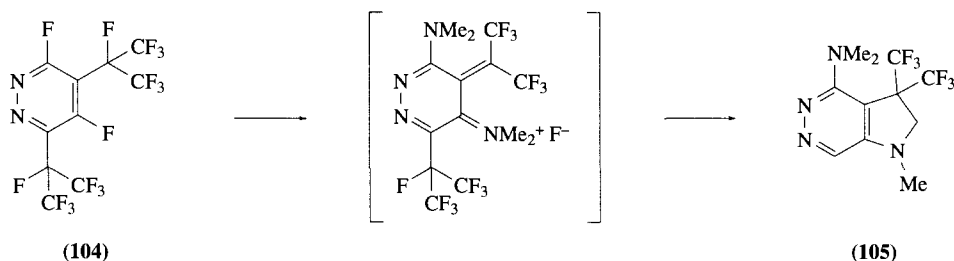


Scheme 7

A synthetic approach designed to produce pyridazino[4,5-*c*]pyridazinones unexpectedly yields pyrrolopyridazines, although in poor yields. The acid-catalyzed reaction between the hydrazine (**101**) and ketodiester (**102**) results in formation of the pyrrolo[2,3-*d*]pyridazine (**103**) (Equation (31)) <92JHC1313>.



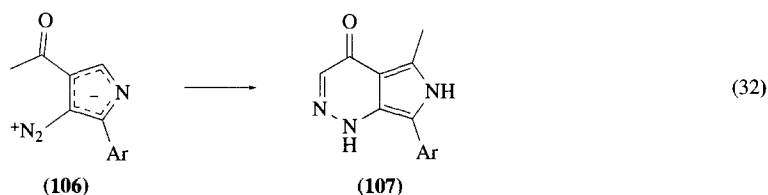
A novel process involving displacement of fluoride provides a route to pyrrolo[2,3-*d*]pyridazines but it is of very limited synthetic application. The highly fluorinated pyridazine (**104**) undergoes displacement of the heteroaryl fluorines by dimethylamine leading to the product (**105**) in 66% yield, via a postulated orthoquinoid intermediate (Scheme 8) <82CC1412>.



Scheme 8

7.07.6.1.3 Pyrrolo[3,4-*c*]pyridazines

An unexpected reaction which leads to pyrrolo[3,4-*c*]pyridazines is the action of acid on the 3-diazopyrrole (**106**), obtained from the corresponding amine. Although pyrrolocinnolines were the target compounds, the pyrrolopyridazine (**107**) was obtained (60%) (Equation (32)) <84H(22)2269>. However, the cinnoline product is obtained when the carbethoxy group is present instead of the acyl group at position 4 <83H(20)255>.



7.07.6.1.4 Pyrrolo[3,4-*d*]pyridazines and pyrrolo[3,2-*c*]pyridazines

No syntheses of these two ring systems have been reported since the early 1980s and there were no details of their synthesis in CHEC-I.

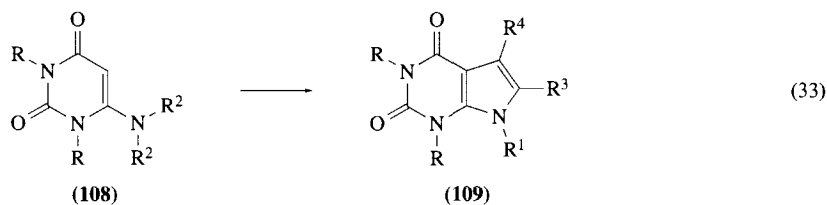
7.07.6.2 Pyrrolopyrimidines

The pyrrolopyrimidines have been much more extensively studied than the pyrrolopyridazines, and a large number of references have been extracted, some of which have been summarized for this section.

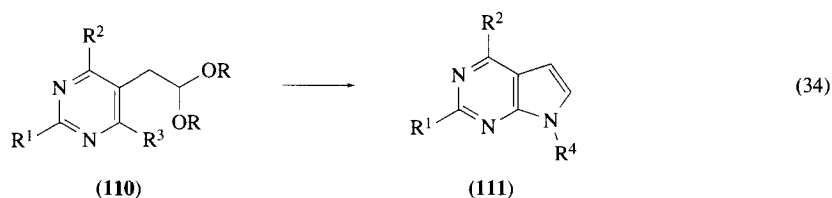
7.07.6.2.1 Pyrrolo[2,3-*d*]pyrimidines

(i) Syntheses from pyrimidines

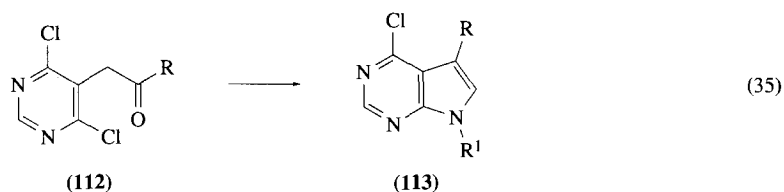
The majority of synthetic approaches to the pyrrolo[2,3-*d*]pyrimidine system involve a 6-amino-pyrimidine as the final precursor. The major variations of this approach either place substituents on the amine which ultimately appear in the C-5 position or place substituents on C-5 which condense with the 6-amino group. Examples of syntheses in which the C-5 position is unsubstituted start with 6-aminouracil derivatives (**108**) and produce the corresponding dioxypyrrolopyrimidines (**109**). Thus, for compound (**108**; R = H, R¹ = Me, R² = allyl) the monomethyl product (**109**; R¹ = Me, R = R³ = R⁴ = H) is obtained <89CPB3184>. In a similar manner compound (**108**; R = Me, R¹ = H, R² = propargyl) leads to the 1,3,5-trimethyl compound (**109**; R = R⁴ = Me, R¹ = R³ = H) <85CPB4740>. This pathway provides access to other derivatives, especially N-7 nucleosides. In a more elaborate series of reactions the compound (**108**; R = H, R² = CH₂CO₂H) has been used to obtain the alkaloid rigidin (**109**; R = R¹ = H, R⁴ = 4-hydroxybenzyl, R⁵ = 4-hydroxyphenyl) <93JOC403>.



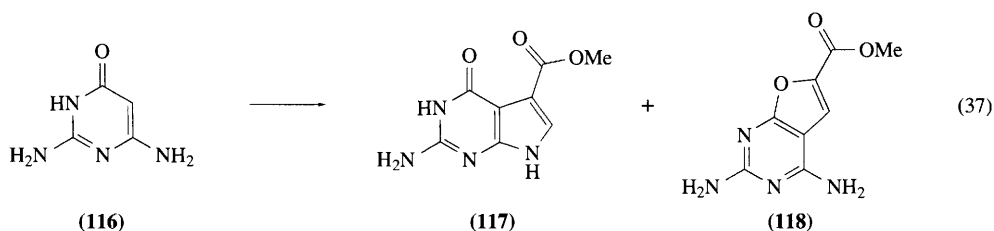
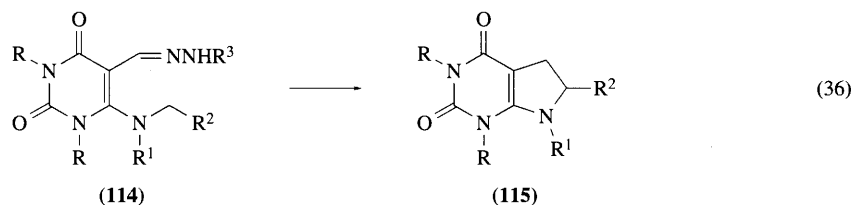
One route which involves a C-5 substituent, and which has been extensively studied, utilizes the acetal moiety, illustrated by the general structure (**110**). The most common synthetic scheme begins with the dichloro compound (**110**; R² = R³ = Cl) which is converted by the appropriate amine into the immediate precursor containing the desired substituent on the amine, very often a carbohydrate moiety. Hydrolysis of the acetal leads to simultaneous cyclization affording the derivatives (**111**) which, upon further manipulation, leads to deazapurine analogues of natural purines and their nucleosides (Equation (34)) <84JMC534, 85TL2001, 85JMC1477, 86MI 707-03, 90JHC2069, 92H(34)739, 92TL2249, 92BMC1279, 93JOC1696>.



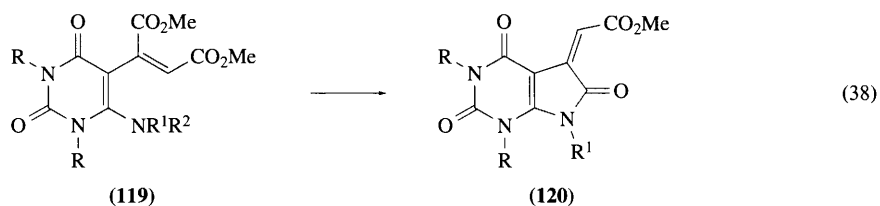
The use of keto groups at C-5 of the pyrimidine ring allows the synthesis of pyrrolo[2,3-*d*]pyrimidines with substituents at either C-5 or C-6 in the product. These carbonyl-containing groups are introduced either through a primary synthesis of the pyrimidine ring, or by alkylation at C-5 of the pyrimidine. One key intermediate structure required for elaboration into a pyrrolopyrimidine is illustrated by the precursors (**112**) which undergo nucleophilic displacement of one of the chlorines, followed by cyclization, to give the desired products (**113**) (Equation (35)) <83EJM269, 85EJM127, 93H(36)1897>. Further manipulation of the ring substituents leads to structures analogous to biologically active molecules. 5-Chloromethylcarbonyl-2,4-dichloropyrimidine <83JHC925>, 5-formyl-2,4-dichloropyrimidine <88JMC390>, and 5-chloromethylcarbonyl-1,6-dihydro-4-β-D-(2,3,4,6-tetra-*O*-acetyl)glucopyranosylamino-1-methyl-2-methoxy-6-oxypyrimidine <86MI 707-02>, all participate in similar chemistry to give N-7 substituted pyrrolo[2,3-*d*]pyrimidines.



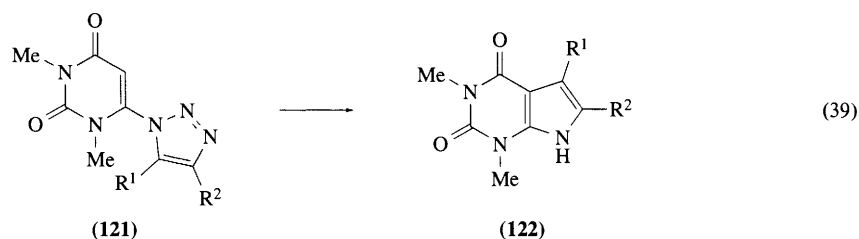
The hydrazone of a 5-formylpyrimidine (**114**) when treated with sodium hydride and then heated to 150°C also results in formation of a pyrrolopyrimidine (**115**) (Equation (36)) <89H(29)1993>. In a related reaction, treatment of 2,4-diamino-6(1*H*)-oxypyrimidine (**116**) with methyl chloroformylacetate gives both the pyrrolopyrimidine (**117**), and the furopyrimidine (**118**) (Equation (37)) <89JCS(P1)2375>. The latter can be converted into pyrrolopyrimidine products. Pyrrolopyrimidines with 5-amino substituents can be prepared from 5-cyanopyrimidines utilizing similar chemistry <88LA633>.



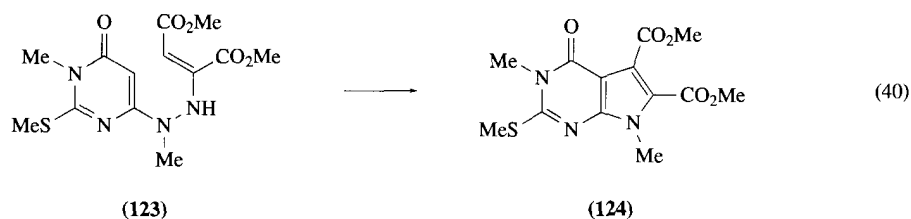
Other pyrimidine precursors with unsaturated chains at C-5 have been effectively employed to achieve a variety of pyrrolo[2,3-*d*]pyrimidines. The pyrimidine (**119**), obtained by reacting a 6-aminouracil with DMAD, upon heating, is converted into the highly oxidized pyrrolopyrimidine (**120**) (Equation (38)) <86H(24)927, 87JHC1215>. The analogous 5-allyl-6-aminouracil compounds lead to 6-methyl products <92CPB846>, whilst 5-allyl-6-chloro-2,4-dimethylpyrimidine reacts with hydrazine to give a 7-aminopyrrolopyrimidine <85KGS678, 89AKZ530>. The corresponding 5-vinyl derivatives form the azido compounds when treated with sodium azide. Thermal or photochemical reaction of the azide leads to 6-substituted-2,4-dimethylpyrrolo[2,3-*d*]pyrimidines <89CPB2933>.



Pyrimidines bearing high nitrogen-containing substituents at C-6 have been shown to form pyrrolopyrimidines. Loss of nitrogen accompanies the cyclization step. For example, the triazolyl ring in compound (**121**) undergoes photochemical degradation leading to the 6,7-disubstituted product (**122**) (Equation (39)) <91TL323>.

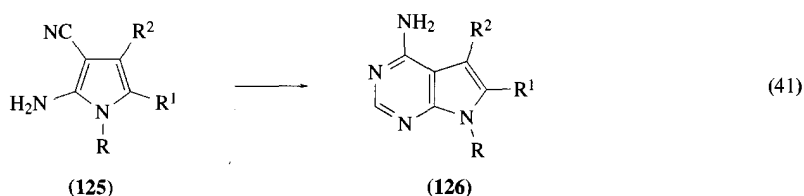


The thermal degradation of the hydrazine (**123**) results in elimination of nitrogen, with concomitant ring formation to give compound (**124**) (Equation (40)) <92JCS(P1)1287>.

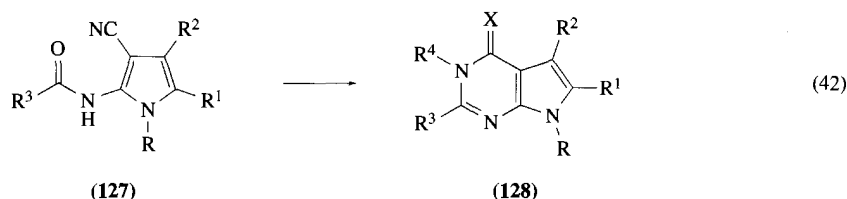


(ii) Syntheses from pyrroles

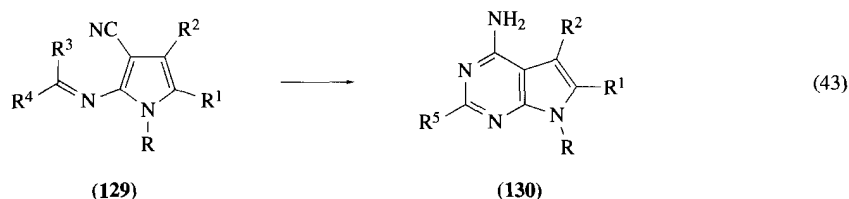
The elaboration of a pyrimidine ring onto another aromatic ring is usually accomplished by cyclization of two adjacent functional groups, one of which is an amine moiety. The majority of pyrrolo[2,3-*d*]pyrimidines developed from pyrroles have been prepared this way. 2-Amino-3-cyanopyrroles (**125**) serve to produce 4-aminopyrrolo[2,3-*d*]pyrimidines (**126**) (Equation (41)). Heating the pyrrole in DMF in the presence of formic acid is effective for this transformation <86JHC393, 86LA1485, 87JIC713, 88H(27)1861, 88IJC(B)778>. Triethylorthoformate, followed by treatment with ammonia, leads to similar products <90JMC2162>.

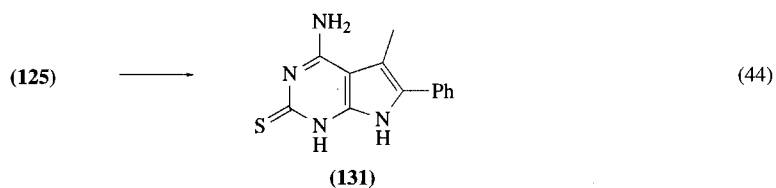


The opportunity to introduce substituents at C-2 of the pyrrolopyrimidine is afforded by the use of 2-(substituted)amino-3-cyanopyrroles. Treatment of acylaminopyrroles (**127**), most commonly with $R^3 = \text{Me}$, with phosphorus pentoxide, an arylamine hydrochloride, and *N,N*-dimethylcyclohexylamine at elevated temperatures, gives the derivatives (**128**; $X = \text{NH}$) (Equation (42)) <83LA2066, 84CS73, 85CS222, 85S101, 88CS303, 90H(31)367, 93AP(326)303>. In some cases the 4-imino derivative has been converted to the 4-oxo derivative (**128**; $X = \text{O}$) by hydrolysis.

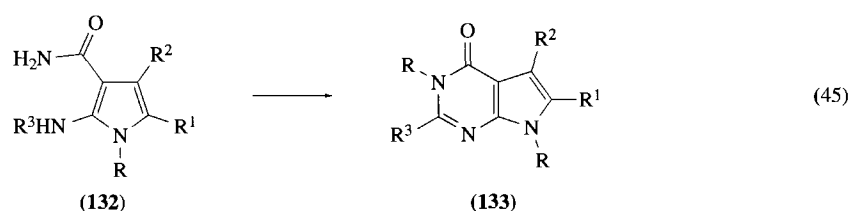


Certain derivatized 2-aminopyrroles (**129**) also provide 4-aminopyrrolopyrimidines unsubstituted at C-2. Thus pyrroles (**129**; $R^3 = \text{EtO}$, $R^4 = \text{H}$) yield the derivatives (**130**; $R^5 = \text{H}$) <86T5869>. However, compounds (**129**; $R^3 = R^4 = \text{NH}_2$) afford the derivatives (**130**; $R^5 = \text{aryl or Me}$) when reacted with the corresponding nitrile (Equation (43)) <87JHC425>. Reduced or partially reduced pyrroles lead to the expected reduced pyrrolopyrimidines <86CPB886, 92KGS1472>. Reaction between the pyrroles (**125**) and isothiocyanates produces 4-amino-2-thiopyrrolopyrimidines (**131**) (Equation (44)) <91JIC396>. A similar reaction between a suitably substituted reduced pyrrole and isocyanates gives the corresponding 2-oxo derivatives <85CB4473>.

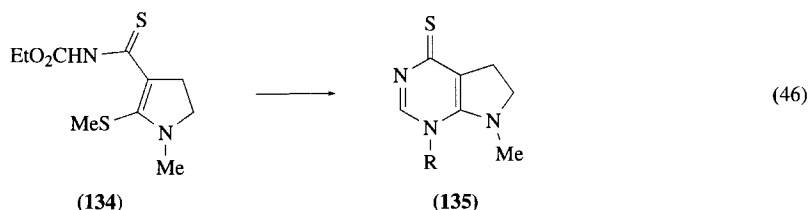




4-Oxopyrrolopyrimidines (**133**) can be prepared directly from 2-amino- (or 2-(substituted)amino)-3-carboxamidopyrroles (**132**) (Equation (45)) <86CS347, 90PHA245>. Reaction of the corresponding 3-carboxamido derivatives with phenylisothiocyanate affords the pyrrolo[2,3-*d*]pyrimidine (**133**; R = Ph, R³ = SH) <86MI 707-04>. In an unusual variation on this type of reaction, 2-triphosphoranylidene-3-carbomethoxy-4,5-dihydro-1-tosylpyrrole undergoes reaction with a series of isocyanates to give the derivatives (**133**; R = alkoxy) <90LA901>. Compounds (**133**) have also been prepared from 2-acylamino-3-carbomethoxypyrroles when treated with phosphorus pentoxide, an aromatic amine and triethylamine <86H(24)997>.

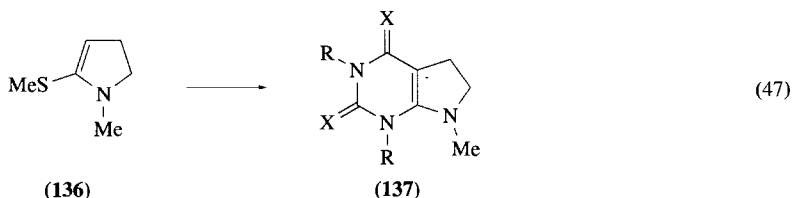


4-Thiopyrrolopyrimidines (**135**) are available directly from thioamide derivatives (**134**) upon heating with substituted amines (Equation (46)) <84S703>.

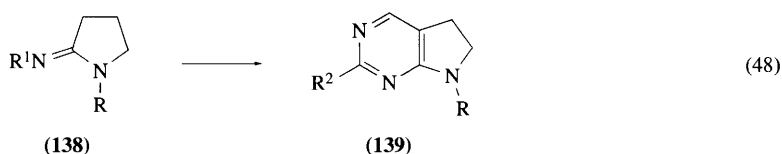


An unusual synthesis of a pyrrolo[2,3-*d*]pyrimidine without a functional group is based on the reaction of benzonitrile with *N*-methyl-2-pyrrolidone. These two compounds, when heated in the presence of sodium telluride, give low yields of 2,4-diphenyl-7-methylpyrrolo[2,3-*d*]pyrimidine <93JOC241>. The yields could not be improved, thereby limiting the usefulness of the method.

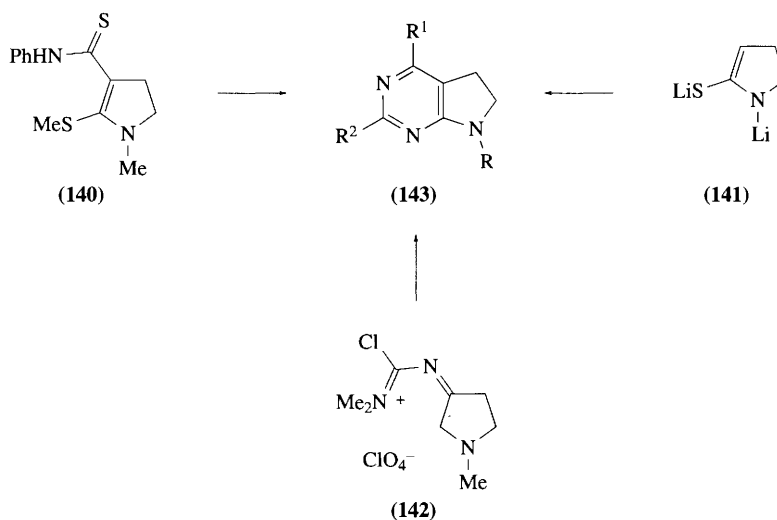
A few less traditional approaches to the synthesis of pyrrolo[2,3-*d*]pyrimidines are worthy of note. Ketene *S,N*-acetals (**136**) serve as convenient precursors to pyrrolopyrimidines which are reduced in the pyrrole ring (**137**) (Equation (47)). Heating compound (**136**) in a 1 : 2 ratio with arylisothiocyanates affords the dithio products (**137**; X = S) <83S225>, whilst similar treatment with arylisocyanates leads to the dioxo compounds (**137**; X = O) <85CPB4299>.



Simple 2-substituted-5,6-dihydropyrrolo[2,3-*d*]pyrimidines (**139**) are readily obtained from reduced pyrroles bearing a nitrogen substituent at C-2 (**138**). Thus compound (**138**; R = H, R¹ = CN) is first treated with DMF diethylacetal and then with alcoholic ammonia to give the 2-amino derivative (**139**; R = H, R¹ = NH₂) (Equation (48)) <85KFZ154>. Alternatively, the precursor (**138**; R = Me, R¹ = CO₂Et) reacts with either (Me₂N)₂CHOEt or DMFDEA to form the 2-hydroxy derivative (**139**; R = Me, R² = OH) <82KGS1553>.



Three different approaches to the preparation of 5,6-dihydropyrrolopyrimidines (**143**) have been employed. The activated lactam (**140**) undergoes facile reaction with amidines to give 4-phenylamino derivatives (**143**; $R^1 = \text{PhNH}$) (Scheme 9) <83S226>.



Scheme 9

Lithiation of the thiolactam affords the dilithio derivative (**141**). Treatment of this organolithium derivative with arylisothiocyanates, followed by methylation of the thio group and cyclization with benzamidine, gives the derivative (**143**; $R^1 = \text{RNH}$, $R^2 = \text{Ph}$) <85H(23)2213>. Reaction of compound (**142**) with tetramethylguanidine, followed by sodium ethoxide, leads to a 58% yield of compound (**143**; $R^1 = R^2 = \text{Me}_2\text{N}$, $R = \text{Me}$) <93IJC(B)422>.

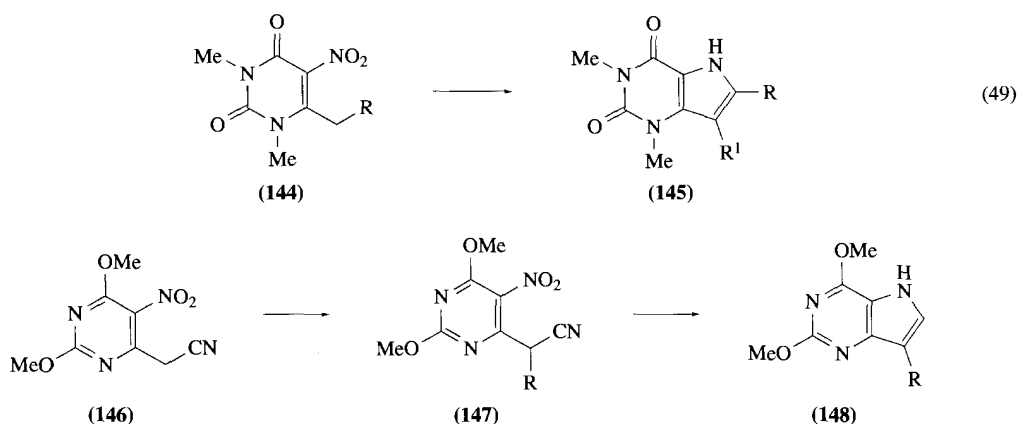
7.07.6.2.2 Pyrrolo[3,2-d]pyrimidines (9-deazapurines)

The desire to develop efficient synthetic routes to 9-deazapurines has meant that there has been substantial research activity in this area, and much has been published since the early 1980s.

(i) Syntheses from pyrimidines

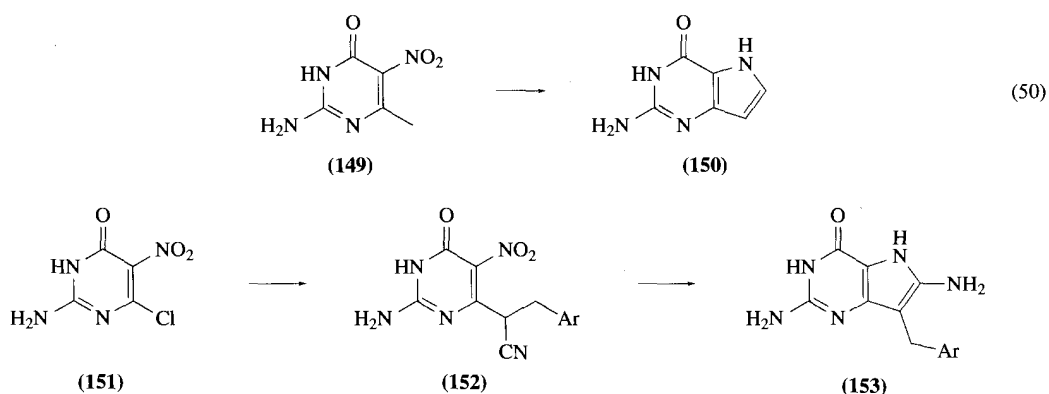
It is to be expected that the majority of examples involve 5-nitropyrimidines as precursors in the formation of pyrrolo[3,2-d]pyrimidines. 5-Nitro-6-alkyluracils (**144**), in which the acidity of the alkyl group plays an important role, have been converted into the corresponding pyrrolopyrimidines (**145**) (Equation (49)) by treatment with aryl aldehydes using either piperidine <82CPB3187> or potassium hydroxide in refluxing alcohol <84JCS(P1)583> as the base. In this case deoxygenation of the resulting *N*-hydroxy group is effected by heating in DMF at 150°C. *C*-Nucleosides have been prepared in an analogous manner commencing with the 2,4-dimethoxypyrimidine (**146**). Alkylation at the α -carbon using sodium hydride and 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranosyl chloride gives the derivative (**147**; $R = \text{protected carbohydrate}$). Reduction of the nitro group using 10% Pd/C catalyst gives the product (**148**) which, on hydrolysis of the methoxy groups and deprotection of the carbohydrate moiety, gives a mixture of nucleosides (Scheme 10) <86JOC1058>. Similarly, reduction of compound (**147**; $R = \text{H}$) leads to compound (**148**; $R = \text{H}$) <82TL4759, 83JOC1060>. Treatment of 2,4-dimethoxy-6-methyl-5-nitropyrimidine with *t*-butoxybis

(dimethylamino)methane, followed by catalytic hydrogenation, also leads to compound **(148)**; $R = H$) <83JOC1060>.



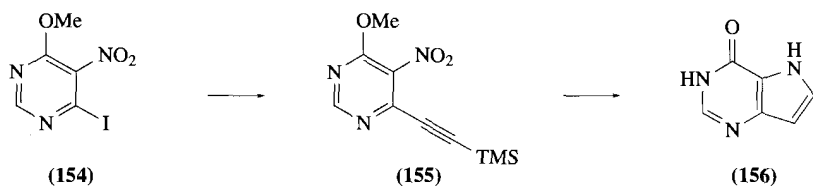
Scheme 10

Taylor *et al.* have devised an improved route to 9-deazaguanine **(150)** <93TL4595>: a five-step process starting from 2-amino-5-nitro-6(1*H*)-oxypyrimidine **(149)** results in an overall yield of 48% (Equation (50)). This modification of the Batcho–Leimgruber indole synthesis involves a key step requiring the protection of N-3. An alternative route (Scheme 11) to 3-substituted-9-deazaguanines **(153)** which begins with the 4-chloropyrimidine **(151)** has been developed by a group at Parke-Davis <92JMC1605>. The key step involves treatment of the pyrimidine **(151)** with the anion of methyl 2-cyano-3-phenylpropanoate which results in the formation of the intermediate **(152)**; $Ar = Ph$).



Scheme 11

A novel route to 9-deazahypoxanthine **(156)** proceeds through a palladium-catalyzed coupling of 4-iodo-6-methyl-5-nitropyrimidine **(154)** with trimethyl(tributylstannylethynyl)silane to give the silylated compound **(155)** (Scheme 12). Cyclization of this alkyne **(155)** is accomplished by treatment with potassium hydroxide, followed by reduction of the nitro group with palladium on carbon and heating with hydrochloric acid, which also hydrolyzes the methoxy group <92JCS(P1)1883>. A similar approach has been described <93CPB81>.

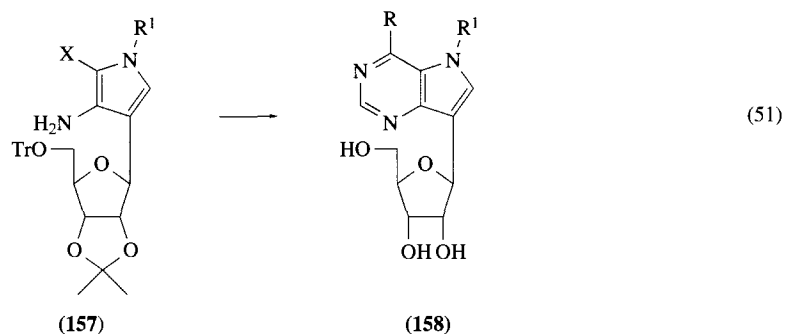


Scheme 12

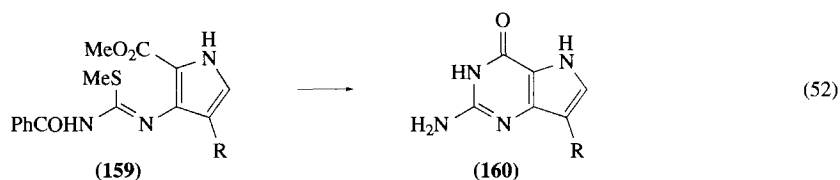
(ii) Syntheses from pyrroles

The classic approach to the formation of a fused pyrimidine ring involves cyclization of adjacent amino and cyano (or carbalkoxy) groups. The formation of pyrrolo[3,2-*d*]pyrimidines, commencing with a suitably substituted pyrrole, follows this route exclusively. Virtually all of the activity using this approach involves the formation of *C*-nucleosides.

The continued interest in 9-deazaadenine derivatives is illustrated by the conversion of ribosylated pyrroles (**157**; X = CN, CO₂Et) into the corresponding *C*-nucleosides (**158**; R = NH₂, OH) using standard reagents for both cyclization and deblocking of the sugar (Equation (51)) <83JOC780, 93MI 707-01>.

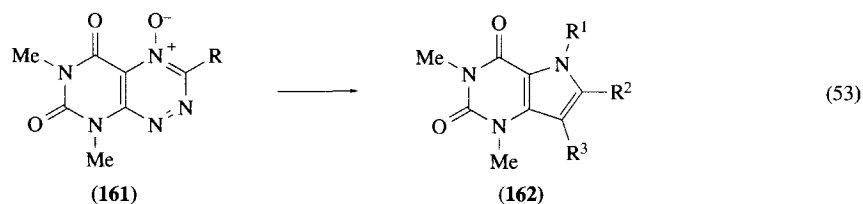


The same approach is taken to prepare 4-amino-7-((*S*)-2,3-dihydroxypropyl)pyrrolo[3,2-*d*]pyrimidine <91JCS(P1)195>. A variation of this approach used to prepare nonnucleoside derivatives proceeds via the activated amines (**159**), derived from the corresponding amine and benzyl isothiocyanate, which is cyclized with methanolic ammonia to yield the derivatives (**160**) (Equation (52)) <93JMC55, 93JMC3771>.



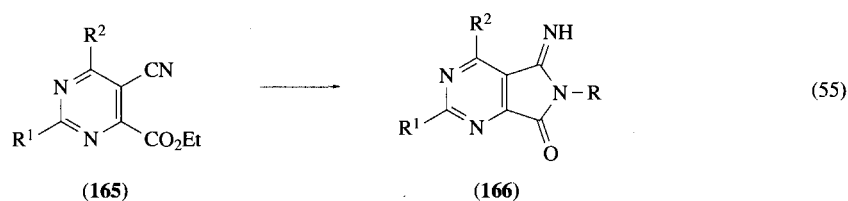
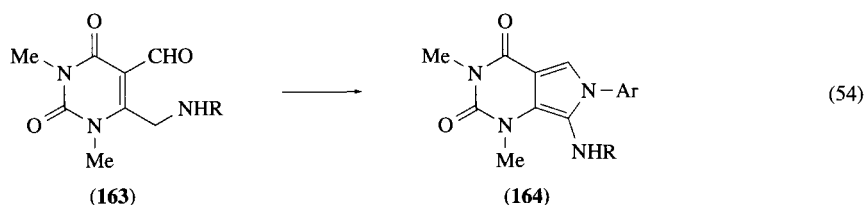
(iii) Syntheses from other rings

Rearrangement of a six-membered ring to give a five-membered ring was described in CHEC-I. Thus, pyrimido[5,4-*c*]pyridazine derivatives were converted into 5*H*-pyrrolo[3,2-*d*]pyrimidines under reductive conditions <78JOC2536>. Extrusion of sulfur from a pyrimidothiazine at 130°C also gives a pyrrolo[3,2-*d*]pyrimidine <71TL4185>. Pyrimido[5,4-*e*]-*as*-triazine 4-oxides (**161**) have been converted into a variety of pyrrolo[3,2-*d*]pyrimidines (**162**) (Equation (53)). These reactions involve 1,3-dipolar cycloaddition of alkynic esters where the specific products depend on the esters used <79JOC3830, 82JHC1309, 85JOC2413>.

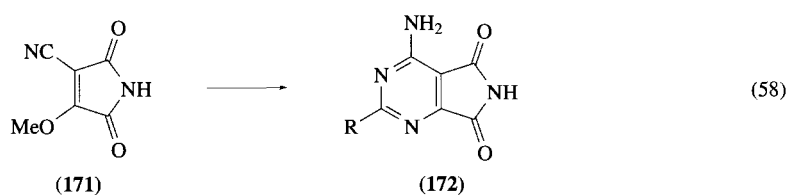
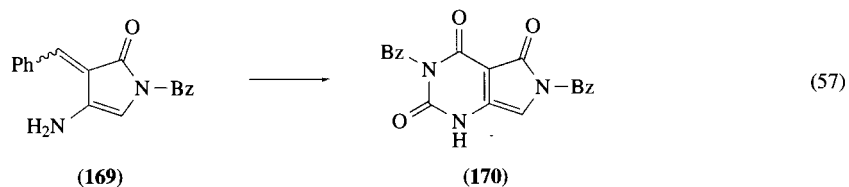
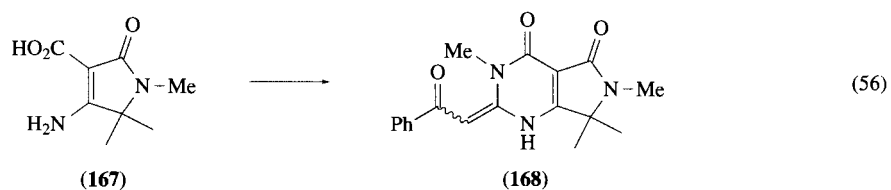


7.07.6.2.3 Pyrrolo[3,4-*d*]pyrimidines

The use of pyrimidines as precursors for pyrrolo[3,4-*d*]pyrimidines is the most common synthetic approach. 6-Phenyl-7-(substituted)amino-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**164**) are readily obtained from the reaction of 5-formylpyrimidines (**163**) with arylamines (Equation (54)) <89BCJ3043>. Formation of the Schiff base, followed by cyclization, is the proposed pathway. A more traditional approach is found in the conversion of the cyanoester (**165**), via the amide, to the corresponding pyrrolopyrimidine (**166**) (Equation (55)) <88LA643>.



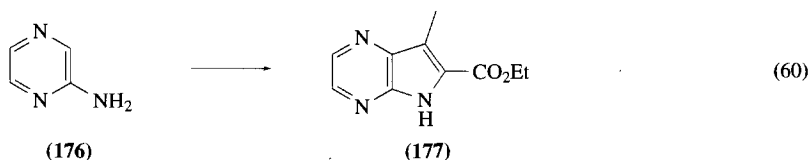
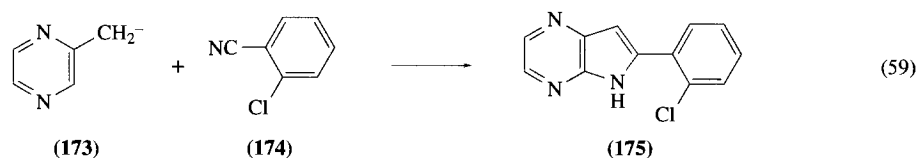
Annellation of a pyrimidine ring usually follows a pathway involving an amine function adjacent to an activated carbon moiety. The aminopyrrole carboxylic acid (**167**) undergoes reaction with 1-methyl-*S*-phenyloxonium methylsulfate to give the tetramethylpyrrolo[3,4-*d*]pyrimidine (**168**) (Equation (56)) <88ZC334>. A similar reaction occurs with the less standard benzylidene derivative (**169**) and benzoyl isothiocyanate to afford the pyrrolopyrimidine (**170**) (Equation (57)) <89ZN(B)233>. In the case of the pyrrole (**171**) advantage is taken of the leaving ability of the methoxy group when reaction with a variety of amidines leads to 2-(substituted)pyrrolo[3,4-*d*]pyrimidines (**172**) (Equation (58)) <87ZC404>.



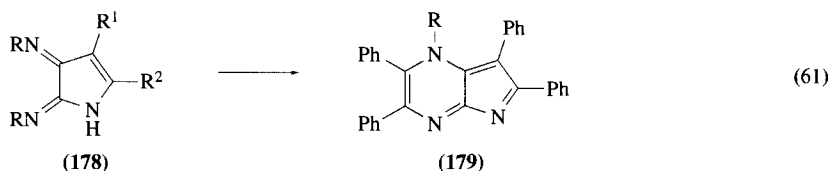
7.07.6.3 Pyrrolopyrazines

7.07.6.3.1 Pyrrolo[2,3-*b*]pyrazines

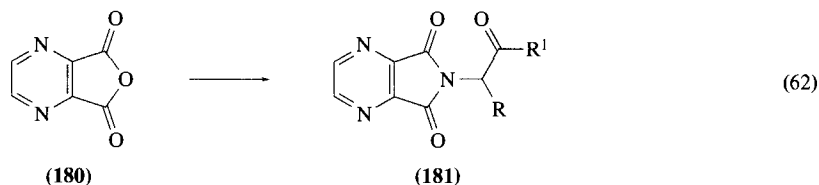
Two very simple precursors combine to produce 2-arylpyrrolo[2,3-*b*]pyrazines. The anion derived from 2-methylpyrazine (**173**) adds to a benzonitrile (e.g. (**174**)) to give the product (**175**) (Equation (59)). This reaction is not the favored pathway; displacement of chlorine is preferred <89TL935> although a similar reaction without the chloro substituent does provide the pyrrolopyrazine as the major product <81TL1219>. However, this reaction does not seem to have been investigated for additional examples. In another simple reaction, 2-aminopyrazine (**176**) reacts with ethyl chloroacetoacetate to give ethyl 6-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine-7-carboxylate (**177**) (Equation (60)) <89BSF467>.



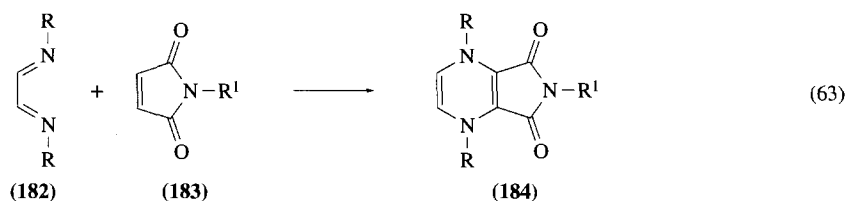
One report of the synthesis of pyrrolo[2,3-*b*]pyrazines from a pyrrole precursor has appeared. 2,3-Diiminopyrroles (**178**) have been cyclized to provide the tetraphenyl product (**179**) (Equation (61)) <88CB271>.

7.07.6.3.2 Pyrrolo[3,4-*b*]pyrazines

Pyrazine-2,3-dicarboxylic acid anhydride (**180**) serves as the basis for the preparation of a series of pyrrolo[3,4-*b*]pyrazine derivatives <89JSC233>. Thus, treatment with a series of amino acids yields compounds of the type (**181**) (Equation (62)).



Intermolecular cycloaddition of ethylenediimines (**182**) with maleimides (**183**) provides the corresponding reduced pyrrolopyrazines (**184**) (Equation (63)) <82IJC(B)589>.

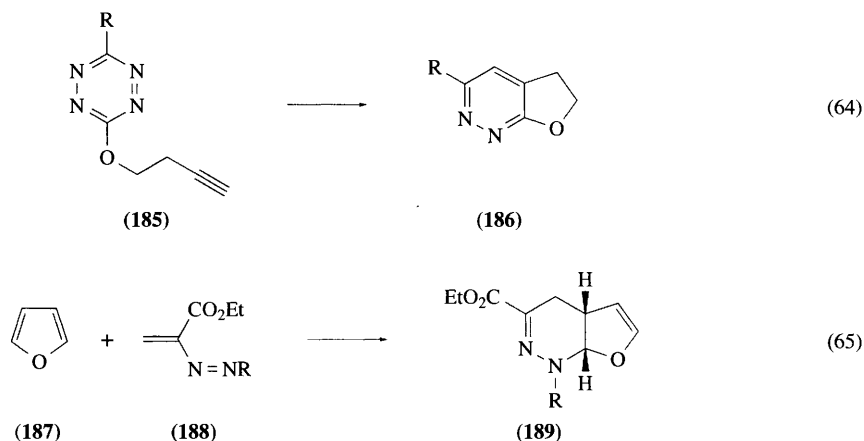


7.07.6.4 Furopyridazines

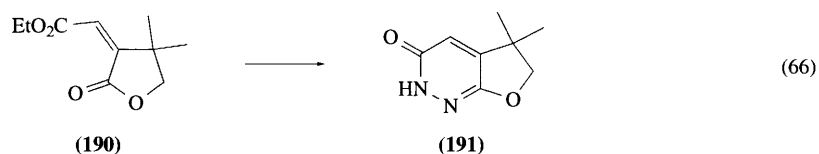
In Chapter 3.17 of CHEC-I only two furopyridazine systems, namely furo[2,3-*d*]- and furo[3,4-*d*]pyridazine, were discussed (84CHEC-I(4)973). Further systems are covered in this chapter.

7.07.6.4.1 Furo[2,3-*c*]pyridazines

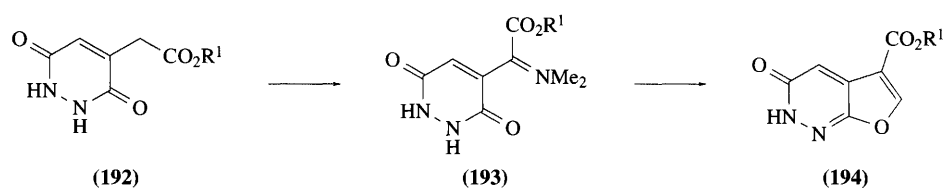
Intramolecular Diels–Alder cycloadditions have also been used in the synthesis of furo[2,3-*c*]pyridazines. The tetrazines (**185**; R = SMe, NMe₂), when heated in solvents such as toluene, form the corresponding furopyridazines (**186**) (Equation (64)). This represents a facile method for preparing simple derivatives which are reduced in the five-membered ring (85TL4355, 87CZ16). An alternative cycloaddition strategy leading to a partially reduced pyridazine ring commences with furan. Treatment of furan (**187**) with the hydrazone (**188**; R = 2,4-dinitrophenyl) affords the stereo-specific product (**189**) in 73% yield (Equation (65)) (91T5615).



The adjacent nitrogen atoms in the furopyridazine ring systems suggest that reactions of hydrazines would be a viable synthetic approach. The furanone (**190**), readily obtained from a furanedione via a Wittig reaction, reacts with hydrazine in aqueous hydrochloric acid to produce compound (**191**) in 52% yield (Equation (66)) (88JOC5704). Less acidic conditions lead to a six-membered ring via a Michael addition reaction.



The pyridazines (**192**) react with DMF dimethylacetal to give the intermediates (**193**) which subsequently cyclize to the furo[2,3-*c*]pyridazines (**194**) (Scheme 13) (83H(20)2347).



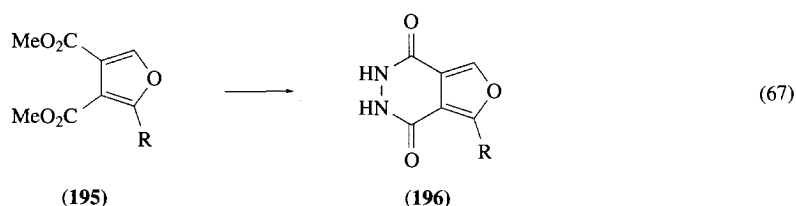
Scheme 13

7.07.6.4.2 Furo[2,3-*d*]pyridazines and furo[3,4-*c*]pyridazines

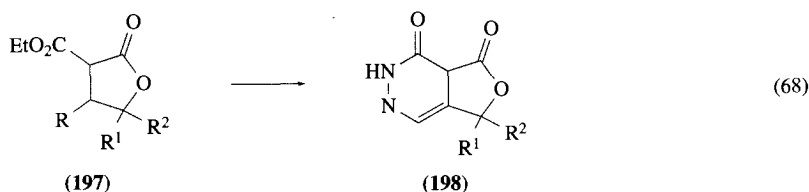
There have been no literature reports of these two ring systems since the early 1980s. Furo[2,3-*d*]pyridazine itself is available from 2,3-dicyanofuran via the dialdehyde which is subsequently reacted with hydrazine. The use of the bishydrazide gives furo[2,3-*d*]pyridazine-4,7-(5*H*,6*H*)dione <56JA159, 66CR(C)313, 66CR(C)814>.

7.07.6.4.3 Furo[3,4-*d*]pyridazines

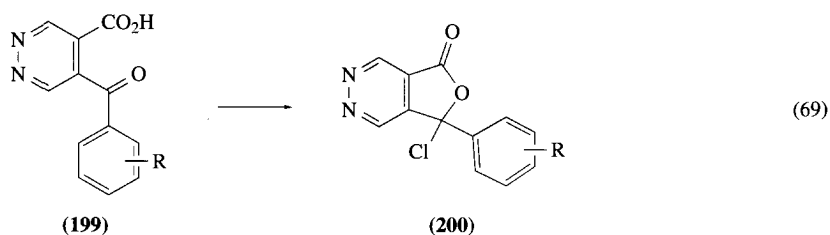
The synthesis of furo[3,4-*d*]pyridazines is most conveniently accomplished by treating a suitably substituted furan with hydrazine. Thus, the furan dicarboxylic ester (**195**; R = substituted phenyl) yields the aryl-substituted furopyridazine (**196**) when so treated (Equation (67)) <83KFZ683>.



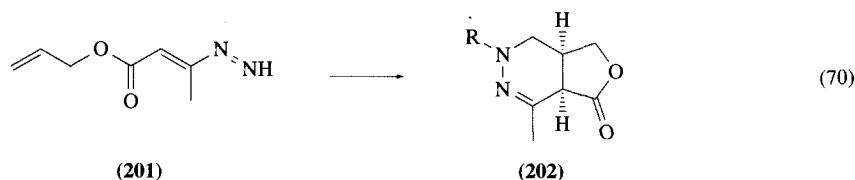
Conversion of the 2-buten-4-olides (**197**; R = Me) into the bromomethyl derivative (**197**; R = CH₂Br), followed by oxidation with DMSO, leads to the dioxo compounds (**198**) (Equation (68)) <84KGS740>.



A simple and efficient route to these furopyridazines involves 5-aryl-4-pyridinecarboxylic acid derivatives (**199**): reaction with thionyl chloride affords the corresponding furopyridazines (**200**) in high yield (Equation (69)) <85LA167>.



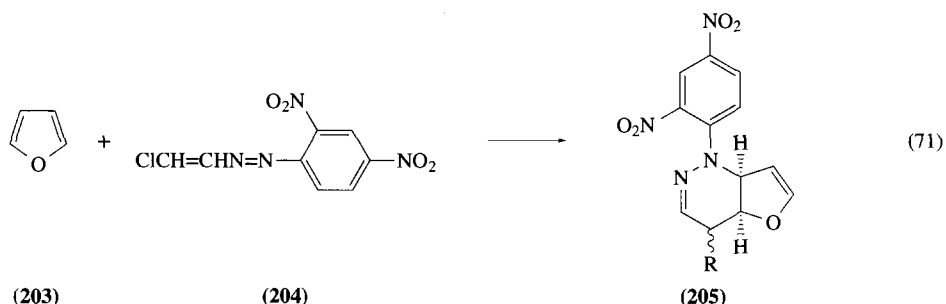
One intramolecular Diels-Alder cycloaddition which does not involve a ring as a starting point has been described. The sequence commences with allylic β-keto ester derivatives (**201**) and ends with the formation of the highly reduced furopyridazine (**202**; R = 2,4-dinitrophenyl or benzoyl) (Equation (70)) <89JCS(P1)353>.



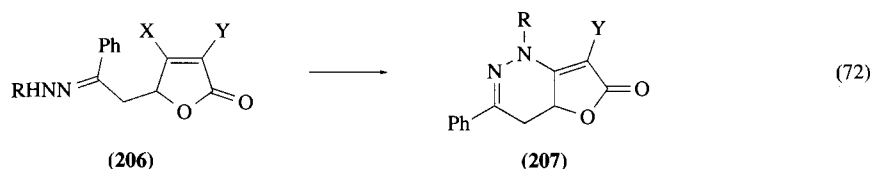
7.07.6.4.4 Furo[3,2-*c*]pyridazines

In contrast to the cycloaddition reaction of furan with hydrazones leading to furo[2,3-*c*]pyridazines <91T5615>, the β-chloroazo alkene (**204**) undergoes a [4 + 2] cycloaddition reaction with

furan (**203**) to yield a furo[3,2-*c*]pyridazine (**205**; R = Cl). The chloro group is capable of undergoing nucleophilic displacement to give other derivatives <85JCS(P1)1741>.



An appropriately substituted furan derivative (**206**; X,Y = Br, Cl), prepared from the corresponding ketone and a hydrazine, can undergo cyclization by displacing a halogen to give a furo[3,2-*c*]pyridazine (**207**) (Equation (72)) <86MI 707-05>.

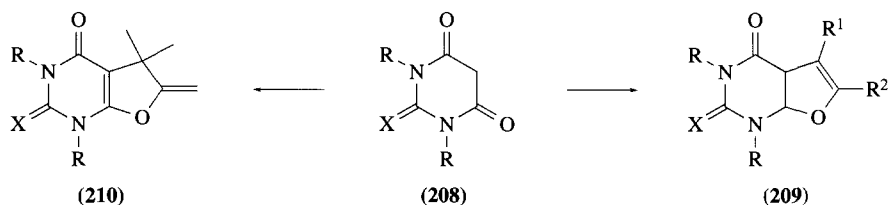


7.07.6.5 Furopyrimidines

7.07.6.5.1 Furo[2,3-*d*]pyrimidines

(i) Syntheses from pyrimidines

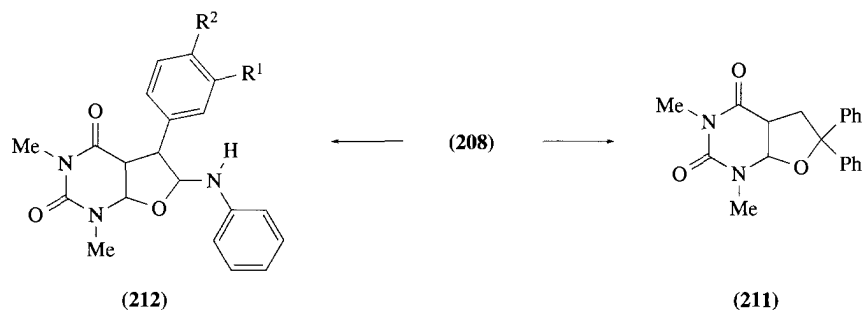
The location of the ring oxygen in furo[2,3-*d*]pyrimidines suggests that pyrimidines bearing an oxygen at C-6 would serve as good candidates for developing the furan ring. Indeed, barbituric acid, and its *N,N'*-disubstituted derivatives, have been exploited in such synthetic schemes (Scheme 14). Alkylation at C-5 of the barbituric acid derivatives (**208**; X = S, R = substituted-phenyl) with chloroacetic acid in the presence of triethylamine is immediately followed by cyclization to the derivatives (**209**; R¹ = H, R² = Me) <90SC1063>. Alkylation of dimethylbarbituric acid (**208**; R = Me) under phase-transfer conditions with 3-chloro-3-methylbut-1-yne is also followed by cyclization to form the derivatives (**210**) <87JHC1409>. However, use of the 3-bromoalkyne results in disubstitution at C-5 of the barbituric acid.



Scheme 14

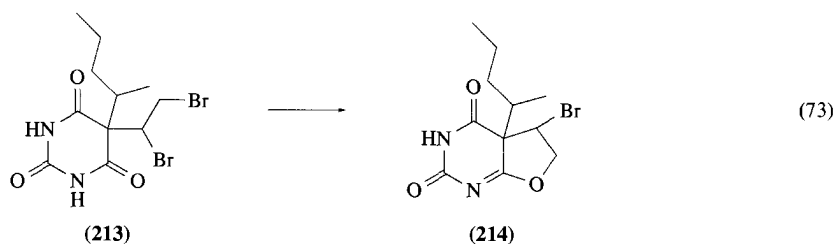
Aromatic substituents have been incorporated into the furopyrimidines (**209**; R¹ = R² = Ph) by treating the thiobarbituric acids (**208**; X = S) with benzoin in the presence of a catalytic amount of *p*-toluenesulfonic acid <90IJC(B)566>. Two phenyl groups have also been introduced into the same position. Thus compound (**208**; X = O, R = Me) reacts with 1,1-diphenylethane in warm acetic acid with manganese(II) acetate as catalyst to form the derivative (**211**) in 63% yield (Scheme 15). The furopyrimidine was not the main target of the reaction and this is the only example cited <93JOC4448>. Not unexpectedly compound (**208**; X = O, R = Me) condenses with substituted benzaldehydes to

give the benzyldiene at C-5 in high yield. Treatment of this intermediate with phenyl isocyanide leads to the phenylamino compounds (**212**) $\langle 92\text{H}(34)891 \rangle$.

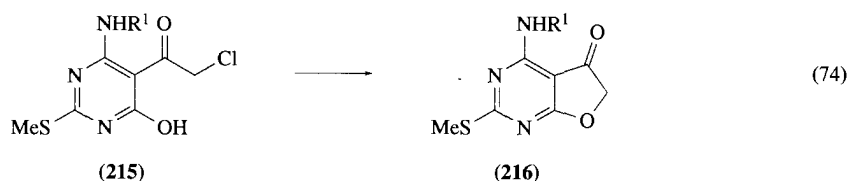


Scheme 15

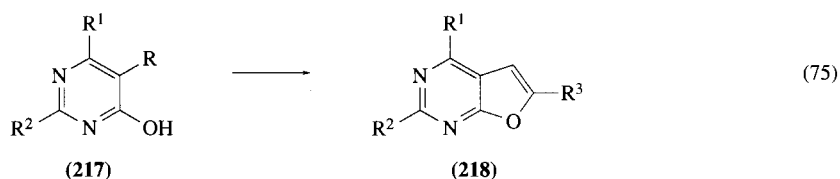
Similarly, the reaction can be started with 5,5-disubstituted barbituric acid derivatives in which one of the substituents possesses some reactive group. Thus, *O*-alkylation occurs in the presence of a dibromo substituent, such as is observed with compound (213) (Equation (73)). The product (214) results from displacement of the terminal bromine by an oxy anion $\langle 92AP(325)333 \rangle$. A similar result is seen with secobarbital $\langle 92AP(325)291 \rangle$. A 5-allyl-5-phenylbarbituric acid derivative, which was previously thought to produce an unusual tricyclic derivative upon treatment with bromine, has been shown to follow this chemical pathway leading to a furopyrimidine $\langle 84JOC3227 \rangle$. Other electrophilic reagents, such as *p*-methoxyphenylselenium bromide and mercury(II) chloride, react with secobarbital to produce 6-(substituted)furo[2,3-*d*]pyrimidines in an analogous manner $\langle 88SC1415 \rangle$.



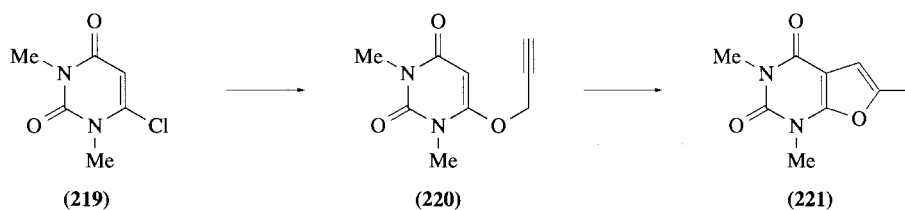
Using similar chemistry 1,3-diaryl-2-thiobarbituric acid is acylated with chloroacetyl chloride in the presence of triethylamine. Subsequent *O*-alkylation under the mildly basic conditions of sodium acetate yields the 5-oxo derivative $\langle 91\text{H}(32)907 \rangle$. It is not necessary to use barbituric acid derivatives to accomplish synthesis of furopyrimidines. Other 6-oxopyrimidines serve well in developing analogues. For example, in a reaction similar to that described above, the acylated pyrimidine (**215**) undergoes cyclization to a 4-(substituted)amino compound (**216**) (Equation (74)) $\langle 92\text{MI } 707-03 \rangle$.



Other examples of similar chemical approaches to those described for barbituric acid derivatives have been reported. Bromination of the derivatives (**217**; R = allyl) is followed by cyclization and oxidation to give the 6-methyl derivatives (**218**; R³ = Me) <88AKZ339>. Periodate oxidation of a similar compound (**217**; R = 2,3-dihydroxypropyl) produces an unsubstituted derivative (**218**; R³ = H) (Equation (75)) <84MI 707-01>.

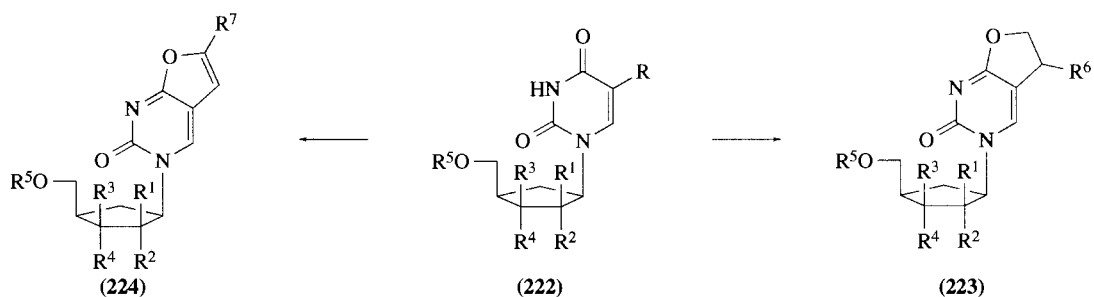


Furo[2,3-*d*]pyrimidines can also be obtained from other 6-substituted-pyrimidines. For example, the 6-chloropyrimidine (219) is converted to the 6-propargyloxy compound (220) which cyclizes to the derivative (221) upon heating ^{<84H(22)2217>}. The formation of a 6-methyl isomer is accounted for by a Claisen rearrangement of the 6-allyloxy group (Scheme 16).



Scheme 16

Efforts to cyclize pyrimidine nucleosides have only been marginally successful, such attempts being prompted by the biological activity of many pyrimidine nucleosides. However, one such example is the reaction of a derivative (222; $R = \text{CH}_2\text{CH}_2\text{Cl}$) with DBU in hot acetonitrile which gives the corresponding product (223; $R^6 = \text{H}$) in 12% yield (Scheme 17) ^{<86CS67>}. The product (223; $R^6 = \text{OH}$) arises from reaction of compound (222; $R = \text{CH}(\text{OH})\text{CH}_2\text{I}$) with sodium carbonate in methanol (17.5% yield) in a reaction which was intended to replace the iodide with a methoxy group. The latter reaction also occurs to yield 26% of the required product ^{<90JMC717>}.

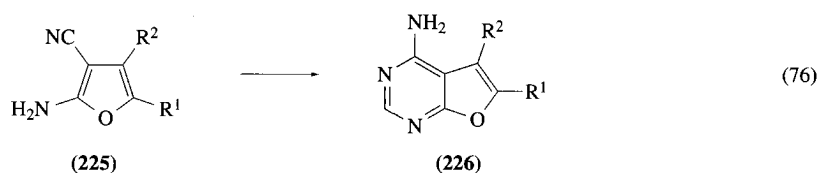


Scheme 17

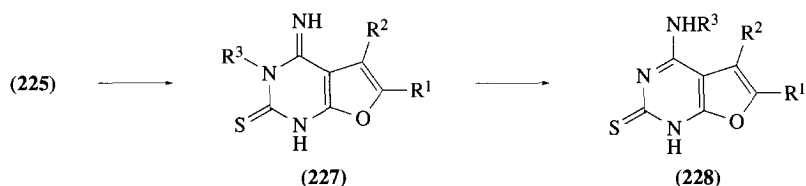
A very low yield of a derivative (224; $R^7 = \text{aryl}$) has been obtained in the palladium-catalyzed reaction between the precursor (222; $R = O\text{-triflate}$) and arylalkynes, a reaction not intended to give the furopyrimidines ^{<93JOC6614>}. Better, but variable, yields of these derivatives are obtained when an iodide (222; $R = \text{I}$) is heated to reflux in acetonitrile containing alkynes, 10% Pd/C, copper(I) iodide, and triethylamine ^{<92IZV1449>}.

(ii) Syntheses from furans

Consistent with other fused pyrimidine ring systems, the simple approach to a new pyrimidine ring involves introducing a one-carbon fragment between two suitable and adjacent functional groups. Heating substituted 2-amino-3-cyanofurans (225) with formamide accomplishes the conversion to 4-aminofuro[2,3-*d*]pyrimidines (226) (Equation (76)) ^{<84CCCC1788>}. Starting with similarly substituted 4,5-dihydrofurans leads to the corresponding reduced ring systems ^{<85CB4782>}.



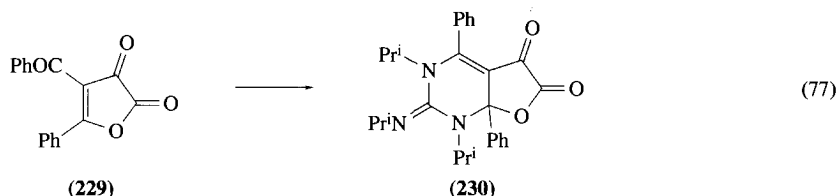
Alkyl- or arylisothiocyanates serve to introduce sulfur at C-2 of the furopyrimidine. Hence the derivative (225) reacts with these compounds to give the 2-thio derivatives (227). Heating these compounds in DMF causes a Dimroth rearrangement to the isomers (228) (Scheme 18) <91JIC660>.



Scheme 18

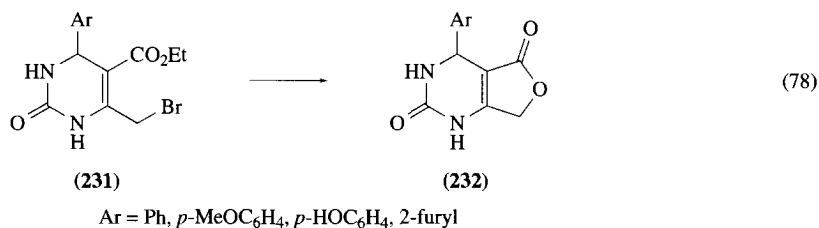
A 2-acetylamino derivative of (225) forms a 2-methyl analogue of system (227) when heated with phosphorus pentoxide and a primary amine. This also undergoes a Dimroth rearrangement to a 4-(substituted)amine compound when heated in DMF <85CS227>. Phosphorus pentoxide and primary amines react with 2-formylamino-3-carboxamidofurans to yield 4-(substituted)aminofuro[2,3-*d*]pyrimidines without a substituent at C-2 of the product <86CS337>.

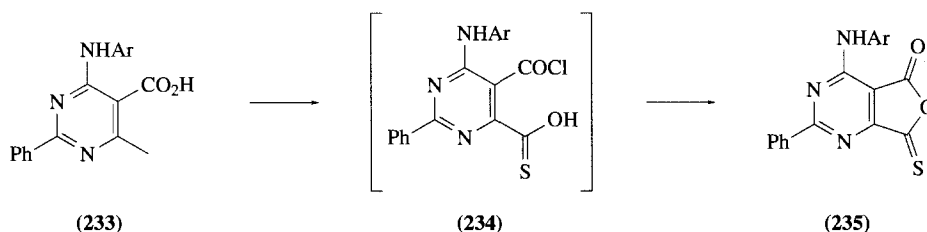
[4 + 2] Cycloadditions can be used to produce some rather esoteric furopyrimidines. For example, the furandione (229) reacts with arylisocyanides or carbodiimides to yield compounds like (230) (Equation (77)) <91JOC235>.



7.07.6.5.2 Furo[3,4-*d*]pyrimidines

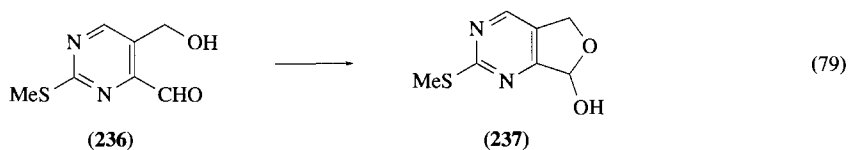
It is much easier to construct the furan ring on an existing ring in this system, and most of the examples cited use this approach. Furthermore, virtually all of the syntheses lead to an oxidized form of the furan ring. Perhaps the simplest, chemically, of the syntheses involves the pyrimidines (231). Heating these esters above 210°C provides the 5-oxofuro[3,4-*d*]pyrimidines (232) in yields ranging from 50–80% (Equation (78)) <84H(22)493>. A seemingly similar pathway is observed for the pyrimidinecarboxylic acids (233). However, reaction of these compounds with thionyl chloride is postulated to involve the intermediates (234) which then cyclize to form the furopyrimidines (235) (Scheme 19). Evidence is presented to support the location of the sulfur and, hence, the role of the intermediate (234) <86S142>.



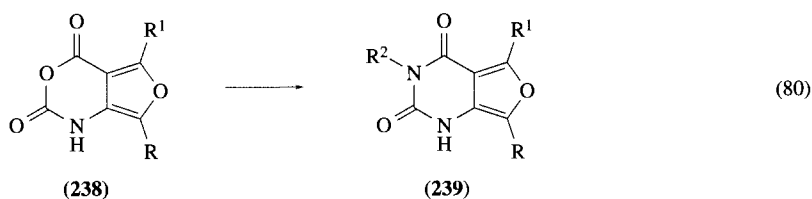


Scheme 19

An interesting, though apparently unique, example of the formation of a furopyrimidine is that of the hemiacetal (237) from the pyrimidinecarboxaldehyde (236) (Equation (79)) <91JOC5610>.

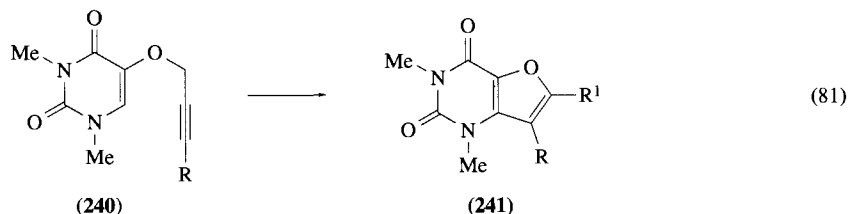


One alternative route to furo[3,4-d]pyrimidines proceeds via a ring interconversion. Thus the furooxazinedione system (238) reacts with a series of primary amines to yield the corresponding 3-(substituted)furopyrimidines (239) (Equation (80)) <89EJM627>.

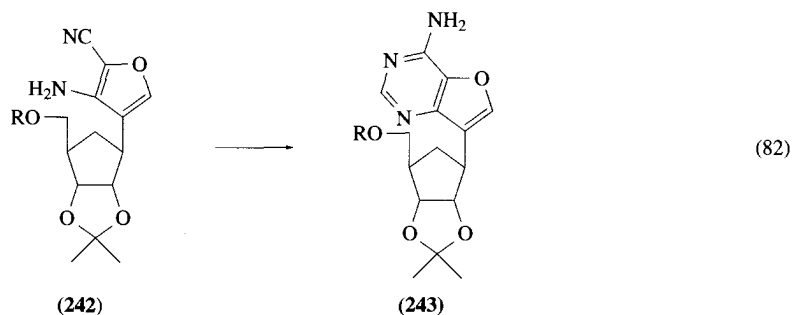


7.07.6.5.3 Furo[3,2-d]pyrimidines

Pyrimidines with an oxygen function at C-5 represent the most efficient precursors to furo[3,2-d]pyrimidines. The formation of 5-propynyloxy pyrimidines (240) allows cyclization to furo[3,2-d]pyrimidines (Equation (81)) (241). Treatment of compound (240; R = H) with sodium methoxide in warm DMSO gives the derivative (241; R = Me, R¹ = H), whilst the methyl analogue (240; R = Me) undergoes thermal cyclization in DMSO to yield compound (241; R = R¹ = Me). A parallel chemistry is described for the sulfur analogues <89JHC1851>.



The common use of amino and cyano groups *ortho* to each other to create a pyrimidine ring has also been employed. For example, the nucleoside (242), which has been synthesized from simple carbohydrate precursors, can be treated with formamidine acetate to give the protected nucleoside (243) in 80% yield (Equation (82)). Deprotection of this compound using standard techniques leads to the free nucleoside <90MI 707-01>.

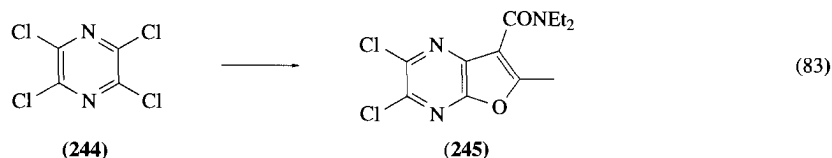


7.07.6.6 Furopyrazines

There were very few references to furopyrazines in CHEC-I, and only to the furo[2,3-*b*]pyrazine system, which had been first reported in 1978 <78RTC81, 78RTC151>. Since then a very limited number of further references has appeared.

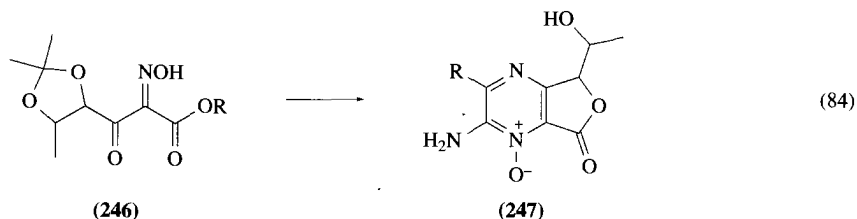
7.07.6.6.1 Furo[2,3-*b*]pyrazines

The anions of active methylene compounds, such as *N,N*-diethylacetoacetamide, react with tetrachloropyrazine (244) to give the furopyrazine (245) by displacement (Equation (83)), enolization, and cyclization, instead of carrying out simple displacement of a chlorine. Yields of about 50% are obtained <83JHC365>.



7.07.6.6.2 Furo[3,4-*b*]pyrazines

The only reference to these compounds records the preparation of the furo[3,4-*b*]pyrazine-*N*-oxides (247) from the oximes (246), which were intended to be used to make pyrazines for further elaboration into pteridines (Equation (84)). It is suggested that in an acidic environment the isopropylidene is cleaved thus allowing cyclization to the lactone structure <84JHC657>.

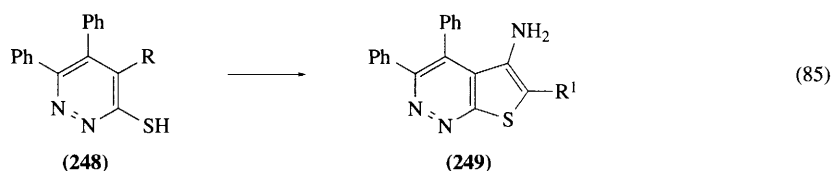


7.07.6.7 Thienopyridazines

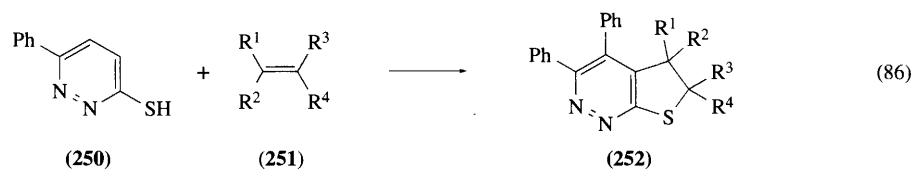
Of the five possible thienopyridazines without a nitrogen common to both rings, three types were mentioned in CHEC-I and these were the [2,3-*d*]-, [3,2-*c*]-, and [3,4-*d*]-isomers <84CHEC-I(4)973>.

7.07.6.7.1 *Thieno[2,3-c]pyridazines*

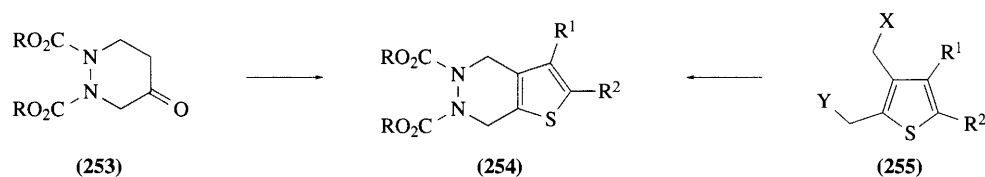
Pyridazine-3-ones are relatively easy molecules to obtain. Conversion of the oxo compounds to the corresponding 3-thiopyridazines allows an easy access to thieno[2,3-*c*]pyridazines. Thus, treatment of compound (**248**; R = CN) with α -halo carbonyl compounds, such as ethyl bromoacetate or bromoacetophenone, gives the alkylthio derivative. Subsequent cyclization produces the 5-aminothienopyridazines (**249**; R¹ = CO₂Et or CPh) (Equation (85)) <90JPR104, 90MI 707-04>. When the derivative (**248**; R¹ = CO₂Et) is used the 5-oxothienopyridazine is obtained. An alternative approach involves commencing with a 3-chloro-4-cyanopyridazine and replacing the chlorine by nucleophilic reaction of an appropriately substituted alkylthiol, followed by cyclization <91M413>.



Simple pyridazine-3-thiones (e.g. (**250**)) undergo photoaddition to a variety of alkenes (**251**) to give the thienopyridazines (**252**) as well as dimers of the starting compounds (Equation (86)) <86CPB3061>.

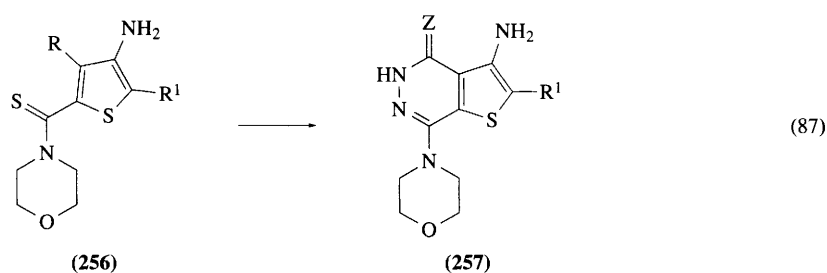
7.07.6.7.2 *Thieno[2,3-d]pyridazines*

Pyridazine-4-ones (**253**; R = Me) can also be used to obtain suitable thieno[2,3-*d*]pyridazines. The Gewald reaction, employing ethyl cyanoacetate and sulfur, leads to the tetrahydrothienopyridazines (Scheme 20) (**254**; R = Me; R¹ = CO₂Et; R² = NHR³; R³ = various alkyl groups) <90AKZ324>. The same type of product (**254**; R = Et, Prⁱ, R¹ = R² = H) is produced in a [4 + 2] cycloaddition reaction. The thiophene (**255**; R¹ = R² = H, X = ⁺NMe₃, Y = TMS), in the presence of tributylammonium fluoride, undergoes elimination to give 2,3-dimethylene-2,3-dihydrothiophene. This structure is well suited to Diels–Alder reaction with azodicarboxylate forming the cycloadduct (**254**) <93RTC7>.



Scheme 20

The thioamides (**256**; R = CN, CO₂Et) undergo S-alkylation at the thioamide. Subsequent hydrazinolysis affords the thienopyridazines (**257**) (Equation (87)) <87AP(320)43>. This approach seems capable of further generalization.

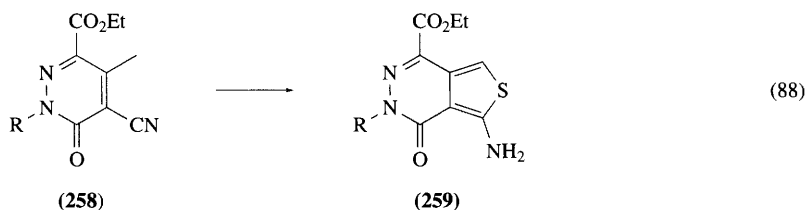


7.07.6.7.3 Thieno[3,4-c]pyridazines

No syntheses of this ring system have been reported and there were no references to it in CHEC-I.

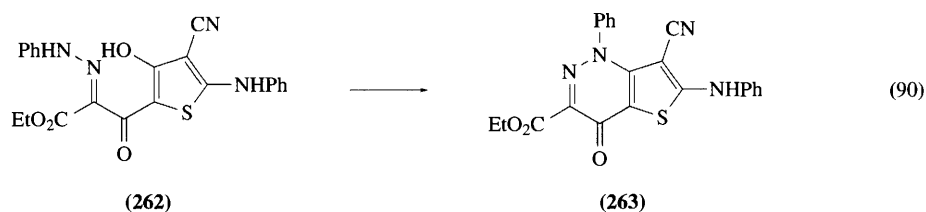
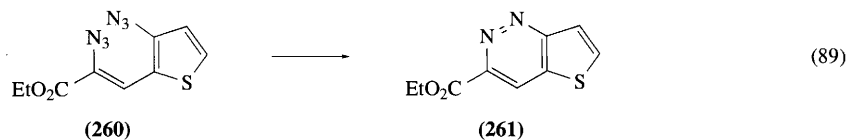
7.07.6.7.4 Thieno[3,4-d]pyridazines

A simple approach to thieno[3,4-d]pyridazines has been explored by several laboratories in Egypt. Commencing with a pyridazine substituted at C-4 with a cyano group and at C-5 with a methyl group (258), the corresponding thienopyridazines (259) are obtained in good yields (Equation (88)). The reaction is carried out with sulfur in a solvent, such as ethanol, and in the presence of a base, such as triethylamine <89LA1255, 90CCC2977, 91MI 707-01>. A similar reaction occurs if the R substituent is attached to the other ring nitrogen. In this case a meso-ionic product results <92G503>.



7.07.6.7.5 Thieno[3,2-c]pyridazines

Only thiophene derivatives have served as precursors to thieno[3,2-c]pyridazines. The thermal reaction of the 3-azidothiophene (260) to give the simple thienopyridazine (261) (Equation (89)) was described in the first edition of CHEC-I <81CC550>. It has subsequently been reported showing low yields in addition to a variety of other products <84JCS(P1)915>. A good yield of the more complex thienopyridazine (263) arises from heating the thiophene (262) with piperidine in DMF (Equation (90)) <91SUL229>.



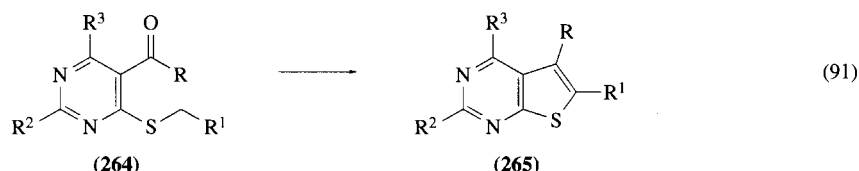
7.07.6.8 Thienopyrimidines

7.07.6.8.1 Thieno[2,3-d]pyrimidines

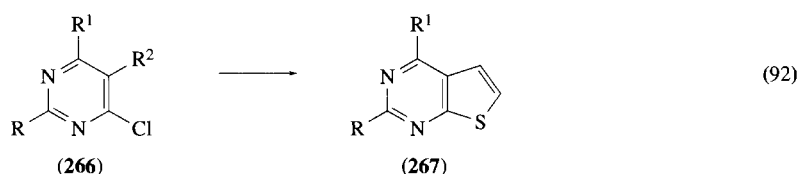
(i) Syntheses from six-membered rings

Although a large number of thieno[2,3-d]pyrimidines have been synthesized from pyrimidine precursors, most have evolved from pyrimidines bearing a carbonyl moiety at C-5 and an alkylated sulfur at C-6. Either 6-thiol- or 6-chloropyrimidines may be used. In the latter case, displacement of the chlorine by a sulfur anion is commonly used. In general, pyrimidines of the type (264) are the immediate precursors or are formed *in situ*. For most of the investigations the derivatives (264; R = R³ = Me; R² = aryl) have been used. The cyclization to the products (265) can be effected by

heating the pyrimidines, or by the use of a weak base such as triethylamine, sodium acetate, or sodium carbonate (<88JIC695, 89PHA348, 90CCC1049, 91PJS4>). When the C-5 substituent of the precursor (**264**) is an ester, the product possesses a 5-hydroxy group (**265**; R = OH) (Equation (91)) (<89SUL201>). Likewise, a cyano group at C-5 of the precursors (**264**) affords products with 5-amino substituents (**265**; R = NH₂) (<84JCS(P1)2447, 87KGS1377, 89SUL101, 90PHA216>), whilst pyrimidine-5-carboxaldehydes provide thienopyrimidines unsubstituted at C-5 (<90JHC717>).

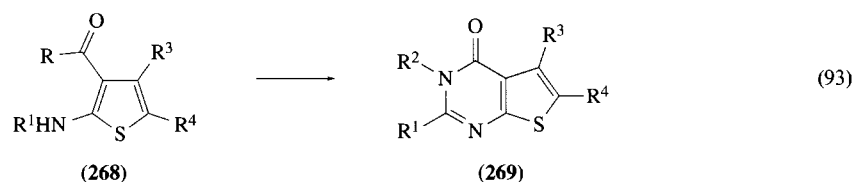


An alternative pathway utilizes the palladium-catalyzed replacement of an iodo group at C-5 of the pyrimidines (**266**; R² = I) to give alkynes (**266**; R² = C≡C-TMS) (Equation (92)) (<86CPB2719>). Replacement of the chlorine by sodium hydrogen sulfide is followed by immediate cyclization to the thienopyrimidines (**267**) in yields of 53–95%.



(ii) Syntheses from five-membered rings

Virtually all of the syntheses of thieno[2,3-*d*]pyrimidines beginning with a thiophene precursor arise from the same synthetic strategy. Thus, thiophenes with a 2-amino- (or (substituted)amino-) function, and either a carboalkoxy, carboxamido, or a cyano group at C-3 are the preferred starting points. Typically, when the thiophene has a carbonyl function at C-3 (**268**; R = OEt or NH₂) cyclization affords the 4-oxothienopyrimidines (**269**) (Equation (93)).

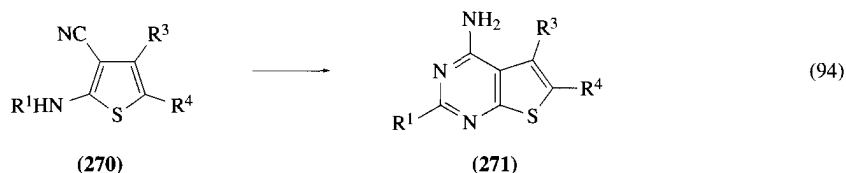


Formamide converts 2-aminothiophenes (**268**; R¹ = H) into 4-oxothienopyrimidines (**269**; R¹ = R² = H) (<83ZC179, 84EJM420, 90DOK32, 93PHA192>). If however, cyclization occurs using a cyano compound as the one-carbon reagent, an amidine is generated at C-2 of the pyrimidine. This results in a product containing a substituent at C-2 which arises from the nature of the cyano compound. Thus, the derivatives (**269**; R¹ = CH₂CO₂Et) form when NCCH₂CO₂Et is used (<89IJC(B)1039, 89PHA790>). The introduction of a desired substituent at C-2 of the system (**269**) is also accomplished by converting the 2-amino group into the desired amide prior to cyclization. In this way a variety of thienopyrimidines (**269**) have been obtained, including derivatives (**269**; R¹ = phenyl (<92MI 707-01>), R¹ = (CH₂)₂CO₂H (<89PHA860>) and R¹ = CO₂R⁵ (<87JHC581>). Acetylation of the amine and hydrazinolysis of the ester leads to the unusual thienopyrimidine (**269**; R¹ = COCH₃, R² = NH₂) (<88EJM453>). Similarly, when the 2-amino group is converted to the ethoxymethylimino moiety and then treated with aniline a thienopyrimidine (**269**; R¹ = Ph) is obtained (<85IJC(B)432>).

Thieno[2,3-*d*]pyrimidin-2-ylidene derivatives can be prepared by cyclization of thiophenes derived from condensation of the 2-amino group and, for example, acrylonitrile (<93PHA347>).

In reactions analogous to those of 2-carboxamidothiophenes, thiophenes bearing 2-(substituted)urea or thiourea moieties cyclize in the presence of base to give 2,4-dioxo- or 2-thio-4-oxothieno[2,3-*d*]pyrimidines bearing a variety of groups at N-3 (<83HCA148, 88JMC1786, 90EJM635, 91EJM807>).

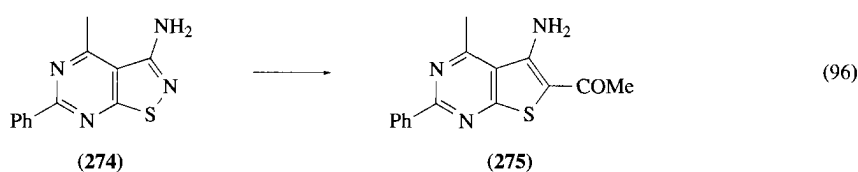
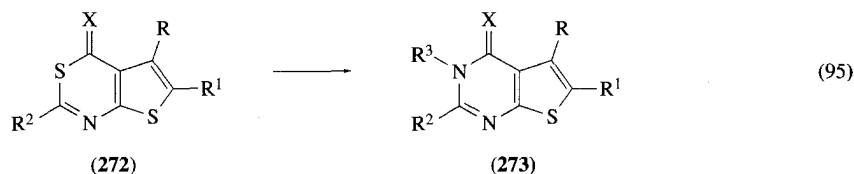
If 4-aminothieno[2,3-*d*]pyrimidines are desired, the simplest approach is to use a 3-cyanothiophene as precursor. Formamide or triethylorthoformate are commonly used to convert the amine (**270**; $R^1 = H$) into the thienopyrimidine (**271**; $R^1 = H$) (Equation (94)) <88JPR585>. The use of formic acid has been reported to give the 4-oxo compound instead <92MI 707-04>. Guanidine reacts with the thiophene (**270**; $R^1 = H$) to give only a 24% yield of product (**271**; $R^1 = NH_2$) <90HCA797>.



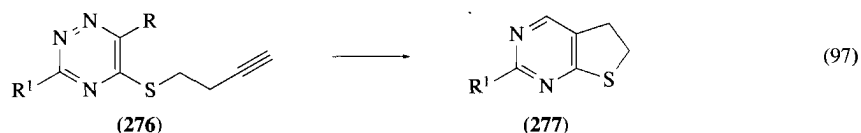
Other 2-(substituted)amino derivatives lead to the expected 2-(substituted)-4-aminothienopyrimidines (**271**) <83CPB1177, 86CPB516, 88CS195, 89AP(322)227>. A trichloromethyl group can be introduced at C-2 of the thienopyrimidine (**271**; $R^1 = CCl_3$) when the thiophene (**270**; $R^1 = H$) is allowed to react with trichloroacetonitrile and formamide <89ZN(B)488>. It is very likely that the intermediate is a trichloroacetamide.

(iii) Syntheses by transformation of another ring

The synthesis of thieno[2,3-*d*]pyrimidines from other bicyclic ring systems has also been accomplished. Thieno[2,3-*d*]1,3-thiazines (**272**; $X = S, NH$) undergo reaction with primary amines to give the corresponding N-3 (substituted)thienopyrimidines (**273**) (Equation (95)) <86PHA96, 89IJC(B)642>. A less obvious conversion occurs when 3-aminoisothiazolo[5,4-*d*]pyrimidines, such as compound (**274**), undergo ring opening upon treatment with chloroacetone with subsequent recyclization to the thienopyrimidine (**275**) (Equation (96)) <88JCR(S)46>.



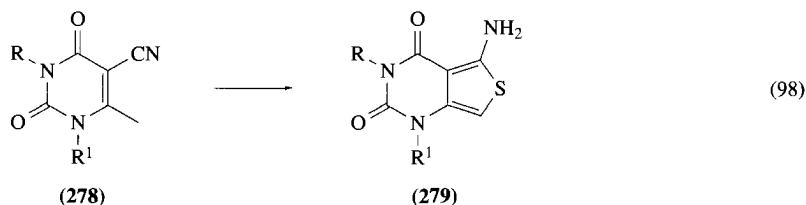
The exploitation of intramolecular Diels–Alder reactions has included synthetic applications in the thienopyrimidine series as well. Thus, the 1,2,4-triazine with a tethered alkyne (**276**) participates in an intramolecular cyclization, with concomitant loss of RCN, to produce the thienopyrimidine (**277**) (Equation (97)) <87JOC4287>. A similar reaction occurs with oxygen analogues.



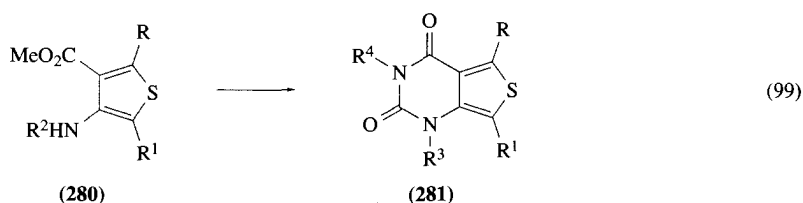
7.07.6.8.2 Thieno[3,4-*d*]pyrimidines

The creation of a thiophene ring from *ortho*-cyano-methylpyrimidines has provided access to thieno[3,4-*d*]pyrimidines. Mono- or di-*N*-(substituted)uracils (**278**) undergo reaction with elemental

sulfur to give the corresponding thienopyrazines (**279**) (Equation (98)) <90MI 707-02, 91MI 707-04>. 2-(Substituted)pyrimidine-4-thiones react in the same manner with sulfur to yield 4-thiothieno[3,4-*d*]pyrimidines <90LA1215>.



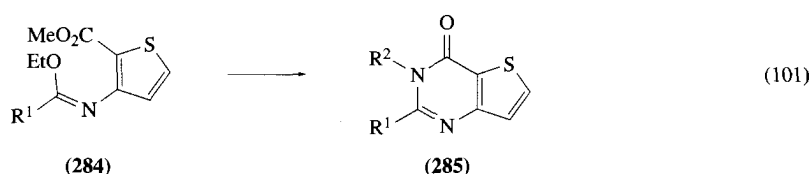
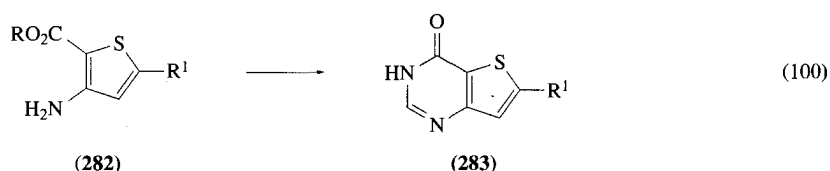
The fusion of a pyrimidine onto an existing thiophene has also been described. The thiophene with *ortho*-amino and ester functions (i.e. (**280**; R = CO₂Et)) is treated first with a series of elaborate primary amines, which form the 4-carboxamido group. Subsequent reaction with trimethylaluminum leads to the dioxothienopyrimidine (**281**) in which the desired variation occurs at R⁴ (Equation (99)) <90JHC1761>.



The simpler thiophene derivative (**280**; R = R¹ = H, R² = CHO) is converted to a C-nucleoside (**281**; R¹ = tribenzoylribose). Reaction with methanolic ammonia at 100°C cyclized the pyrimidine ring affording no substituent at C-2, and deblocked the nucleoside <88TL3537>.

7.07.6.8.3 Thieno[3,2-*d*]pyrimidines

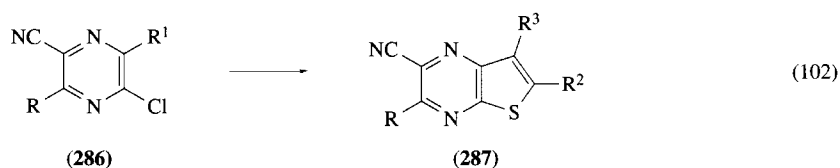
3-Aminothiophene-2-carboxylates (**282**) undergo cyclization to the corresponding thieno[3,2-*d*]pyrimidines (**283**), either with formamide alone <85IZV1858> or with prior reaction involving formic acid and sodium acetate (Equation (100)) <86MI 707-01>. 3-Amino-2-cyanothiophenes are converted to the acetamidate upon treatment with trimethylorthoacetate and acetic anhydride. The acetamidate leads to the thienopyrimidine when heated in a sealed vessel with sodium amide in liquid ammonia <86JHC1757>. Imidates (e.g. (**284**)) react with amines and hydrazines to give *N*-(substituted)thienopyrimidines (**285**) (Equation (101)) <92BSB445>. Similar thiophenes, arising from reaction of 3-aminothiophene-2-carboxylate (**282**; R = Me, R¹ = H) with 1,1-dicyano-2-alkoxy-2-hydroxyethene, cyclize in hot DMF to give 4-oxothienopyrimidines with an exocyclic double bond at C-2 <91HCA579>.



7.07.6.9 Thienopyrazines

7.07.6.9.1 Thieno[2,3-*b*]pyrazines

In chemistry designed to provide pteridine-based ring systems, Taylor *et al.* have utilized tetra-substituted pyrazines (**286**) to generate thieno[2,3-*b*]pyrazines which retain the functionality necessary for anellating a pyrimidine ring. When compounds (**286**; R = NH₂, R¹ = CH=CHR²) are allowed to react with thiourea in an alcoholic solvent, the fused pyrazines (**287**; R³ = H) are obtained (Equation (102)). If sodium sulfide is used with this pyrazine the product obtained is reduced in the thiophene ring <88JOC5839>. Displacement of the chlorine in compound (**286**; R = N=CHNMe₂; R¹ = CN) with an α -thiolketone in the presence of triethylamine, followed by treatment with the mildly basic sodium acetate, leads to derivatives (**287**; R² = CH₂CO₂Me, R³ = NH₂) <89JA285>.



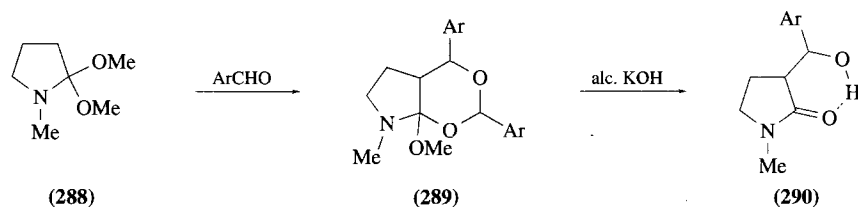
7.07.6.9.2 Thieno[3,4-*b*]pyrazines

Thieno[3,4-*b*]pyrazines have only been described sporadically and no new syntheses of this ring system have been reported since 1979. 3,4-Diaminothiophenes have been used for the synthesis of these compounds <77H(6)1871, 79YZ1081> but examples of the system are rare.

7.07.6.10 Miscellaneous fused pyrrolo systems

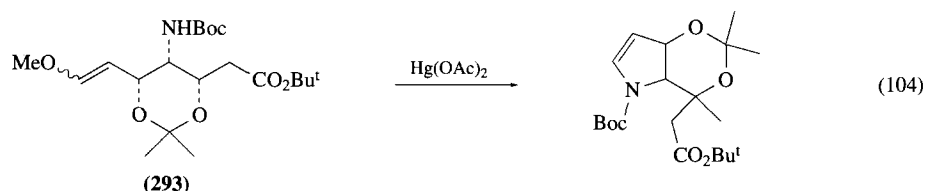
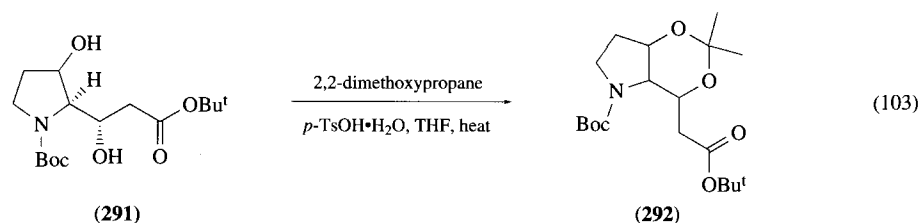
7.07.6.10.1 Dioxinopyrroles

There are few references to dioxinopyrroles which are compounds which do lend themselves to systematic study. The lactam acetal of 1-methylpyrrole (**288**) reacts with aldehydes in anhydrous ether (or in the absence of solvent) at room temperature to give the tetrahydro-1,3-dioxino[4,5-*b*]pyrroles (**289**) (Scheme 21). These lose one molecule of aldehyde when treated with alcoholic potassium hydroxide to yield the benzhydryls (**290**) <83IJC(B)1079>.



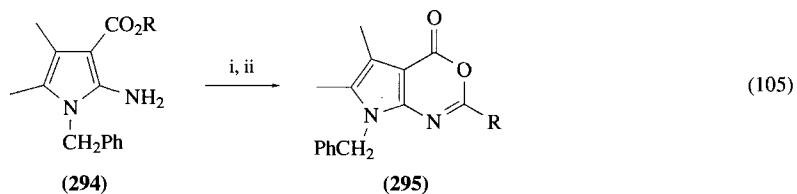
Scheme 21

The tetrahydro-1,3-dioxino[5,4-*b*]pyrrole (**292**), an intermediate in the total synthesis of (–)-detoxinine, has been obtained from the precursor (**291**) (Equation (103)) <91JOC240, 93T785>. An alternative synthesis of detoxinine is that of Ohfuné and Nishio who obtained it in 20% yield as a side product in the reaction of the acetal (**293**) with mercuric acetate in aqueous THF, followed by the action of potassium iodide (Equation (104)) <84TL4133>.



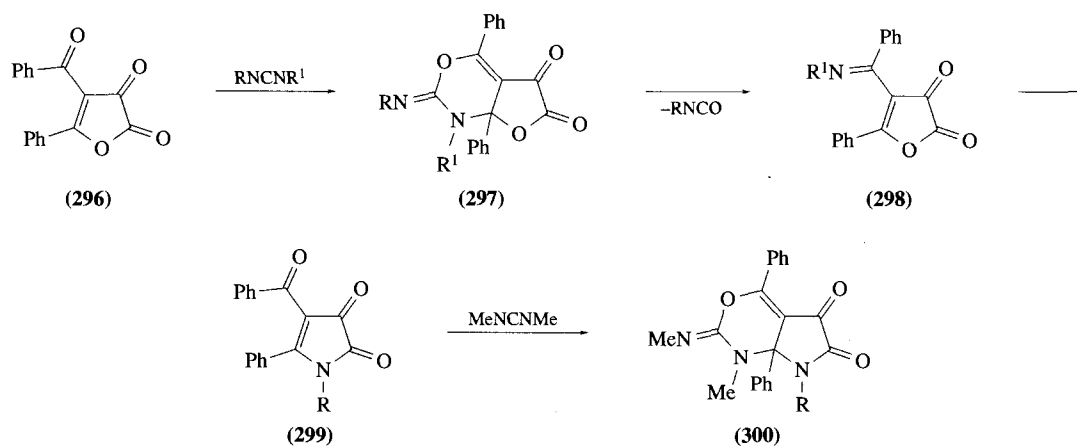
7.07.6.10.2 Pyrrolooxazines

A number of oxazine-fused systems, including the pyrrolo[2,3-*d*][1,3]oxazine (**295**; R = PhCH₂), have been obtained by reacting dichlorotriphenylphosphorane with a 1,2-aminoester (e.g. (**294**; R = Et)) (Equation (105)). The *t*-butyl ester (**294**; R = Bu^t) reacts with methyl pyruvate in the presence of acetic acid and sodium acetate to yield the pyrrolooxazine (**295**; R = Me) <90MI 707-05>.

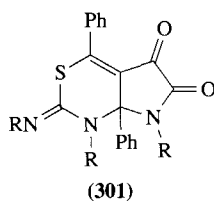


i, Ph₃PX₂ (X = Cl, Br), Et₃N, RT to reflux, 2 h; ii, toluene or MeCN, heat

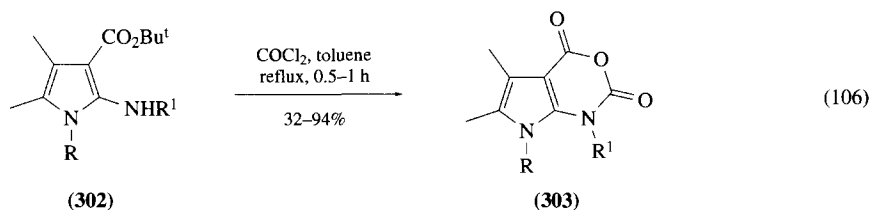
The furandione (**296**) reacts with diaryl or dialkylcarbodiimides to give, via the furooxazine (**297**), the products (**298**) which isomerize above 60 °C to the pyrrolediones (**299**) (Scheme 22). These products (**299**) react with dimethylcarbodiimide to give pyrrolo[2,3-*d*][1,3]oxazinediones (**300**). In a similar way 2,3-thiophenedione yields pyrrolo[2,3-*d*][1,3]thiazines (**301**) <84CB1310>. The structures (**300**) and (**301**) were confirmed by x-ray crystallography.



Scheme 22

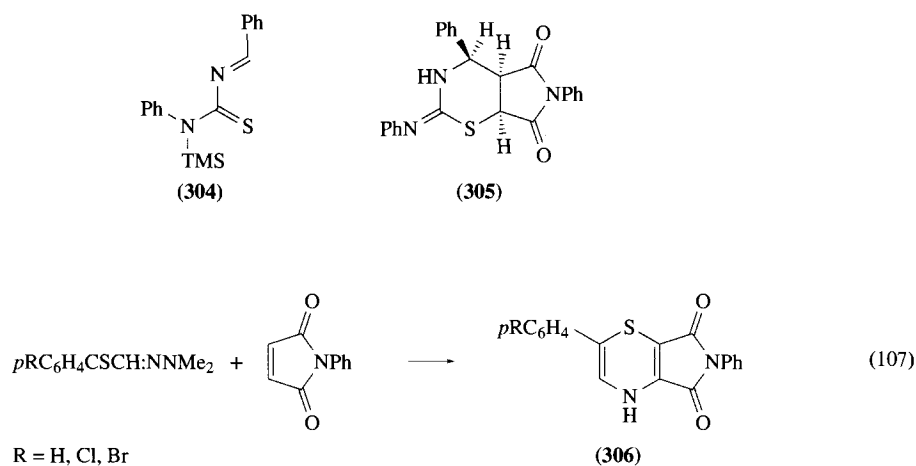


There is an easy route to pyrrolooxazinediones (**303**) from the pyrroles (**302**) by simply refluxing with carbonyl chloride in toluene (Equation (106)) <85S796>.

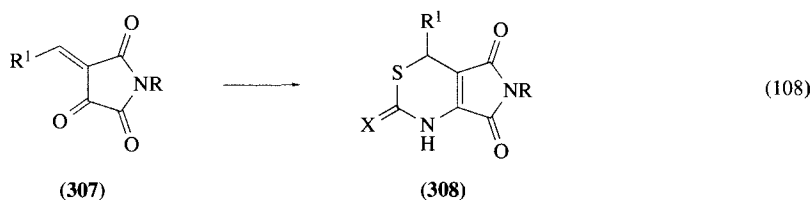


7.07.6.10.3 Pyrrolothiazines

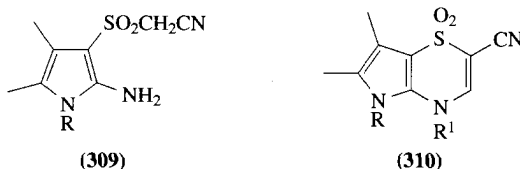
The pyrrolo[3,4-*e*][1,3]thiazine (**305**) is obtained, stereoselectively as the *endo* isomer, by [4 + 2] cycloaddition of the heterodiene (**304**) with *N*-phenylmaleimide in toluene at 60 °C (10 h) <89TL6923>. *N*-Phenylmaleimide also reacts with 2-(dialkylhydrazono)thioacetophenones via [4 + 2] cycloaddition to give 4-amino-3,4-dihydro-2*H*-1,4-thiazines which readily convert to the pyrrolothiazines (**306**) (Equation (107)) <92PS(70)211>.



Another route to pyrrolothiazines is the acid-catalyzed treatment of the pyrrolidinetrione (**307**) with bifunctional nucleophiles, such as thiourea and phenylthiourea, to yield the compounds (**308**) in yields of up to 55% (Equation (108)) <87JPR626>.



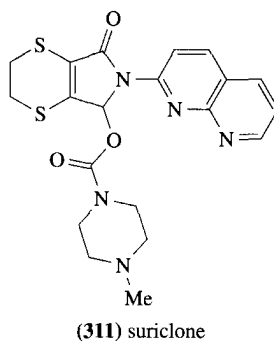
Simply heating the pyrrole (309) with triethyl orthoformate (140–155°C, 3.5 h) gives the pyrrolo[3,2-*b*][1,4]thiazine-1,1-dioxides (310), some of which show muscle relaxant properties <88PJS242>.



R = PhCH₂, PhCH₂CH₂, cyclohexyl, Bu, morpholino, pyridylmethyl; R¹ = H, Et

7.07.6.10.4 Dithiinopyrroles

The 1,4-dithiino[2,3-*c*]pyrrole, suriclone (Rhone-Poulenc) (311), was first synthesized in the 1970s. Since then it has been widely used as an anxiolytic and many studies of its metabolism and pharmacology have been carried out. There are many patents which have been taken out on analogues of suriclone. However, there seem to have been no reports of the chemistry of the thiinopyrrole ring system up to 1995.



(311) suriclone

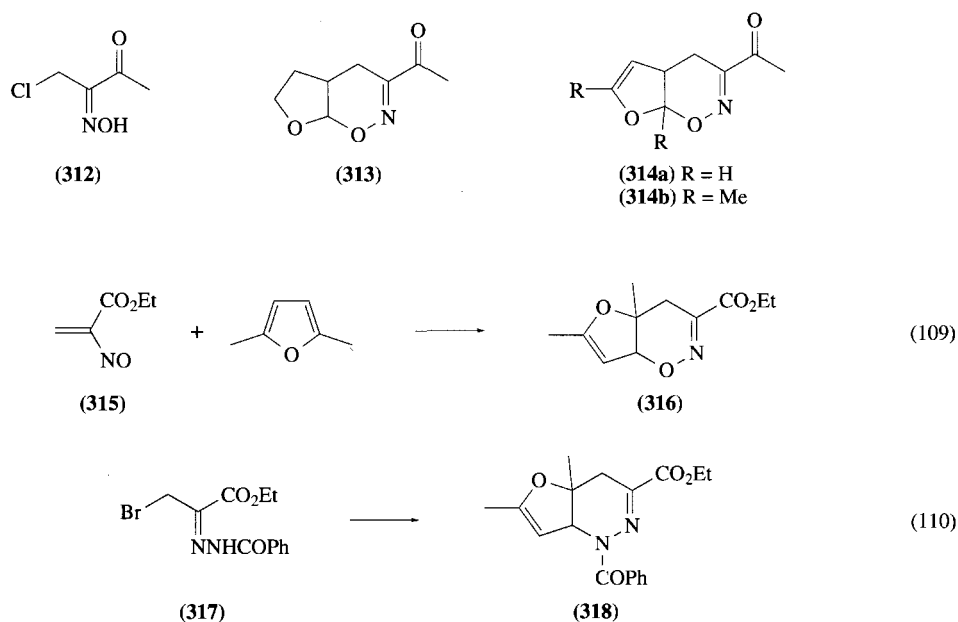
7.07.6.11 Miscellaneous Fused Furo Systems

The furodioxins, and cyclic peroxides, as mentioned in Section 7.07.1, will not be dealt with here. Other furo-based systems are considered below, although there seem to be few systematic studies of such ring systems.

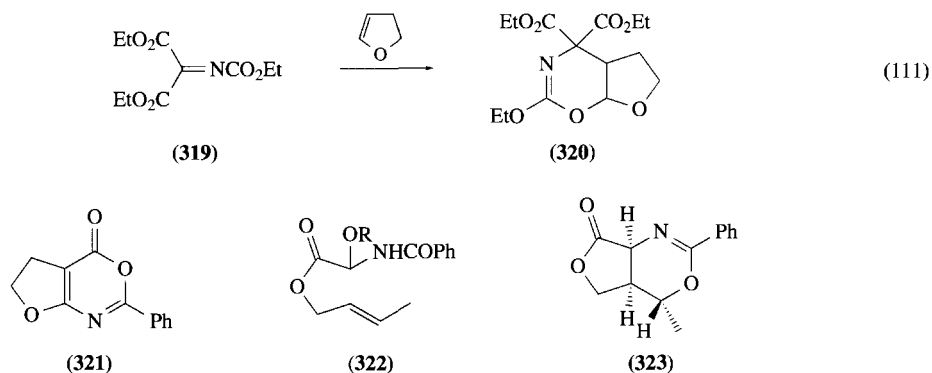
7.07.6.11.1 Furooxazines

The use of a chlorooxime as the precursor to α -nitrostyrene, and its subsequent cycloaddition to produce a furo[2,3-*e*]-1,2-oxazine, was referred to in CHEC-I (vol. 3, p. 1013 and <76CC581>). Much further work has since been carried out on this reaction, principally by Gilchrist and co-workers. The chlorooxime (312) reacts with 3,4-dihydrofuran to yield 3-acetyl-4a,5,6,7a-tetrahydrofuro[3,2-*e*]-1,2-oxazine (313) which has been characterized as its 2,4-dinitrophenyl hydrazone <85JCS(P1)2769>. Similar reactions of furan and 2,5-dimethylfuran have yielded *cis*-3-acetyl-4a,7a-dihydro-4*H*-furo[2,3-*e*]-1,2-oxazine (314a), and the 4a,7a-dimethyl analogue (314b) <83JCS(P1)1283>. This approach to the synthesis of furooxazines has been developed using the cycloaddition of nitrosoalkenes, generated *in situ* from halogenooximes, to furans <79JCS(P1)249, 83JCS(P1)1283, 90JCS(P1)1497>. The vinylnitroso compound (315) reacts with 2,5-dimethylfuran to yield the furooxazine (316)

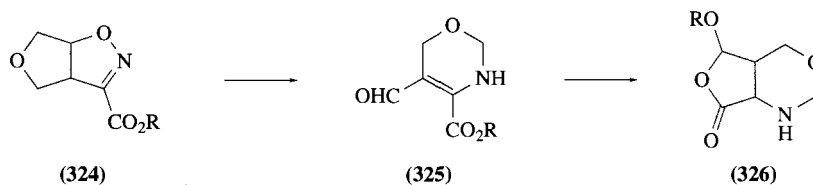
(Equation (109)) <87JCR(S)180>. A similar reaction starting with the benzoylhydrazone of ethyl 3-bromo-2-oxopropanoate (**317**) gives a furopyridazine (**318**) (Equation (110)) <87JCS(P1)2505>.



Triethyl azomethinetricarboxylate (**319**) reacts with electron-rich alkenes in chloroform at room temperature to give Diels–Alder products (e.g. **(320)**) (Equation (111)) <84TL943>. Furooxazines (e.g. **(321)**) have also been obtained by reacting α -aminoesters and dichlorotriphenylphosphorane <84CB1310, 85S796>. The furooxazine (**323**) has been made by an intramolecular [4 + 2] cycloaddition involving an *N*-acylamine and an alkene. The acetylation of compound (**322**; R = H) gives the ester (**322**; R = Ac) which on heating in refluxing *o*-dichlorobenzene gives the furooxazine (**323**) (64%) as a single stereoisomer, confirmed by high field ^1H NMR spectroscopy <84JOC5058>.

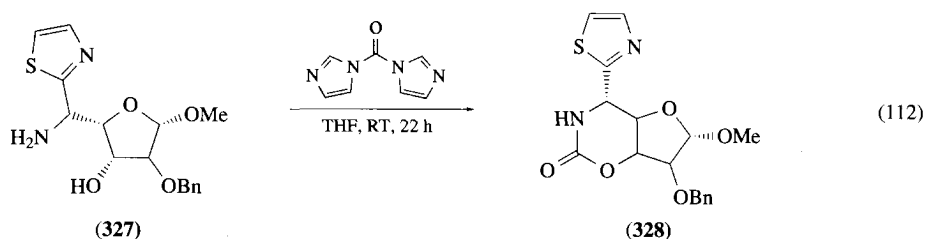


The oxazines (**325**) are formed as primary products in the photoreactions of tetrahydro[3,4-*d*]isoxazoles (**324**), but themselves undergo cyclization to give the furooxazines (**326**) on further irradiation (Scheme 23). This reaction (**325**) $\rightarrow$ (**326**) seems to be a concerted process involving migration of OR. This process seems to be similar to the classical d- π -methane rearrangement <88CCC3171, 88ZC22>.

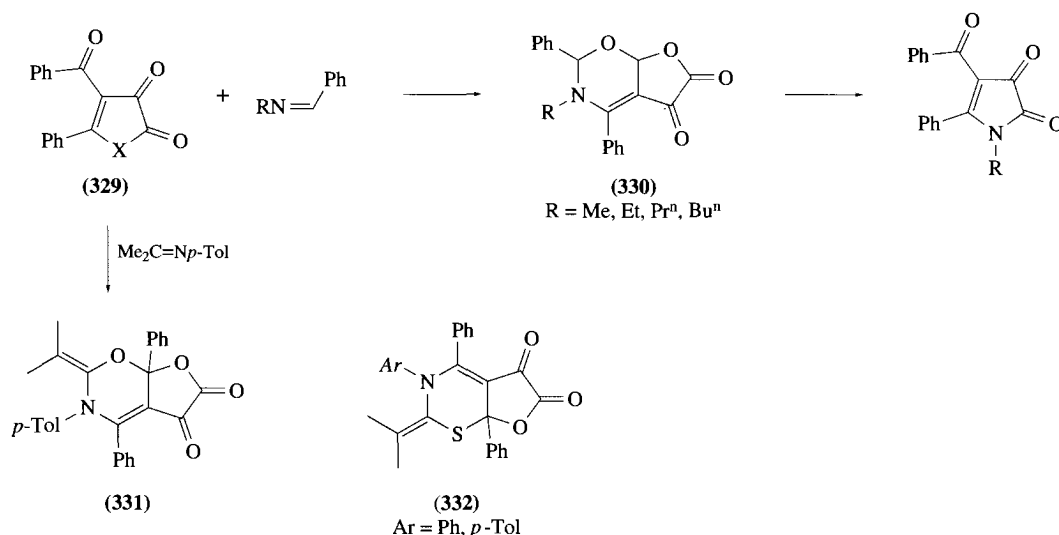


Scheme 23

The tetrahydrofuro[2,3-*e*]-1,3-oxazin-2-one (**328**) has been obtained from the precursor (**327**) and the structure confirmed by x-ray crystallography (Equation (112)) <88T3215>.



The reaction products of *N*-alkyl(phenylmethan)imines and 4-benzoyl-5-phenylfuran-2,3-dione (**329**; X = O) have been confirmed as furo[3,2-*e*][1,3]oxazines (**330**) by extensive ¹H and ¹³C NMR studies. These compounds undergo subsequent reaction to yield pyrrolidinediones (Scheme 24). The compound (**329**; X = O) reacts with dimethyl-*p*-tolylketenimine to give the furooxazine (**331**). Under similar conditions the sulfur analogue (**329**; X = S) gives the furothiazines (**332**); the structure of the product being confirmed by x-ray crystallography and NMR spectroscopy. This reaction is different from that of the furo analogue, and is obviously more complex, since it results in a change from a thiophene to a furothiazine system <84CB1310, 87H(26)625>.

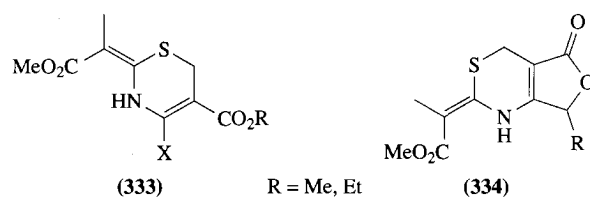


Scheme 24

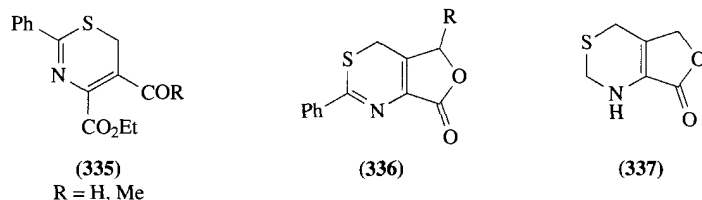
Some derivatives of 2*H*-furo[3,2-*d*][1,3]oxazine-2,6-(1*H*)dione have been reported to have been made, but without any details <88BCJ461>.

7.07.6.11.2 Furothiazines

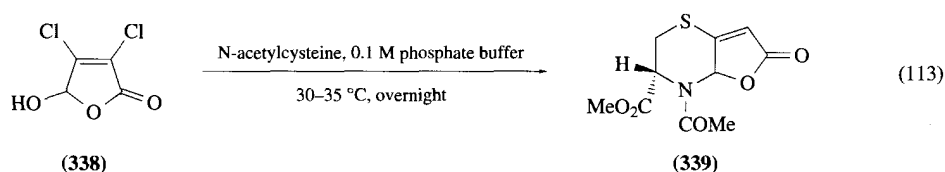
Treatment of the bromomethylthiazine esters (**333**; X = CH₂Br) with sodium acetate yields the lactone which is a furothiazinone (**334**; R = H). The aldehydes (**333**; X = CHO) react with potassium hydroxide to give the lactones (**334**; R = OMe, OEt) in 80–90% yield <86PS(28)361>.



The thiazine lactones (**336**) have been made by reduction of the thiazines (**335**) <85TL745, 87T2709>. A similar thiazine lactone (**337**) has been isolated from cultures of a cephalosporin C producing strain of *Cephalosporium acremonium* <88TL2101>.



A thiazine lactone (**339**) has also been made, albeit in very low yield (0.3%), by reacting 3,4-dichloro-5-hydroxy-2(5*H*)-furanone (**338**) with *N*-acetylcysteine (Equation (113)). The structure of the product was confirmed by NMR spectroscopy <92MI 707-05>.

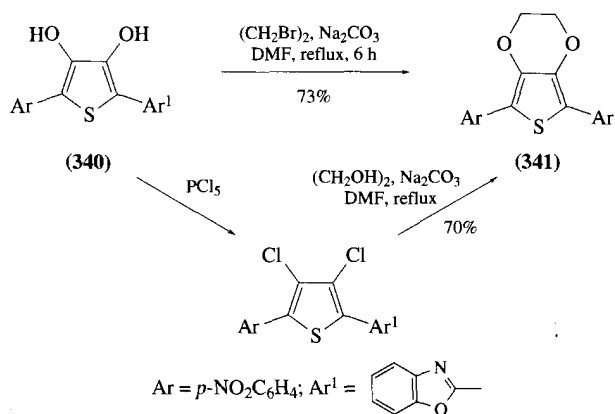


7.07.6.12 Miscellaneous Fused Thieno Systems

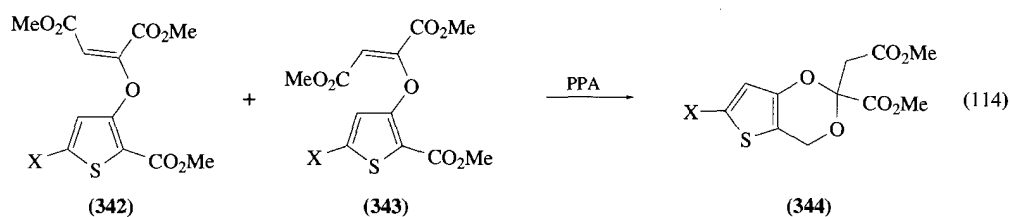
7.07.6.12.1 Thienodioxins

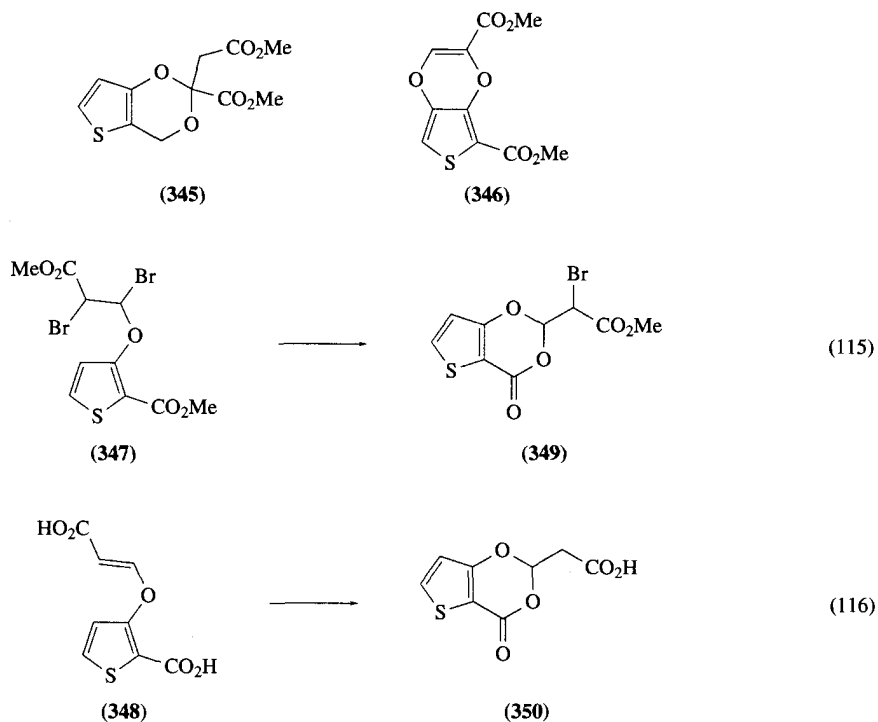
The thieno[3,4-*b*][1,4]dioxins (**341**) have been obtained from the 3,4-dihydroxythiophenes (**340**) by the two routes shown in Scheme 25. The use of ethane-1,2-diamine allows the synthesis of the tetrahydrothieno[3,4-*b*][1,4]pyrazine system <91JHC1449>.

Treating the thiophenes (**342**; X = CO₂Me) and (**343**; X = CO₂Me) with polyphosphoric acid yields only the 4*H*-thieno[3,2-*b*]-1,3-dioxin-4-one (**344**; X = CO₂Me) (Equation (114)). However thiophenes (**342**; X = H) and (**343**; X = H) give both product (**345**; X = H), and thienopyranone (**346**). Polyphosphoric acid also cyclizes the thiophenes (**347**) and (**348**) to the bicyclic products (**349**) and (**350**) (Equations (115) and (116), respectively) <85JCR(S)386>.

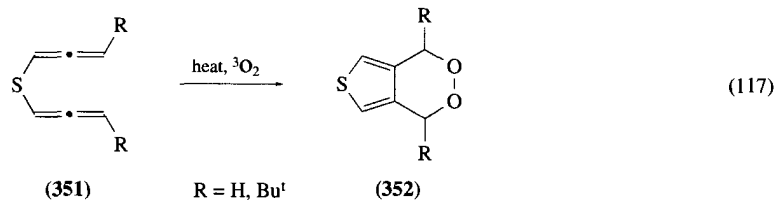


Scheme 25



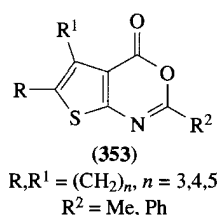


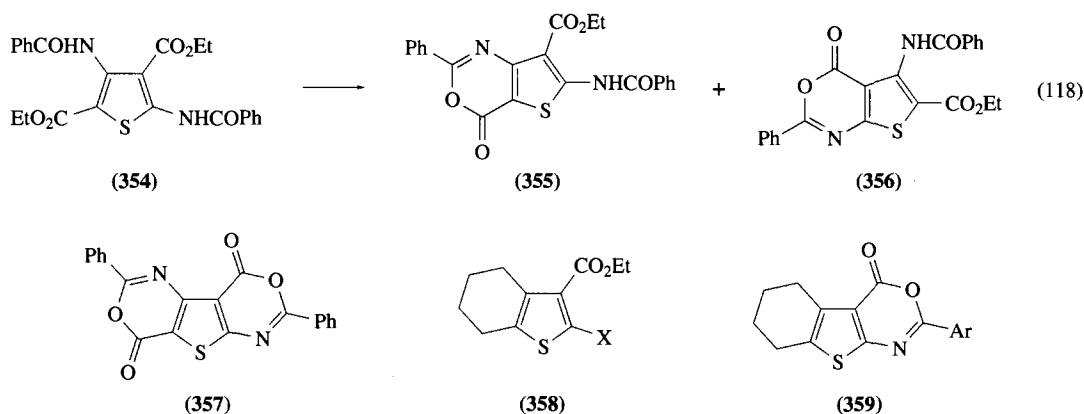
The 1*H*,4*H*-thieno[3,4-*d*][1,2]dioxins (352) are obtained, as crystalline solids, by thermolysis of the bisallene sulfides (351) in the dark and in the presence of oxygen (Equation (117)) <85IJ101>.



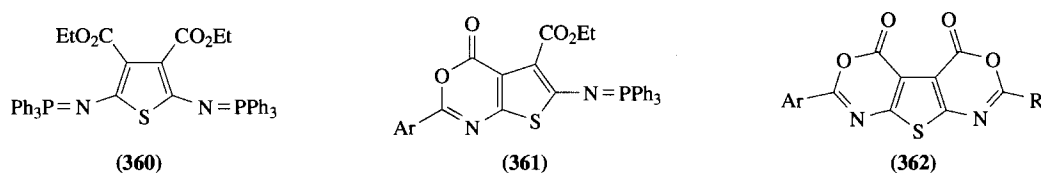
7.07.6.12.2 Thienooxazines

The thienooxazines (353) have been known since 1981 <81CB3188, 81JIC982>. The synthetic route to these which has been most used being the reaction of dihalotriphenylphosphoranes with α -aminoesters (cf. the synthesis of furooxazines, Section 7.07.6.11.1). The thiophene (354) reacts with dichlorotriphenylphosphorane to give the isomers (355) and (356) (Equation (118)) together with the tricyclic compound (357), 26% of the product being (355) and (356) and 61% being (357) <81CB3188>. These reactions have been developed and general syntheses for heteroannulated 3,1-oxazin-4-ones which give high yields of these products have been formulated involving the use of β -(*N*-triphenylphosphoranylidene)-enaminoesters with aroyl chlorides. Thus using dichlorophenylphosphorane the thiophene (358; X = NH₂) is converted to the derivative (358; X = N:PPh₃) which on heating with an aroyl chloride gives the thienooxazine (359).

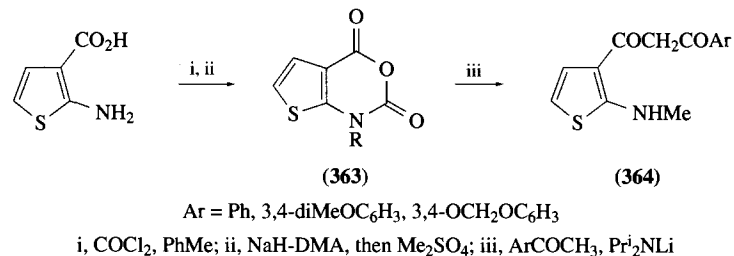




In a similar reaction, the bisphosphoranylideneaminothiophene **(360)** with an aroyl chloride gives first the product **(361)** and then the tricyclic product **(362)**. The use of other reagents in the second step enables various R groups to be introduced (93T581).

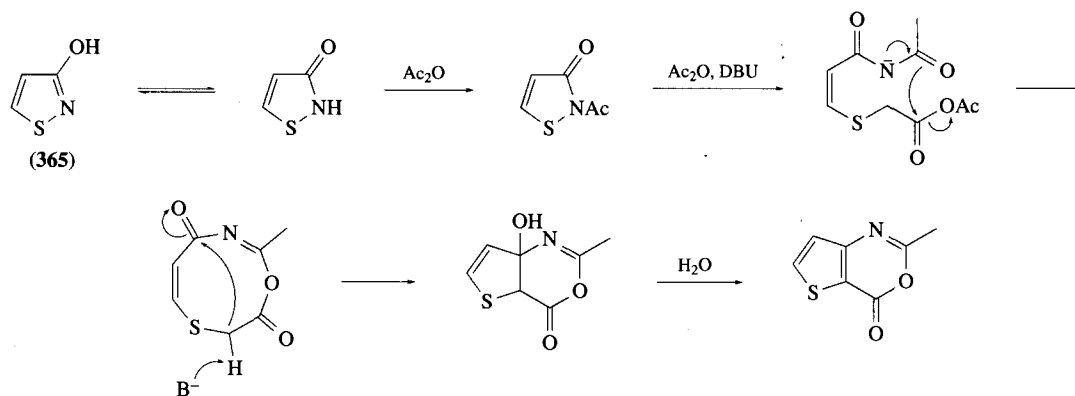


Thienooxazinediones **(363)** are obtained by reacting 2-aminothiophene-3-carboxylic acids with carbonyl chloride. These may then be alkylated and reacted with aldehydes to yield 3-substituted thiophenes **(364)** (Scheme 26) (86JCR(M)1063, 86JCR(M)2828, 86JCR(S)155, 86JCR(S)328).



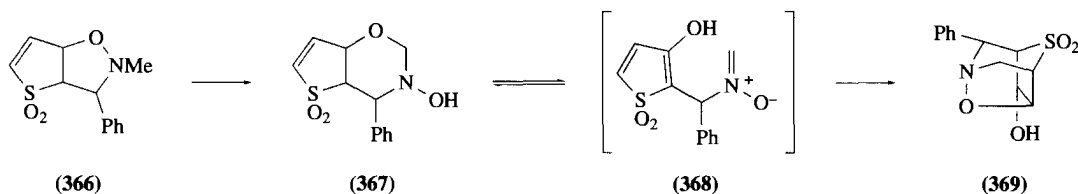
Scheme 26

Thienooxazines can also be made from 3-hydroxyisothiazoles **(365)** by a process involving ring opening of the isothiazole ring, followed by two ring closures (Scheme 27) (85JHC1497).



Scheme 27

An example of a ring enlargement of a thienoisoxazole to yield a thienooxazine system is that of 2-methyl-3 β -phenyl-2,3 α ,3 $\alpha\beta$,6 $\alpha\beta$ -tetrahydrothieno[2,3-*d*]isoxazole-4,4-dioxide (366) which yields compound (367) on treatment with MCPBA (Scheme 28). This product undergoes an interesting reaction on treatment with *t*-butanol in boiling toluene to give the tricyclic product (369) via the nitron (368). The structure of compound (369) was confirmed by x-ray crystallography <86T4661>.



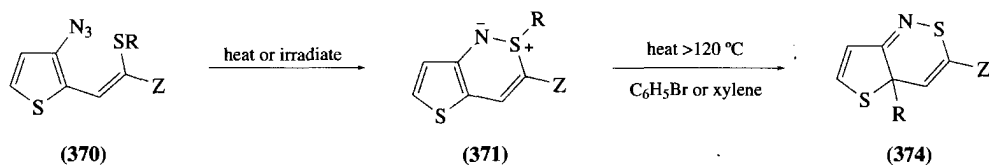
Scheme 28

7.07.6.12.3 Thienothiazines

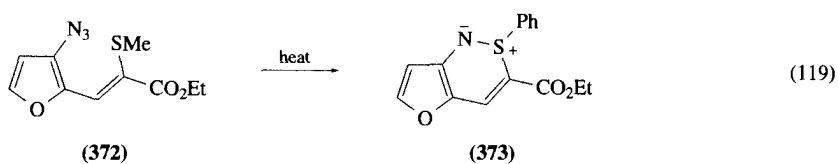
Thieno[3,2-*c*][1 λ^4 ,2]thiazines (371) were first reported in 1981 and were obtained by heating or irradiating the thiophenes (370) (Scheme 29) (Table 3) <81CC927, 86JCS(P1)483>. Similar thermolysis of the azidofuran (372) gives the product (373) (Equation (119)). At higher temperatures (> 120°C) these compounds undergo thermal [1,4] shifts to yield the derivatives (374) <86JCS(P1)491>, and they also undergo photochemical rearrangements <82CC884, 86JCS(P1)497>. Attempts to make the isomeric thieno[3,4-*c*][1 λ^4 ,2]thiazines have been less successful, and the only one to be isolated (as an unstable gum) has been compound (375) (Equation (120)) <86JCS(P1)483>.

Table 3 Synthesis of thieno[3,2-*c*][1 λ^4 ,2]thiazines (371) <81CC927, 86JCS(P1)483>.

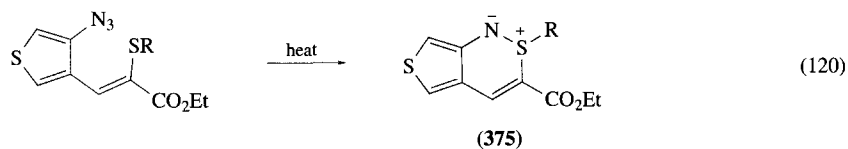
<i>R</i>	<i>Z</i>	Yield (%)
Me	CO ₂ Et	80
Et	CO ₂ Et	30
CH ₂ CH:CH ₂	CO ₂ Et	0
Ph	CO ₂ Et	89
Ph	COMe	90
Ph	CHO	75
Ph	CN	90
Me	H	4



Scheme 29

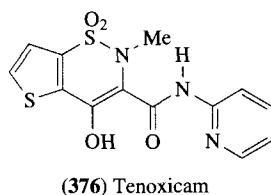


(119)

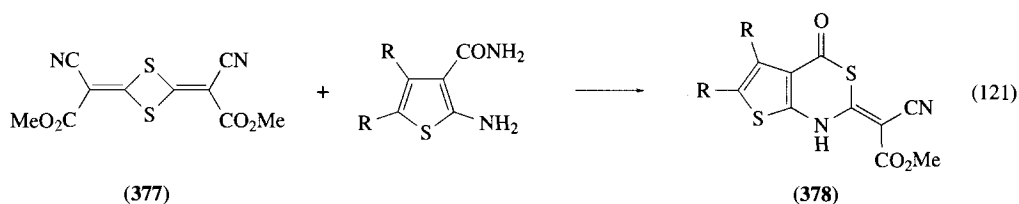


The thienothiazine system can also be obtained from the “reversed” azidothiazines. However, such reactions are not successful for the synthesis of the [3,4-*c*] system due to the nitrene preferentially cyclizing to the thiophene 2-position resulting in thienopyrroles, or thienopyridines, and only the thieno[2,3-*c*][1,2]thiazines are obtained <86JCS(P1)483>.

There has been considerable interest in the thienothiazine ring system from the pharmaceutical and pharmacological view point since 1976 when tenoxicam (4-hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-thieno[2,3-*c*]-1,2-thiazine-3-carboxamide-1,1-dioxide) (376) was patented by Hoffmann-La Roche as an antiinflammatory agent. Since then there have been hundreds of references to analogues, and to related compounds, and their pharmacological action, metabolism, and analytical methods for these compounds. It would be beyond the scope of this chapter to attempt to review these data.

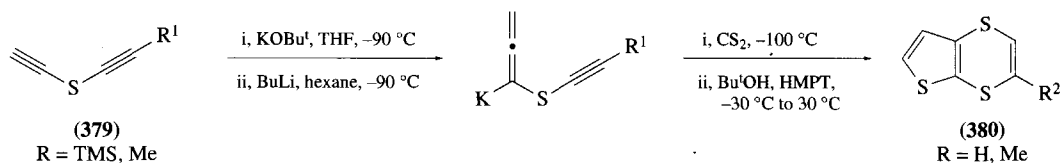


One of the methods which leads to a thienothiazine ring system is the reaction of the dithietane (377) with 2-amino-4,5-di(substituted)-3-thiophenecarboxamides to yield the derivatives (378) (Equation (121)) <86JAP(K)61151177>.

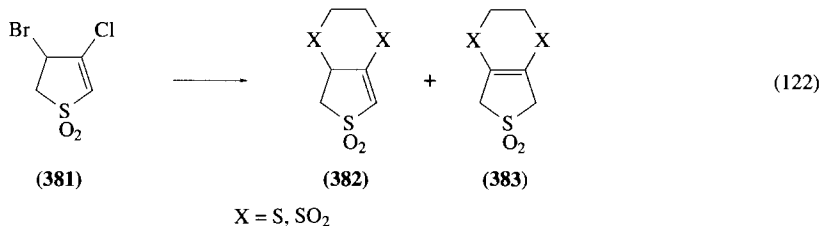


7.07.6.12.4 Thienodithiins

Thieno-1,4-dithiins (380) have been obtained (ca. 40% yield) from the diynes (379) (Scheme 30) <83CC1056, 87MI 707-02>. Thieno-1,4-dithiins (382) and (383) have also been obtained from 4-bromo-3-chloro-2-sulfolene (381) and the sodium salt of ethane-1,3-dithiol (Equation (122)). These products are oxidized by peracetic acid to yield the further *S*-oxides <89CC1020, 92CB499>.

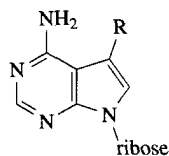


Scheme 30



7.07.7 IMPORTANT COMPOUNDS AND APPLICATIONS

A number of derivatives of the fused diazines, particularly nucleoside derivatives, are naturally occurring antibiotics. Examples of such compounds are sangivamycin (**384a**), which is an inhibitor of protein kinase C, and the related 7-deazaadeninine antibiotics tubercidin (**384b**) and toyocamycin (**384c**), which are not <88JBC1682, 89JAN102>.



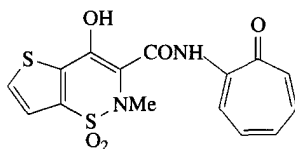
(**384a**) (R = CONH₂) Sangivamycin

(**384b**) (R = H) Tubercidin

(**384c**) (R = CN) Toyocamycin

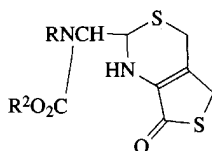
Several other ring systems covered by this chapter have other types of biological activity, for example, the 1,4-dithiino[2,3-*c*]pyrrole system provides suriclone (**311**) which is a useful anxiolytic agent. Many analogues have been synthesized and patented since the 1970s but few have been marketed. The thieno[2,3-*c*]thiazine dioxide, tenoxicam (**376**) is used as an antiinflammatory agent and, again, many analogues have been synthesized, a few of which have been developed.

2*H*-Thieno[3,2-*e*]-1,3-thiazines have also been patented as inhibitors of inflammation, and for their analgesic and antirheumatic properties (for example see <79GEP(O)2838851, 80SZP617705>). Similarly, the thieno[2,3-*e*]-1,2-thiazines (e.g. (**385**)) have also been shown to have antiinflammatory properties <85EUP138223>.



(**385**)

The 4*H*-thieno[3,4-*d*][1,3]thiazine (**386**) is an intermediate in a synthesis of cephalosporin <77JAP32637, 78JAP(K)83884>.



R = phthalamido, R¹ = Bu^t
R = H, R¹ = Bu^t
R = R¹ = H

(**386**)

Much of the chemistry of the ring systems covered in this chapter has centered on their uses as pharmaceuticals, and as synthetic analogues of natural products, or as intermediates in the synthesis of natural products. Only a few examples have been cited here. No doubt this research effort into the synthesis and studies of biological activity will continue, unabated, in the future.

7.08

Bicyclic 5-6 Systems: Three Heteroatoms 2 : 1

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7.08.1 INTRODUCTION

This chapter is confined to a review of 5 : 6 or 5 : 6 : 6 ring-fused heterocyclic ring systems with C—C fusion points and three heteroatoms. More specifically, these ring systems have two heteroatoms in the five-membered ring and one heteroatom in the adjacent fused six-membered ring. A search of the literature revealed over one hundred examples of ring systems that fit these criteria and parent ring systems together with their systematic names are shown in structures (1)–(86). This chapter contains a selection of data and includes updates of the chemistry of ring systems which were included in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) together with chemistry of ring systems which were not covered in CHEC-I. Imidazopyridines <84CHEC-I(5)607>, pyrazolopyridines <84CHEC-I(5)305>, oxazolopyridines <84CHEC-I(6)613>, isoxazolopyridines <84CHEC-I(6)613>, thiazolopyridines <84CHEC-I(6)613>, and isothiazolopyridines <84CHEC-I(6)613> were all reviewed in CHEC-I and the material covered in this chapter concerning these systems is from 1983 to 1994. Earlier work has been included but only where it is required to put more later developments in context. Not included in this chapter are bicyclic systems derived from carbohydrates. Although several trivial nomenclatures are found in the literature, for example azaindazoles and deazapurines, IUPAC nomenclature is used in this chapter. This review is self-limiting in nature and as a result the research trends are illustrated with representative rather than exhaustive examples.

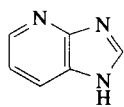
7.08.2 THEORETICAL METHODS

Few publications are found which deal solely with a discussion of the structural properties of any one of the bicyclic ring systems in this chapter. Instead, theoretical calculations are found, for example INDO and CNDO, together with x-ray analysis, NMR and UV spectroscopy, and tautomerism scattered throughout publications using them as a tool to describe a compound or to predict the outcome of a reaction. These applications are generally used with classes of compounds which contain multisubstitution which alters the reactivity of the whole system from that of the unsubstituted ring system. X-ray analysis, nuclear magnetic resonances, UV spectroscopy, etc. are also found in the analysis of compounds whose synthesis may provide more than one stereoisomer. For example, x-ray analysis has become a routine tool in the determination of the anomeric configuration of nucleosides prepared by a condensation of the heterocyclic ring with a sugar moiety. In many of these cases the structure of the heterocycle is incidental and only a Fortran thermal ellipsoid plot (ORTEP II) drawing of the molecule is presented as proof of structure. With the advent of accessible molecular modeling programs, one can now easily generate a three-dimensional structure, calculate energy minimums, dynamics and dynamic animation, hydrogen-bond calculations, etc. These types of structural analyses are also found in a few of the publications. Some publications related to structural studies are to be found in the following sections.

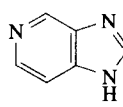
7.08.3 EXPERIMENTAL STRUCTURAL METHODS

7.08.3.1 X-ray Determinations

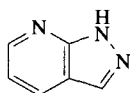
There are very few examples of x-ray studies of the various classes of compounds in this chapter. Generally, the crystal structures reported are of compounds with potential biological activity.

Imidazopyridines

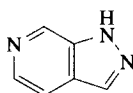
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Imidazo[4,5-*b*]pyridine

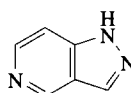
(2)

Imidazo[4,5-*c*]pyridine**Pyrazolopyridines**

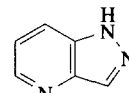
(3)

Pyrazolo[3,4-*b*]pyridine

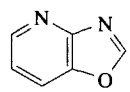
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Pyrazolo[3,4-*c*]pyridine

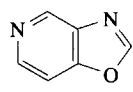
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Pyrazolo[4,3-*c*]pyridine

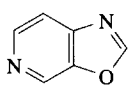
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Pyrazolo[4,3-*b*]pyridine**Oxazolopyridines**

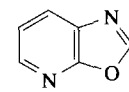
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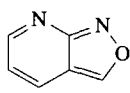
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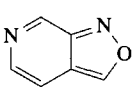
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Oxazolo[5,4-*c*]pyridine

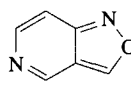
(10)

Oxazolo[5,4-*b*]pyridine**Isoxazolopyridines**

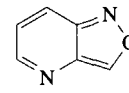
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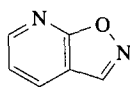
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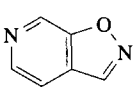
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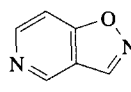
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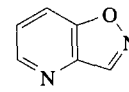
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Isoxazolo[5,4-*b*]pyridine

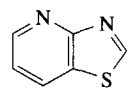
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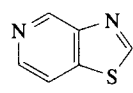
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Isoxazolo[4,5-*c*]pyridine

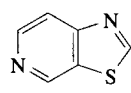
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Isoxazolo[4,5-*b*]pyridine**Thiazolopyridines**

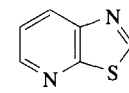
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Thiazolo[4,5-*b*]pyridine

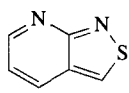
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Thiazolo[4,5-*c*]pyridine

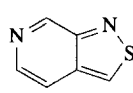
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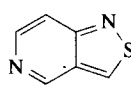
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Thiazolo[4,5-*b*]pyridine**Isothiazolopyridines**

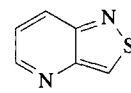
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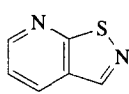
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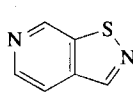
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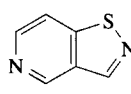
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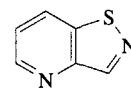
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Isothiazolo[5,4-*b*]pyridine

(28)

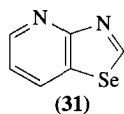
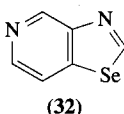
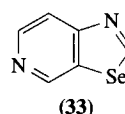
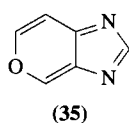
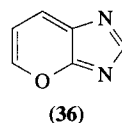
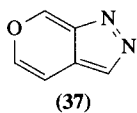
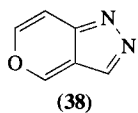
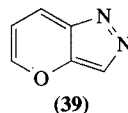
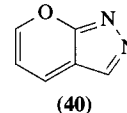
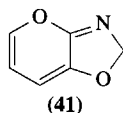
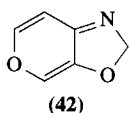
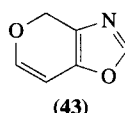
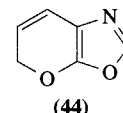
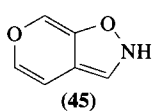
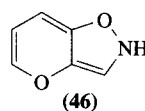
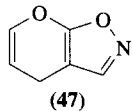
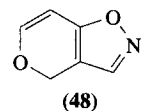
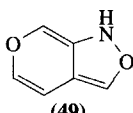
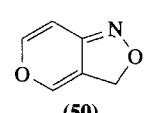
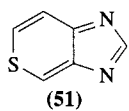
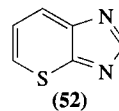
Isothiazolo[5,4-*c*]pyridine

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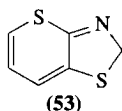
Isothiazolo[4,5-*c*]pyridine

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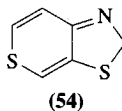
Isothiazolo[4,5-*b*]pyridine

SelenazolopyridinesSelenazolo[4,5-*b*]pyridineSelenazolo[4,5-*c*]pyridineSelenazolo[5,4-*c*]pyridineSelenazolo[5,4-*b*]pyridine**Pyranoimidazoles**Pyrano[3,4-*d*]imidazolePyrano[2,3-*d*]imidazole**Pyranoprazoles**Pyrano[3,4-*c*]pyrazolePyrano[4,3-*c*]pyrazolePyrano[3,2-*c*]pyrazolePyrano[2,3-*c*]pyrazole**Pyranooxazoles**2*H*-Pyrano[2,3-*d*]oxazole2*H*-Pyrano[4,3-*c*]oxazole4*H*-Pyrano[3,4-*d*]oxazole5*H*-Pyrano[3,2-*d*]oxazole**Pyranoisoxazoles**2*H*-Pyrano[4,3-*d*]isoxazole2*H*-Pyrano[2,3-*d*]isoxazole4*H*-Pyrano[3,2-*d*]isoxazole4*H*-Pyrano[3,4-*d*]isoxazole1*H*-Pyrano[3,4-*d*]isoxazole3*H*-Pyrano[4,3-*c*]isoxazole**Thiopyranoimidazoles**Thiopyrano[3,4-*d*]imidazoleThiopyrano[2,3-*d*]imidazole

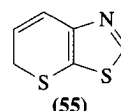
Thiopyranothiazoles



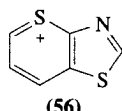
2H-Thiopyrano[2,3-d]thiazole



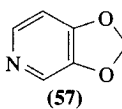
2H-Thiopyrano[4,3-d]thiazole



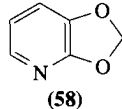
5H-Thiopyrano[3,2-d]thiazole



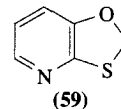
Thiopyrano[3,4-d]thiazol-4-ium



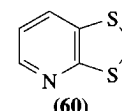
2H-1,3-Dioxolo[4,5-c]pyridine



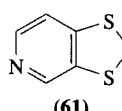
2H-1,3-Dioxolo[4,5-b]pyridine



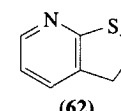
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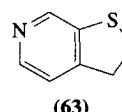
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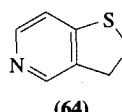
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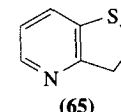
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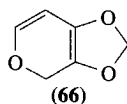
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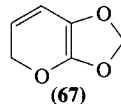
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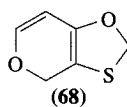
3H-1,2-Dithiolo[4,3-b]pyridine



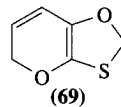
2H,4H-1,3-Dioxolo[4,5-c]pyran



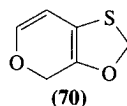
2H,5H-1,3-Dioxolo[4,5-b]pyran



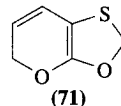
2H,4H-1,3-Oxathiolo[4,5-c]pyran



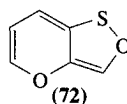
2H,5H-1,3-Oxathiolo[4,5-b]pyran



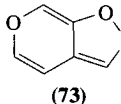
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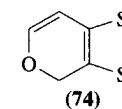
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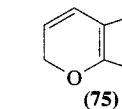
1,2-Oxathiolo[4,3-b]pyran



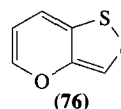
1,2-Oxathiolo[5,4-c]pyran



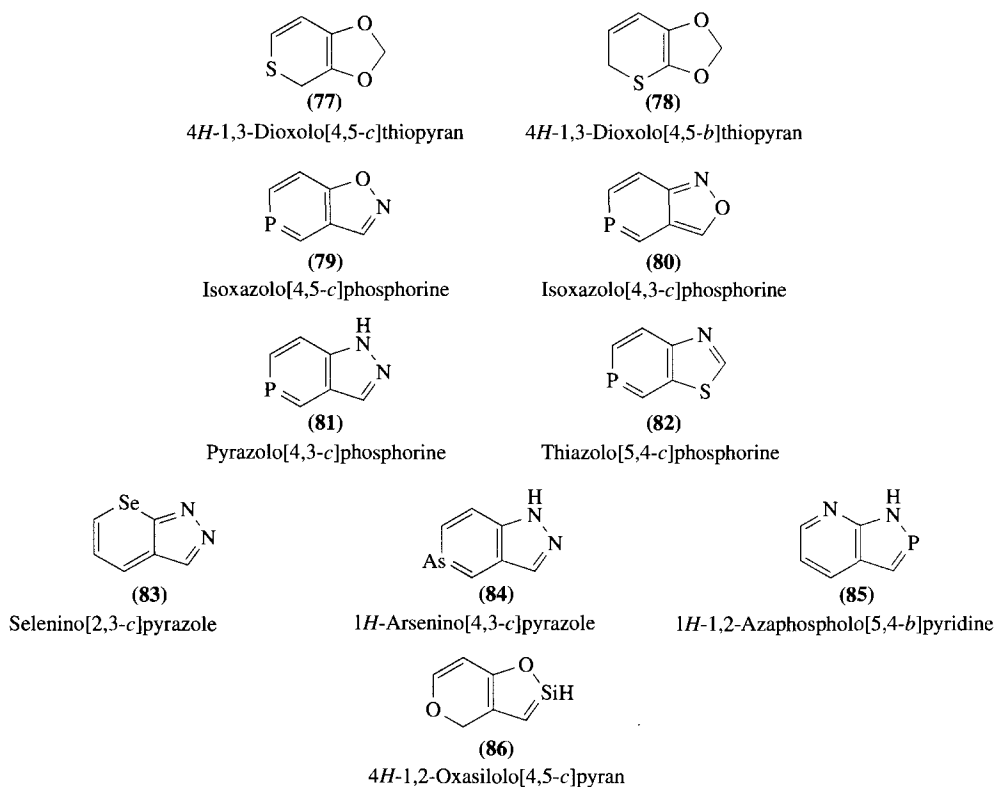
2H,4H-1,3-Dithiolo[4,5-c]pyran



2H,5H-1,3-Dithiolo[4,5-b]pyran

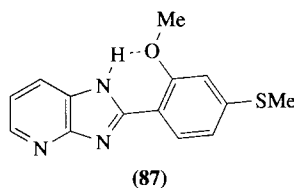


1,2-Dithiolo[4,3-b]pyran



7.08.3.1.1 Imidazo[4,5-*b*]pyridines

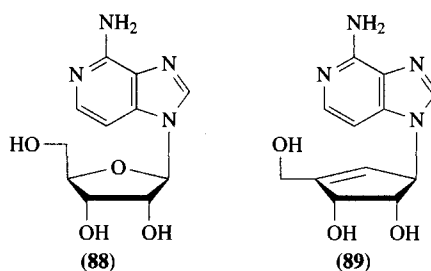
The structure of the cardiotonic drug 2-[(2-methoxy-4-methylthio)phenyl]-1*H*-imidazo[4,5-*b*]pyridine (**87**) has been determined to be planar <87AX(C)1937>. The imidazole ring hydrogen atom was determined to be located at N-1 and not at N-3. This is due to intramolecular hydrogen bonding between the hydrogen atom located at N-1 and the 2-methoxy group on the phenyl ring. The bond lengths and angles of the imidazo[4,5-*b*]pyridine ring system in compound (**87**) were not distorted by the hydrogen bonding.



7.08.3.1.2 Imidazo[4,5-*c*]pyridines

The crystal structures of 4-amino-1-(β -D-ribofuranosyl)imidazo[4,5-*c*]pyridine (**88**) <76JA825> and its neplanocin A analogue (**89**) <89JMC1442> have been determined. In both structures the imidazo[4,5-*c*]pyridine ring system is planar within ± 0.03 Å. The pyridine ring is distorted slightly relative to the pyrimidine ring in adenosine. Most notably, the exocyclic angle defined by C(7)—C(7a)—N(1) is increased by about 6.6° when compared to the same angle in adenosine. This distortion minimizes the steric interactions between the proton attached to C-7 and the imidazole ring. This results in a shifting of the positions for N-5 and the exocyclic amine function by about 0.2 Å relative to the N-1 atom and the exocyclic amino group in adenosine.

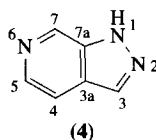
The single-crystal x-ray analysis of a series of 2'-deoxy-3-deazaguanosines has been reported to confirm the configuration about the anomeric carbon atom as β <84JMC1389>.



7.08.3.1.3 Pyrazolo[3,4-c]pyridines

The crystallographic data for unsubstituted pyrazolo[3,4-c]pyridine (**4**) is presented in Table 1 along with the calculated INDO bond orders, π -electron densities, and straight charges <89AP(322)885>. The molecular structure shows that the C(4)—C(5) and N(2)—C(3) bonds have pronounced double-bond character and that the molecule is nearly planar. The pyridine nitrogen was found to be the most basic. Comparison of the π -electron densities clearly indicates that the 3-position is most susceptible to electrophilic substitution. This is in agreement with chlorination, bromination, and nitration studies which all gave the 3-substituted derivative <73JCS(P1)2901, 89AP(322)885>.

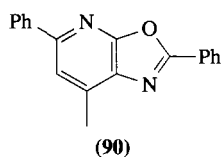
Table 1 X-ray bond lengths ($\text{\AA}$) and bond angles ($^\circ$), bond orders, π -electron densities, and straight charges from INDO calculations of 1*H*-pyrazolo[3,4-c]pyridine hydrochloride monohydrate <89AP(322)885>.



Atoms	Distances ($\text{\AA}$) (angles ($^\circ$))	Bond order neutral (protonated)	Atom	Distance to plane ($\text{\AA}$)	π -electron density, neutral (protonated)	Straight charge, neutral (protonated)
1-2 (1-2-3)	1.354 (107.2)	0.419(0.463)	1	0.002	1.6672(1.628)	0.0358(−0.0026)
1-7a (2-3-3a)	1.354 (110.6)	0.4535(0.4595)	2	0.001	1.139(1.042)	−0.1257(−0.0250)
2-3 (3-3a-7a)	1.322 (104.3)	0.819(0.802)	3	−0.008	1.048(1.057)	0.0740(0.0713)
3-3a (3-3a-4)	1.412 (136.2)	0.475(0.507)	3a	0.001	1.031(0.948)	−0.0062(0.0461)
3a-4 (4-3a-7a)	1.398 (119.6)	0.553(0.539)	4	0.003	1.0082(0.980)	−0.0079(0.0204)
3a-7a (3a-4-5)	1.404 (117.5)	0.572(0.522)	5	0.003	1.0128(0.977)	0.1187(0.1258)
4-5 (4-5-6)	1.359 (121.0)	0.746(0.765)	6	−0.005	1.065(1.392)	−0.1889(0.0804)
5-6 (5-6-7)	1.353 (124.5)	0.581(0.530)	7	−0.003	1.014(0.934)	0.0989(0.1461)
6-7 (6-7-7a)	1.334 (116.3)	0.725(0.646)	7a	0.005	1.012(1.022)	0.0658(0.0787)
7-7a (7-7a-3a)	1.385 (121.1)	0.581(0.631)				
(7-7a-1)	(131.7)					
(2-1-7a)	(110.7)					
(1-7a-3a)	(107.2)					

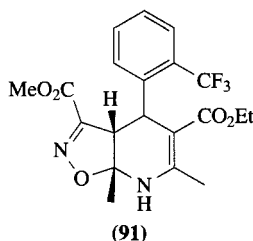
7.08.3.1.4 Oxazolo[5,4-b]pyridines

Single crystal analysis of 2,6-diphenyl-4-methyloxazolo[5,4-*b*]pyridine (**90**) was used to confirm its structure, and the structure of several similarly substituted compounds <92JCS(P1)701>.



7.08.3.1.5 Isoxazolo[5,4-*b*]pyridines

The crystal structure of the tetrahydroisoxazolo[5,4-*b*]pyridine (**91**) has been determined <89JOC5585>. The geometry of the pyridine nitrogen atom was found to be intermediate between a planar and tetrahedral.



7.08.3.2 NMR Spectroscopy

7.08.3.2.1 Proton NMR spectroscopy

Several Proton NMR studies are summarized in Table 2.

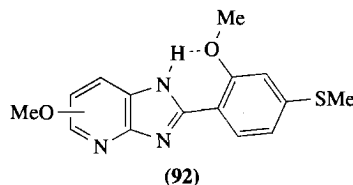
Table 2 Proton NMR spectra of certain 5-6 bicyclic ring systems.

Compound	1H Chemical shifts (δ , ppm)							Solvent	Ref.
	H-1	H-2	H-3	H-4	H-5	H-6	H-7		
(1) (2-aryl)					7.67	6.59	7.41	D ₂ O	90MRC573
(1)·(HCl) (2-aryl)					8.13	8.11	6.83	D ₂ O	90MRC573
(2) (2-aryl)				7.72		7.35	6.56	D ₂ O	90MRC573
(2)·(HCl) (2-aryl)				8.75		8.19	7.70	D ₂ O	90MRC573
(2) (4-chloro, 1-cyclopentyl)		7.94				8.24	7.42	CDCl ₃	89JMC1442
(2) (4-chloro, 3-cyclopentyl)		7.90				8.20	7.63	CDCl ₃	89JMC1442
(2)·(HCl) (4-amino, 1-cyclopentyl)		8.22				7.54	7.11	CDCl ₃	89JMC1442
(6) (3-methyl)			2.58(Me)	9.05		8.30	7.42	DMSO	88H(27)1899
(61) (3-oxo)					8.20	7.65	8.85	DMSO	82JHC1393
(62) (3-oxo)				9.30	8.44	8.88		DMSO	82JHC1393
(63) (3-oxo)				8.60	7.75		9.05	DMSO	82JHC1393
(63) (3-thione)				8.65	7.86		9.48	DMSO	82JHC1393
(64) (3-oxo)				8.23	7.37	8.83		CDCl ₃	82JHC1393
(64) (3-thione)				8.40	7.63	8.99		DMSO	82JHC1393

(i) Imidazopyridines

Proton NMR and carbon-13 NMR studies have been carried out to establish whether methoxy substitution in the pyridine ring of a series of 2-(2-methoxyphenyl)imidazo[4,5-*b*]pyridines (**92**) and related 2-(2-methoxyphenyl)imidazo[4,5-*c*]pyridines alters the major site of protonation from the pyridine ring to the imidazole ring <87AX(C)1937>. By comparing the ¹³C chemical shifts for the carbon atoms in the pyridine ring in both the free base and the corresponding hydrochloride salts,

it was found that substitution did not significantly alter the position of the ^{13}C signals throughout both of the series. It was concluded that the pyridine nitrogen is the most basic site for all compounds in the series and that initial protonation occurred predominantly at the pyridine nitrogen.



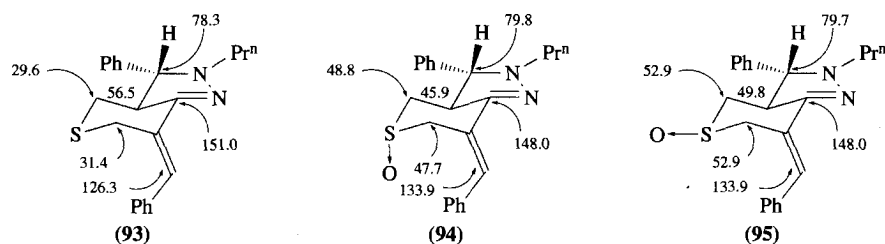
(ii) Isothiazolo[5,4-b]pyridines

Characteristic ^1H NMR spectra signals for the protons on the pyridine ring of 3-oxo-isothiazolo[5,4-b]pyridines <85JHC1353> are located at δ 7.3–7.5 (d, H-5, 1H), 8.1–8.4 (dd, H-4, 1H, $J_{4,5} = 7.5$ Hz), and 8.60–8.85 (dd, H-6, 1H, $J_{6,5} = 4.5$ Hz).

7.08.3.2.2 Carbon-13 NMR spectroscopy

(i) Thiopyrano[4,3-c]pyrazoles

The isolation of the isomeric axial and equatorial sulfoxides (94) and (95), from the preparation of a series of hexahydrothiopyrano[4,3-c]pyrazoles (93), prompted a study <79JOC2513> to determine what effect the introduction of an S—O bond had on the carbon shifts of the methylene carbons α to sulfur. When the oxygen atom is situated in an axial position as in isomer (94), it has a deshielding effect of +17 ppm on the β carbon atoms and a shielding effect on the carbons γ (–10 ppm and –9 ppm) and δ (–3 ppm) relative to the carbon atoms in the unsubstituted derivative (93). The trends are similar for the equatorial derivative (94). The magnitude and trends are comparable to reported data on monocyclic thiopyran derivatives. The chemical shifts of the carbon atoms of the sulfone derivative are comparable to the signals in both sulfoxides (94) and (95).



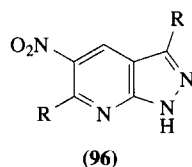
7.08.3.3 Mass Spectrometry

7.08.3.3.1 Imidazopyridines

In the mass spectra <68JOC2543> of imidazo[4,5-b]pyridin-2-ones and their benzo derivatives <91JMC2906>, the molecular ion is the most abundant ion followed by the ion corresponding to a loss of CO.

7.08.3.3.2 Pyrazolo[3,4-*b*]pyridines

A loss of the nitro group is the first fragmentation of 5-nitropyrazolo[3,4-*b*]pyridines (**96**) <92KGS1560>. The second fragmentation involves the consecutive elimination of HCN and RCN.

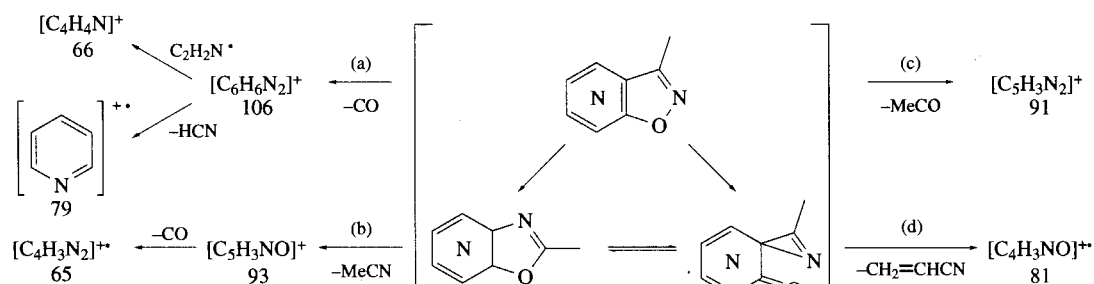


7.08.3.3.3 Oxazolopyridines

The electron impact (EI) ionization mass spectra of all four 2-methyloxazolopyridine isomers has been reported <93OMR(28)451>, and are discussed in Section 7.08.3.3.4.

7.08.3.3.4 Isoxazolopyridines

The EI ionization mass spectra of all four 3-methylisoxazolopyridine isomers has been reported, and are similar to one another. This similarity is due to an isoxazole-to-oxazole rearrangement which occurs during fragmentation. Thus the fragmentations of the isoxazolo derivatives are strikingly similar to those of the corresponding oxazolopyridines <93OMR(28)451>. Although the molecular ion is the most abundant ion in each case, the subsequent decomposition of the molecule via pathway (a) or (b) (Scheme 1) strongly depends on the ring system. The fragmentation of 3-methylisoxazolo[4,5-*b*]pyridine, and the corresponding 2-methyloxazolo[4,5-*b*]pyridine mainly follow path (b), while the remaining isomers follow path (a) suggesting that the spiroazirine formation is not as favorable in the isoxazolo[4,5-*b*]pyridine system as it is in the other systems. Paths (c) and (d) are of minor importance in all cases.



EI mass spectra fragmentation of 3-methylisoxazolopyridines

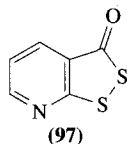
Scheme 1

7.08.3.3.5 Isothiazolopyridines

A series of isothiazolopyridin-3-ones all demonstrated an intense molecular-ion peak indicative of the stability of the system <88CHE385>. Characteristic of the fragmentation in the mass spectra of these compounds is a $(M-16)^+$ peak corresponding to loss of an oxygen atom. In addition peaks corresponding to $(M-\text{CHO})^+$, $(M-\text{COS})^+$, and $(M-\text{CHO}-\text{S})^+$ are seen in each case.

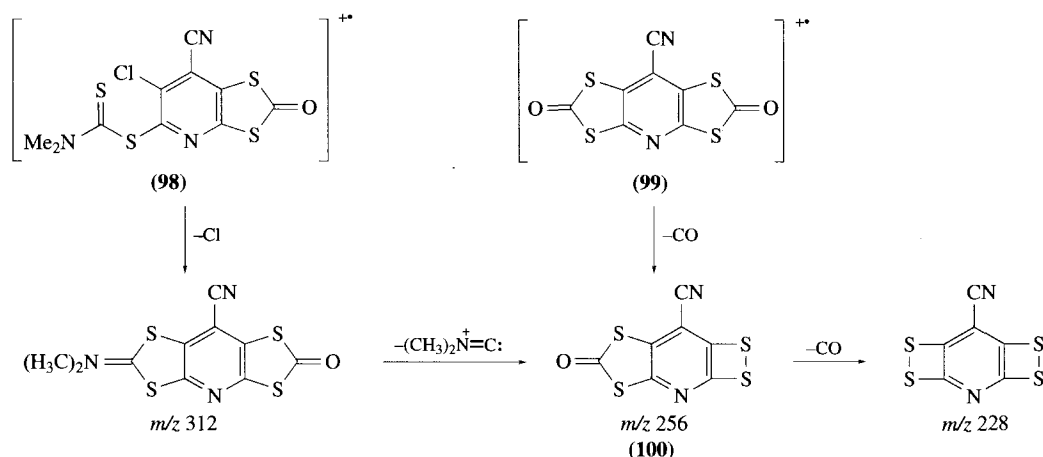
7.08.3.3.6 3H-1,2-Dithiolo[3,4-b]pyridines

Two fragmentation paths are observed in the ionization of 1,2-dithiolo[3,4-*b*]pyridin-3-one (**97**). The major pathway is the loss of two sulfur atoms from the molecular ion and the second pathway is the loss of CO from the molecular ion $\langle 94\text{H}(38)333 \rangle$.



7.08.3.3.7 1,3-Dithiolo[4,5-b]pyridines

The mass spectral fragmentation of 5-(*N,N*-dimethylthiocarbamoylthio)-6-chloro-7-cyano-1,3-dithiolo[4,5-*b*]pyridin-2-one (**98**), and 8-cyano-bis-1,3-dithiolo[4,5-*b*:4',5'-*e*]pyridine-2,6-dione (**99**) both proceed through the intermediate (**100**) (Scheme 2) $\langle 90\text{DOK}(312)147 \rangle$. The molecular ion was not observed for either (**98**) or (**99**).



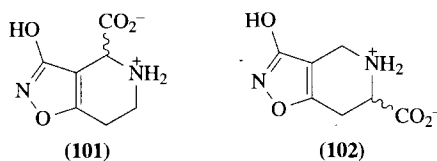
Scheme 2

7.08.3.4 Ultraviolet Spectroscopy

Table 3 presents the ultraviolet spectra of several of the ring systems in this review.

7.08.3.4.1 Tetrahydroisoxazolo[4,5-*c*]pyridines

Although not determined by UV spectroscopy, the $\text{p}K_a$ values of the tetrahydroisoxazolo[4,5-*c*]pyridines (**101**) and (**102**) were determined by titration. It was found that these compounds have exceptionally low $\text{p}K_a$ values, (**101**) 1.6, 5.8, 8.5 and (**102**) < 1.2, 4.2, 8.2 at 25°C in water $\langle 86\text{ACS}(B)92 \rangle$.



7.08.3.5 Infrared Spectroscopy

7.08.3.5.1 Imidazopyridines

The IR spectra of a large number of 2-thione derivatives of both imidazo[4,5-*b*]pyridine and imidazo[4,5-*c*]pyridine have been reported. In the study it was shown that these compounds exist

Table 3 UV spectral maxima (nm) for selected bicyclic compounds.

Compound	Solvent	λ (log ϵ or ϵ)	p <i>K</i> _a	Ref.
(1) (1-methyl)	H ₂ O (pH1)	235(1960), 277(7870), 282(8700), 289(7260)	4.10	63JOC1837
	H ₂ O (pH12)	282(9660), 289(sh) (7920)		63JOC1837
(1) (3-methyl)	H ₂ O (pH1)	236(4470), 275(10,640), 281(8930)	3.94	63JOC1837
	H ₂ O (pH11)	252(4510), 282(9010), 288 (sh) (6940)		63JOC1837
(1) (1-methyl) 4-oxide	H ₂ O (pH1)	295		82MI 708-01
	H ₂ O (pH12)	296.5, 304sh		82MI 708-01
(1) (3-methyl) 4-oxide	H ₂ O (pH1)	280sh, 301.5		82MI 708-01
	H ₂ O (pH12)	273, 304, 309sh		82MI 708-01
(2)			(basic) 6.10 ± 0.02 (acidic) 10.88 ± 0.04	86T1511
(2) (1-methyl)	H ₂ O (pH1)	263(4400)	6.36	63JOC1837
	H ₂ O (pH12)	255(4800), 263(4600)		63JOC1837
(2) (3-methyl)	H ₂ O (pH4)	253(5000), 285(6100),	6.15	63JOC1837
	H ₂ O (pH13)	249(4300), 275(5400),		63JOC1837
(2) (4-amino)(1-subst.)	C	263(4.002), 217(4.056)		89JMC1442
(2) (4-amino)(3-subst.)	C	285, 210		89JMC1442
(3) (3-acylamino)	B	303		82JCS(P1)759
(6) (5-nitro)	A	242(4.12), 257(4.11), 312(3.94)		92KGS1560
(6) (1-methyl)(5-nitro)	A	244(4.00), 263(4.14), 320(3.88)		92KGS1560
(6) (2-ethyl)(5-nitro)	A	265(4.21), 330(3.83)		92KGS1560
(18) (3-methyl)	A	202(3.81), 234(3.67), 278sh(3.77), 282(3.81), 287sh(3.75), 292(3.62)		82JCS(P1)2391
(18) (5,7-dihydroxy) (3-methyl)	A	222(4.04), 252(3.66), 306(3.86)		82JCS(P1)2391
5 <i>H</i> -Thiopyrano[4,3- <i>d'</i>]- isoxazol-4(7 <i>H</i>)-one	B	235.5(3.80)		84JHC1437

Solvent systems: A = methanol; B = ethanol; C = water.

predominantly as the thione tautomers in both the solid and liquid state <88CHE653>. While N—H stretching bands were observed, no bands which could be associated with S—H stretching were observed.

7.08.4 THERMODYNAMIC ASPECTS

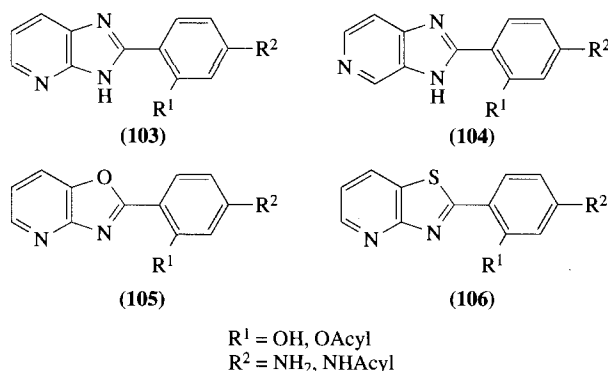
7.08.4.1 General Discussion

Correlation of melting points, chromatographic, and solubility properties for the whole spectrum of ring systems reviewed is not possible. However, a few individual studies involving the preparation of a series of similar derivatives have correlated the melting points, *R*_f values and solubilities between sub-sets of analogous compounds. For example, a comparison of the above properties for a series of imidazo[4,5-*b*]pyridines (**103**), imidazo[4,5-*c*]pyridines (**104**), oxazolo[4,5-*b*]pyridines (**105**), and thiazolo[4,5-*b*]pyridines (**106**) which contain a 2-(*m*-acylamino)phenyl- or 2-(*p*-acylamino)phenyl-substituent has been reported <89JHC289, 90JHC1825>. Within this series, it was observed that the imidazo-fused systems had higher melting points than those of the oxazolo- and thiazolo-fused counterparts, probably because of either intermolecular or intramolecular hydrogen bonding. Within each series, the thiazolo[4,5-*b*]pyridine analogues possessed the lowest melting points. Imidazo[4,5-*c*]pyridines, in general, had lower melting points than the corresponding imidazo[4,5-*b*]pyridines. The chromatographic properties show a trend, within a series, on silica gel 60 F-254 thin-layer chromatography plates using the same solvent system. The order of retention was imidazo[4,5-*c*]pyridine > imidazo[4,5-*b*]pyridine > oxazolo[4,5-*b*]pyridine > thiazolo[4,5-*b*]pyridines.

7.08.4.2 Solubilities and Chromatographic Behavior

The following are some general observations on select ring systems:

- 4-Nitroimidazo[4,5-*c*]pyridin-2-ones, like many 2-oxo derivatives, are only soluble in aqueous base.



• A study on the preparation of a relatively large number of imidazo[4,5-*b*]pyridine-2-thiones and imidazo[4,5-*c*]pyridine-2-thiones demonstrates that the solubility of these compounds is poor in most solvents <88CHE653>.

• Imidazo[4,5-*b*]quinolin-2-one derivatives and 2,3,9,9a-tetrahydroimidazo[4,5-*b*]quinolin-2-ones <91JMC2906, 93JMC3251> are only soluble in DMF or DMSO.

• The chromatographic mobility of a series of chlorinated isothiazolo[5,4-*b*]pyridines compared to the fully dehalogenated system using the same chromatographic conditions is in the order 4,6-dichloro-3-methylisothiazolo[5,4-*b*]pyridine > 4-chloro-3-methylisothiazolo[5,4-*b*]pyridine > 6-chloro-3-methylisothiazolo[5,4-*b*]pyridine > 3-methylisothiazolo[5,4-*b*]pyridine <90JCS(P1)1477>.

• 3*H*-1,2-Dithiolo[4,3-*c*]pyridine-3-thione is only relatively soluble in pyridine, DMF, hot aqueous bases, i.e. sodium hydroxide solutions or acids <54JOC711>. Neutralization of these solutions precipitate the compound unchanged.

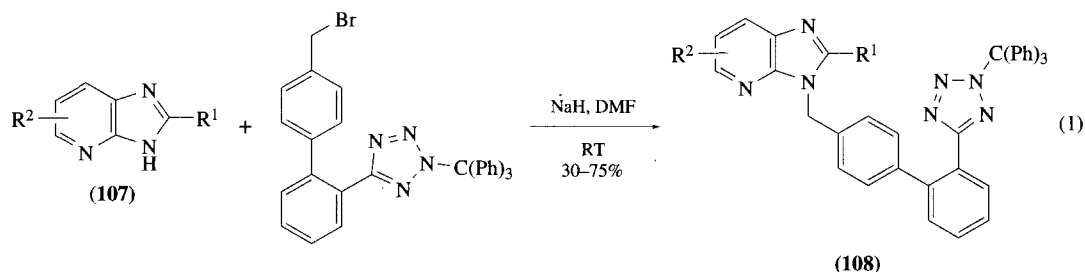
7.08.4.3 Conformations and Tautomerism

Conformations and tautomerisms of the various ring systems are discussed in the body of the chapter as they relate to the reactivity of the ring system.

7.08.5 REACTIVITY OF FULLY CONJUGATED RINGS

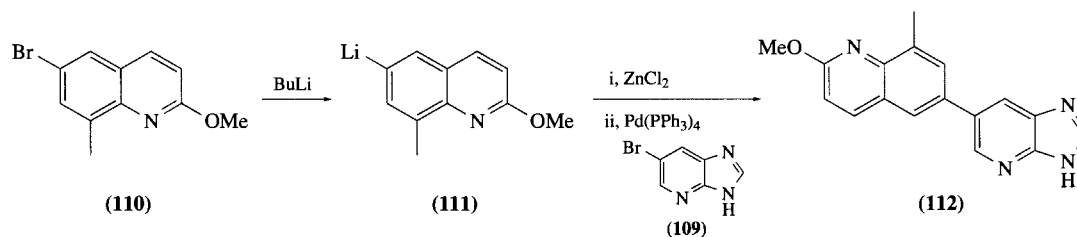
7.08.5.1 Imidazo[4,5-*b*]pyridines

Using standard alkylating conditions, a series of imidazo[4,5-*b*]pyridines (**107**) were alkylated exclusively at N-3 to give the derivatives (**108**) (Equation (1)) <91JMC2919>.



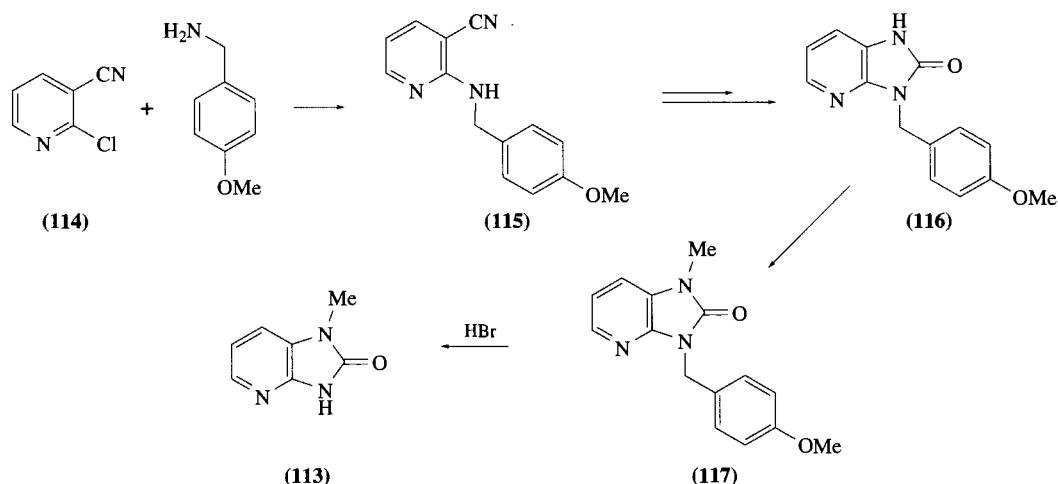
A palladium-catalyzed reaction has been reported to C-6 alkylate 6-bromoimidazo[4,5-*b*]pyridine (**109**) <87EUP290153>. In this reaction, 2-methoxy-6-bromo-8-methylquinoline (**110**) was treated with butyllithium to give the 6-lithiated derivative (**111**). To this compound (**111**) was added zinc chloride, followed by 6-bromoimidazo[4,5-*b*]pyridine (**109**) and tetrakis(triphenylphosphine)palladium(0)

which upon heating under reflux gave 6-(2-methoxy-8-methylquinolin-6-yl)imidazo[4,5-*b*]pyridine (**112**) (Scheme 3).



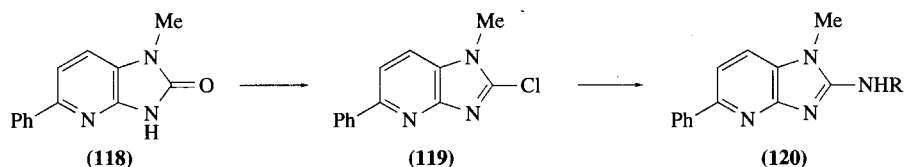
Scheme 3

A regioselective synthesis of *N*(1)-substituted imidazo[4,5-*b*]pyridin-2-ones (**113**) has been reported (Scheme 4) <94JMC248>. In this procedure, a 4-methoxybenzyl group was introduced at N-3 by treating the appropriately substituted 2-chloro-3-cyanopyridine (**114**) with 4-methoxybenzylamine to give a 3-(4-methoxybenzyl)imidazo[4,5-*b*]pyridin-2-one derivative (**115**). Ring closure afforded the 3-(4-methoxybenzyl)imidazo[4,5-*b*]pyridin-2-one (**116**) and subsequent methylation gave the 1,3-disubstituted derivative (**117**). Debenzylation by treatment with hydrobromic acid gave the 1-methylimidazo[4,5-*b*]pyridin-2-one (**113**).



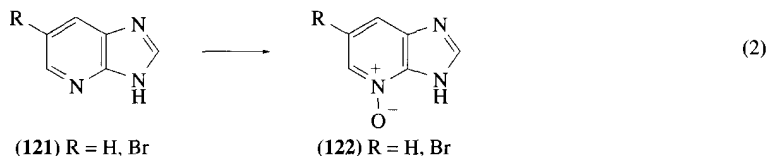
Scheme 4

Imidazo[4,5-*b*]pyridin-2-ones (e.g. **118**) have been readily converted into the 2-amino derivatives (**120**) by using standard methodology (Scheme 5). This involves the reaction of compound (**118**) with phosphorus oxychloride, isolating the intermediate 2-chloro derivative (**119**) and subsequently reacting it with nucleophiles such as amines <88JAP63275582>.

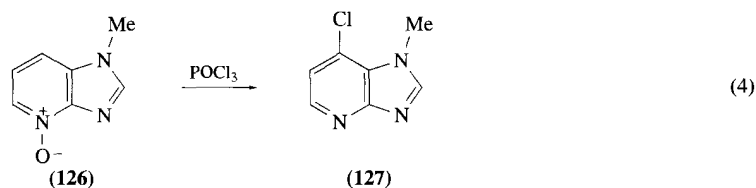
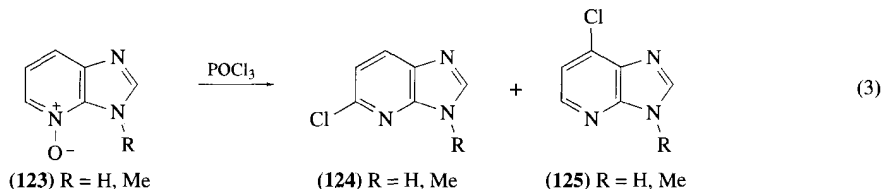


Scheme 5

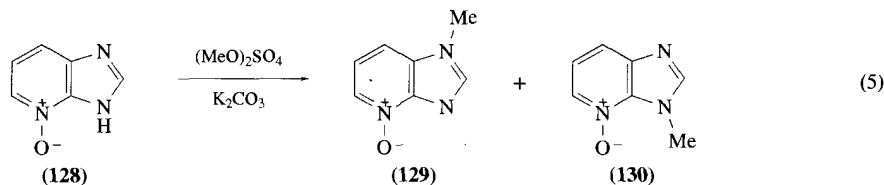
Imidazo[4,5-*b*]pyridine 4-oxides (**122**) have been reported to be easily prepared in excellent yield from imidazo[4,5-*b*]pyridines (**121**) by oxidation with either hydrogen peroxide in acetic acid or MCPBA (Equation (2)) <65JOC4066, 82JHC513>.



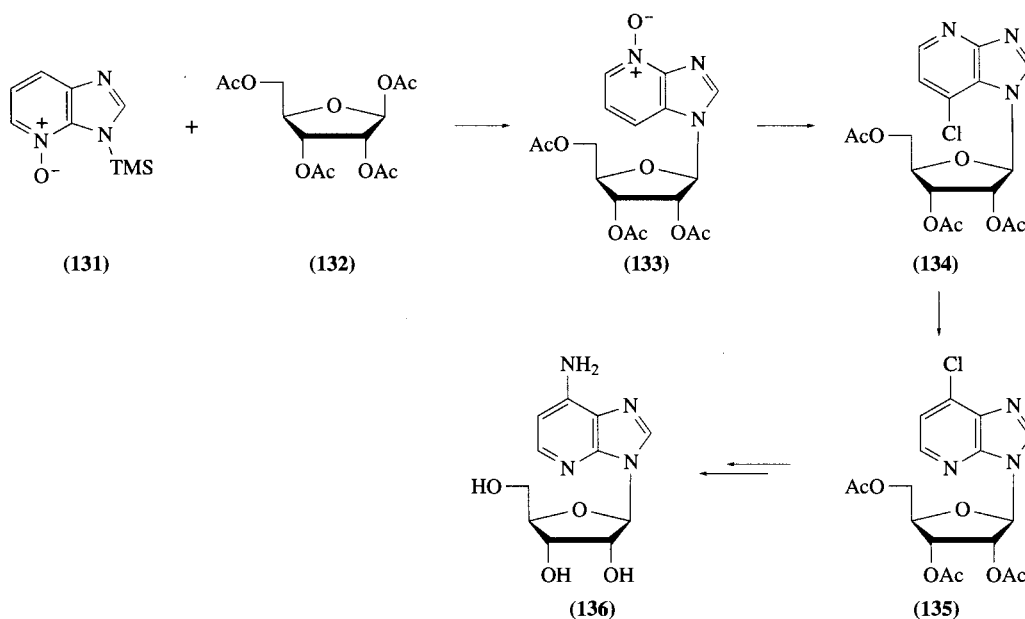
Halogenation of the imidazo[4,5-*b*]pyridine 4-oxides has provided some interesting results. Treatment of compound (123; R = H) with phosphorus oxychloride gave, with loss of the *N*-oxide group, a mixture of the 5-chloro (124) and 7-chloro (125) isomers in comparable amounts in an overall 74% yield (Equation 3) <82JHC513>. The reaction of 3-methylimidazo[4,5-*b*]pyridine 4-oxide (123; R = CH₃) with phosphorus oxychloride also gave a mixture of products but the yields were different, i.e. 5-chloro (124) (20%) and 7-chloro (125) (41%). However, with 1-methylimidazo[4,5-*b*]pyridine 4-oxide (126), the chlorine atom was introduced exclusively into the more sterically hindered 7 position to give the 7-isomer (127). None of the 5-isomer was detected in this reaction (Equation (4)).



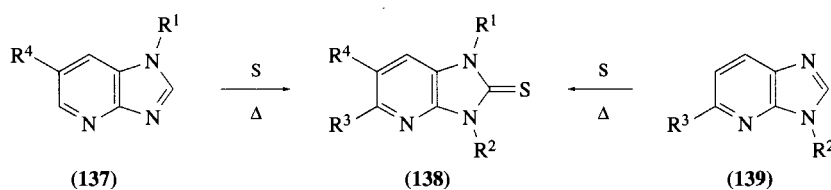
Methylation of imidazo[4,5-*b*]pyridine 4-oxide (128) with dimethyl sulfate in the presence of potassium carbonate afforded a mixture of the 1-methyl derivative (129) (36%), along with the 3-methyl derivative (130) (no yield reported) (Equation (5)) <82JHC513>. Condensation of the trimethylsilyl derivative (131) with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (132) in the presence of stannic chloride, in contrast, gave only (as determined by a UV study) the 1-glycosylated derivative (133) (82%). Chlorination of compound (133) with phosphorus oxychloride gave the chloro derivative (134), which on treatment with mercuric bromide at reflux in toluene gave a mixture of both (134) and the 3-glycosylated isomer (135). If the reaction is carried out in the presence of additional (132), the 3-glycosylated derivative (135) is obtained in 76% yield. Compound (135) was further elaborated to 7-amino-3-(β -D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (1-dezaadenosine) (136), in an overall yield of 25%, by treatment with hydrazine hydrate under a nitrogen atmosphere at reflux temperature, followed by a Raney nickel reduction (Scheme 6) <82MI 708-01>.



Thionation of imidazo[4,5-*b*]pyridines has been shown to be general in nature <88CHE653>. Heating equimolar quantities of a variety of imidazo[4,5-*b*]pyridines (for example (137) or (139)) with sulfur at 230–260°C for 15–60 min gave 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridine-2-thiones (138), generally in excellent yields (Scheme 7). Substituents on the ring do affect the yield. Unsubstituted, *N*-methyl, *N*-aryl, and *N*-benzyl compounds give the 2-thione derivatives in 80% to quantitative yields, and 6-halogenated or 6-nitro derivatives also proceed smoothly in the reaction.



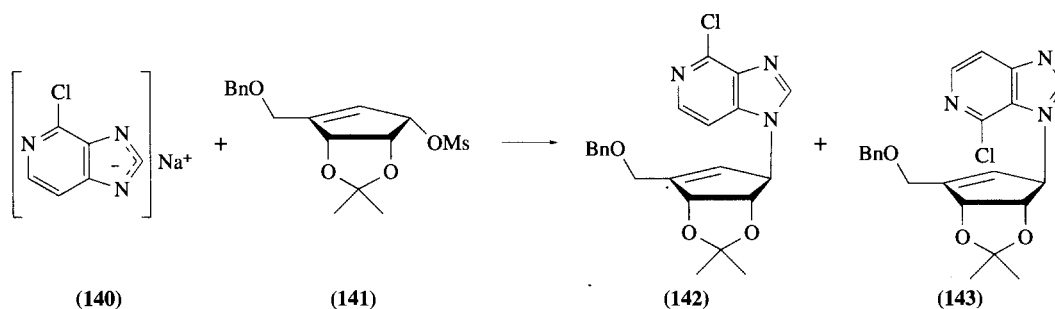
Scheme 6



Scheme 7

7.08.5.2 Imidazo[4,5-*c*]pyridines

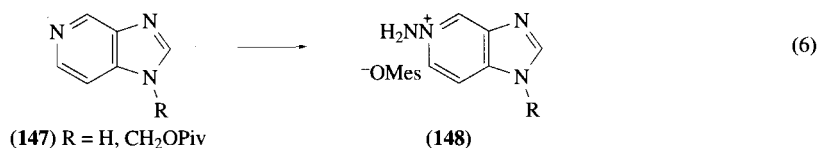
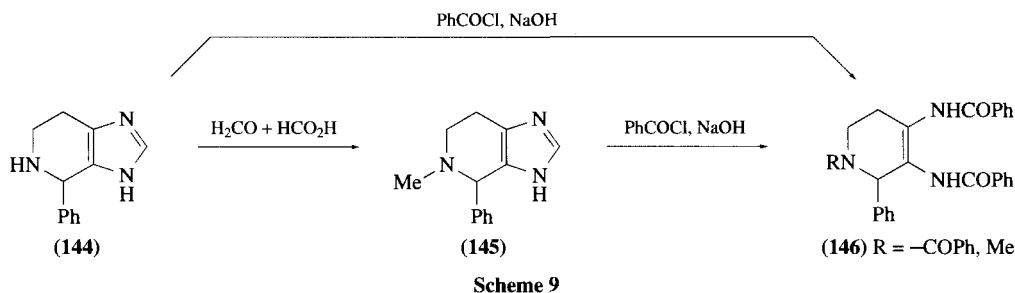
Treatment of the sodium salt of 4-chloroimidazo[4,5-*c*]pyridine (**140**) with the mesylate (**141**) afforded a 97:3 isomeric mixture of the N-1 (**142**) and N-3 (**143**) alkylated derivatives in 23% overall yield (Scheme 8) <89JMC1442>.



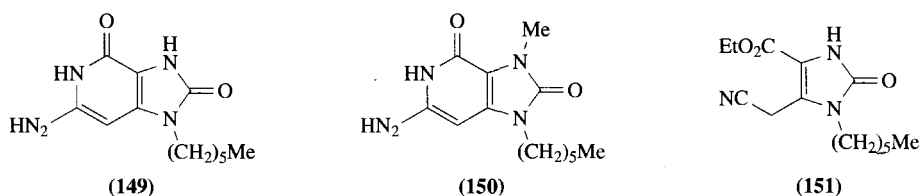
Scheme 8

4-Phenyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (**144**) has been selectively methylated at the pyridine nitrogen using Eschweiler–Clarke conditions (Scheme 9) <90JOC3370>. In this reaction compound (**144**) was treated with formaldehyde in formic acid at steam bath temperature to afford the methylated derivative (**145**) in yields averaging 75%. The imidazole ring may be cleaved by reacting either (**144**) or (**145**) with excess benzoyl chloride in aqueous NaOH solution producing 6-phenyl-4,5-dibenzamido-1,2,3,6-tetrahydropyridines (**146**) <90JOC3370>.

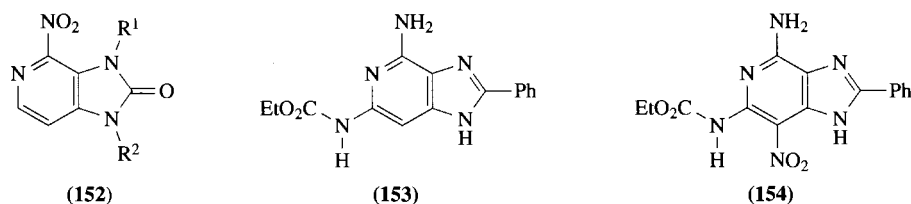
The reaction of the derivatives (**147**) with *O*-mesitylenesulfonylhydroxylamine in methanol affords 5-aminoimidazo[4,5-*c*]pyridine (**148**) (Equation (6)) <86T1511>.



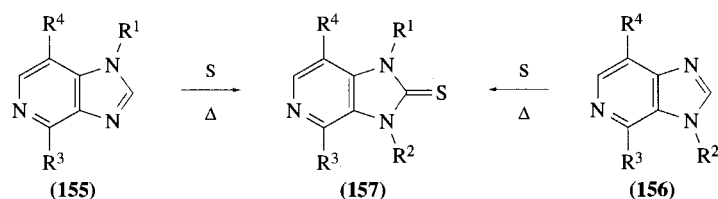
1-Substituted imidazo[4,5-*c*]pyridin-2-ones such as compound (149) upon reaction with iodo-methane gave intractable mixtures rather than the desired product (150). To prepare compound (150) one must first *N*-alkylate the imidazole (151) and subsequently annulate <93JMC1341>.



While imidazo[4,5-*c*]pyridine and its 1- and 3-methyl derivatives are resistant to nitration, imidazo[4,5-*c*]pyridin-2-one and its 1-methyl, 3-methyl, and 1,3-dimethyl derivatives have been readily nitrated at the 4-position (i.e. (152)) <86KGS97>. If the 4- and 6-positions are substituted, as in compound (153), then nitration occurs at the 7-position (e.g. (154)) <87JMC1746>.



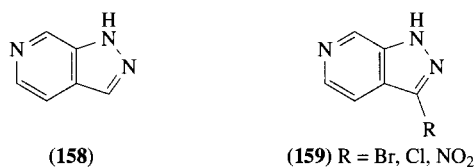
Thiation of imidazo[4,5-*c*]pyridines, like the thiation of imidazo[4,5-*b*]pyridines, has been shown to be general in nature <88CHE653>. Heating equimolar quantities of a variety of imidazo[4,5-*c*]pyridines (155) or (156) with sulfur at 230–260 °C for 15–60 min gave 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridine-2-thiones (157), generally in excellent yield (Scheme 10). Unsubstituted, *N*-methyl, *N*-aryl, and *N*-benzyl compounds gave the 2-thione derivatives in 80% to quantitative yields, and 6-halo-genated or 6-nitro derivatives also reacted smoothly. Only in the case of 4-chloroimidazo[4,5-*c*]pyridine does the reaction fail to give the 2-thione derivative, giving instead the 4-thione derivative.



Scheme 10

7.08.5.3 Pyrazolo[3,4-*c*]pyridines

As predicted by theoretical calculations <89AP(322)885>, the site of electrophilic attack on pyrazolo[3,4-*c*]pyridines is C-3. Reactions such as chlorination, bromination, and nitration of the parent compound (**158**) all give the 3-substituted derivatives (**159**) <73JCS(P1)2901, 89AP(322)885>.

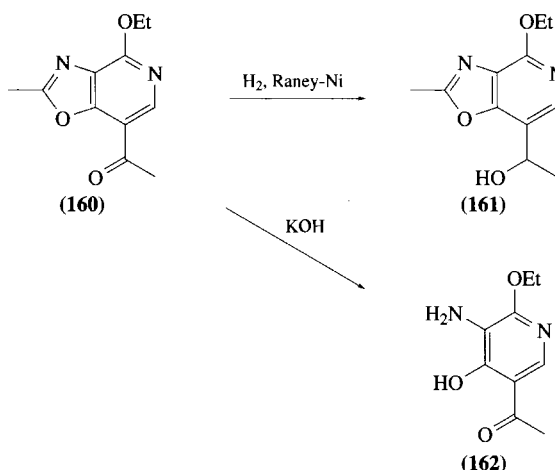


7.08.5.4 Pyrazolo[4,3-*c*]pyridines

No halogenations of the pyrazolo[4,3-*c*]pyridine ring system have been reported.

7.08.5.5 Oxazolo[4,5-*c*]pyridines

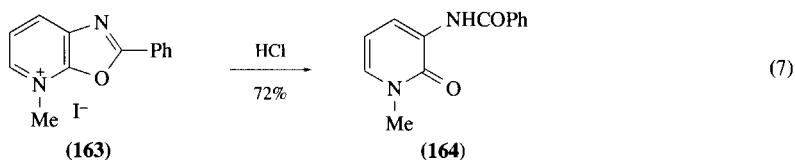
Catalytic hydrogenation of the ketone (**160**) in the presence of Raney nickel resulted in reduction of the carbonyl function affording the alcohol (**161**) (57%) <88CPB168>. Treatment of the same ketone (**160**) with potassium hydroxide in aqueous ethanol at reflux opened the oxazole ring and gave compound (**162**) (63%) (Scheme 11).



Scheme 11

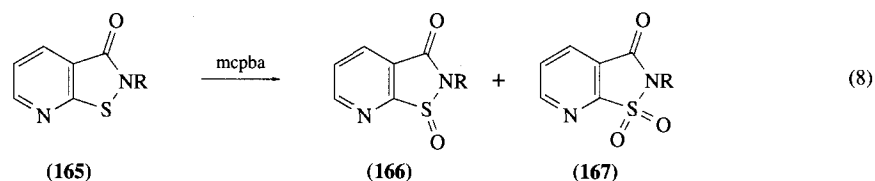
7.08.5.6 Oxazolo[5,4-*b*]pyridines

7-Methyl-2-phenyloxazolo[5,4-*b*]pyridinium iodide (**163**) may be ring opened to afford the 3-benzamido-1-methylpyridin-2-one (**164**) by refluxing in concentrated HCl for 2 h and then adjusting the pH to 4.5 with sodium acetate (Equation (7)) <89JHC289>.

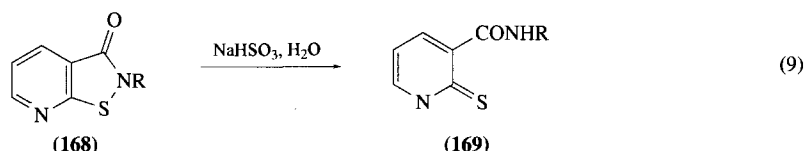


7.08.5.7 Isothiazolo[5,4-*b*]pyridines

Oxidation of the ring sulfur atoms of the derivatives (**165**) with *m*-chloroperbenzoic acid in CHCl₃ at 0°C gives mixtures of the sulfoxides (**166**) and the sulfones (**167**) (Equation (8)) <85S861>.

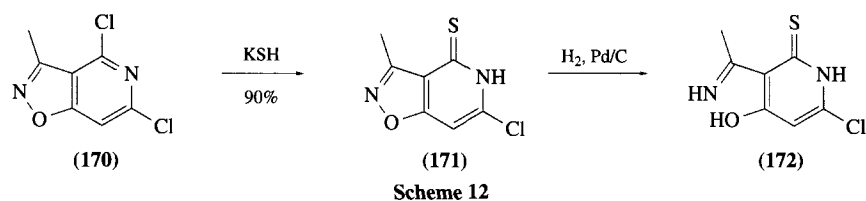


Compounds (168) are easily reduced by sodium bisulfite in dilute HCl to give the amides (169) in about 90% yield (Equation (9)) <85JHC1353>.

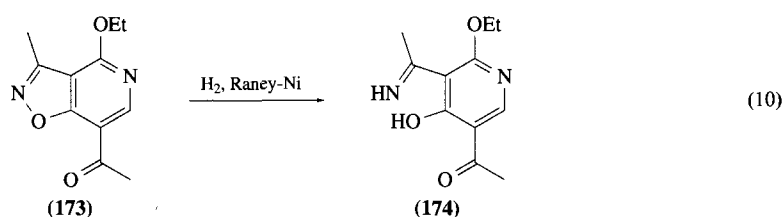


7.08.5.8 Isoxazolo[4,5-c]pyridines

The reaction of 4,6-dichloro-3-methylisoxazolo[4,5-c]pyridine (170) with excess freshly prepared potassium hydrosulfide in refluxing ethanol regioselectively gives 6-chloro-3-methylisoxazolo[4,5-c]pyridin-4-thione (171) (Scheme 12) <90JCS(P1)1477>. Catalytic hydrogenation of compound (171) with palladium on carbon (10%) in aqueous sodium hydroxide at 50 psi of hydrogen, followed by neutralization with HCl selectively cleaves the isoxazole ring, without dehydrohalogenation or hydrolysis of the imine, to give 6-chloro-3-(1-iminoethyl)-4-hydroxypyridine-2-thione (172) (57%).

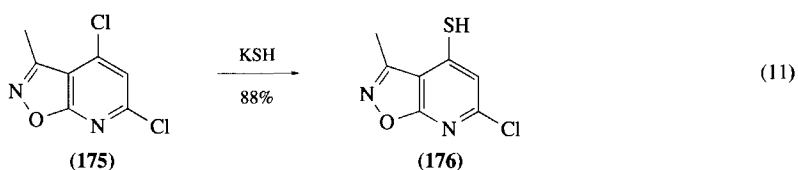


Catalytic hydrogenation of compound (173) in the presence of Raney nickel results in ring cleavage and gives the imine (174) (57%) (Equation (10)) <88CPB168>.

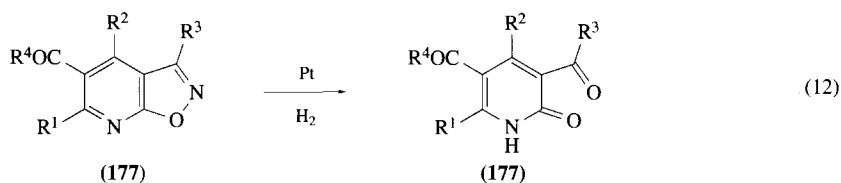


7.08.5.9 Isoxazolo[5,4-b]pyridines

Treatment of 4,6-dichloro-3-methylisoxazolo[5,4-b]pyridine (175) with potassium hydrosulfide led only to the nucleophilic displacement of the 4-chloro moiety (Equation (11)). The ¹H NMR spectrum of the product (176) showed an exchangeable signal at δ 4.09 indicating that the major tautomer was the 4-thiol rather than the 4-thione.

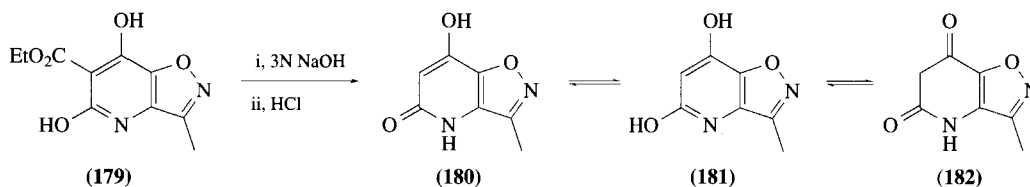


Treatment of the derivatives (177) with hydrogen in the presence of platinum cleaves the oxazole ring to give the pyridones (178) (Equation (12)) <85T913>.



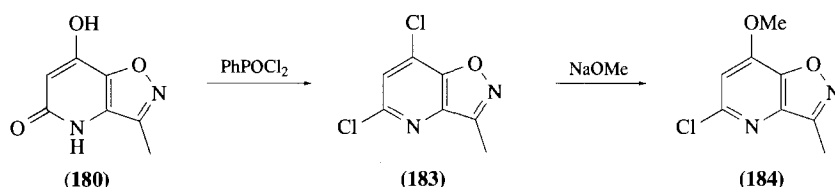
7.08.5.10 Isoxazolo[4,5-*b*]pyridines

The decarboxylation of 5,7-dihydroxy-3-methylisoxazolo[4,5-*b*]pyridine (179) was readily accomplished and gave compound (180) (92%) (Scheme 13) <82JCS(P1)2391>. It was postulated, based upon the infrared spectra bands (ν_{OH} 3300–2300 and ν_{CO} 1660 cm^{-1}), that in the solid state the product exists in the 7-hydroxy-5-oxo tautomeric form (180). In solution it most probably exists as a mixture of tautomers (180)–(182) since in the ^1H NMR spectrum in $(\text{CD}_3)_2\text{SO}$ solution the C-6 proton was exchangeable upon the addition of D_2O .

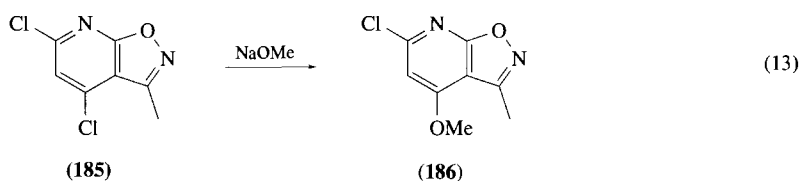


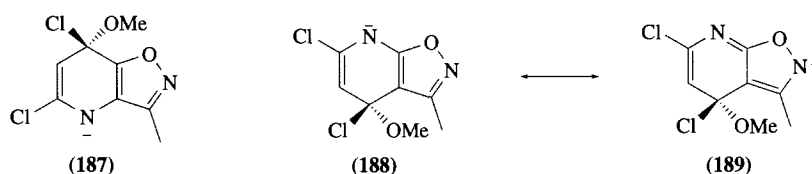
Scheme 13

Compound (180) was chlorinated with phenylphosphonic dichloride to afford 5,7-dichloro-3-methylisoxazolo[4,5-*b*]pyridine (183) in moderate yield (Scheme 14) <82JCS(P1)2391>. Nucleophilic substitution of the dichloro compound (183) with methoxide proceeded regioselectively at C-7 to give the 7-methoxy derivative (184), showing that the more reactive chlorine atom towards nucleophiles is the chlorine atom adjacent to the ring fusion. The relative rate of the second-order methoxylation of compound (183) is less than that of isomeric halogenated isoxazolopyridines. For example, the relative rate for methoxylation of the 4-chloro function in the isomeric compound, 4,6-dichloro-3-methylisoxazolo[5,4-*b*]pyridine (185), which gave 4-methoxy-6-chloro-3-methylisoxazolo[5,4-*b*]pyridine (186) (Equation (13)), is 21.1 times greater than the methoxylation of the analogous 7-chloro group in compound (183). This decrease in the rate of the reaction may be rationalized on the basis of negative-charge delocalizations in the intermediate's σ -complex. The negative charge in the intermediate in the reaction of (183) with methoxide may only be located on the pyridine nitrogen as shown in (187), while the negative charge in the intermediate in the reaction of (185) with methoxide may be distributed over both rings as shown in (188) and (189).

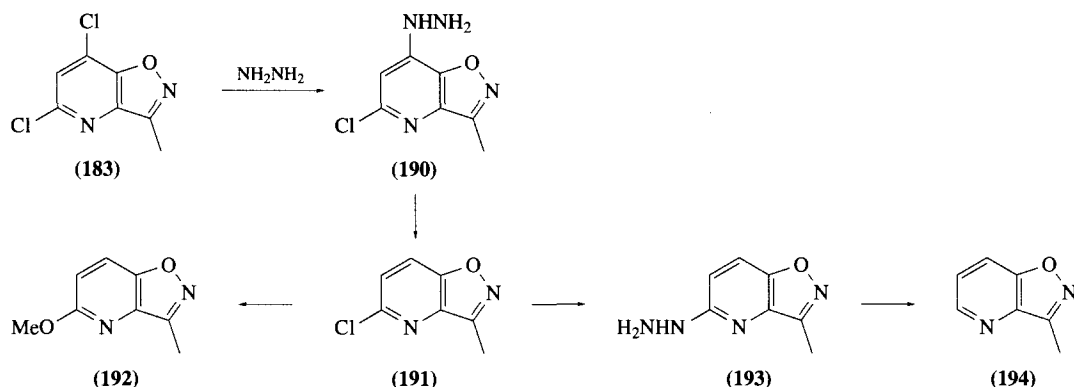


Scheme 14



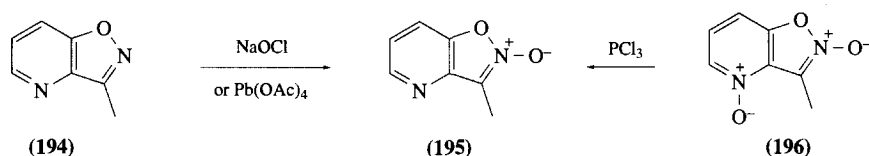


Hydrazinolysis of compound (183) also shows that the more readily displaced chlorine is located next to the ring fusion affording (190) (92%) <82JCS(P1)2391>. Oxidative decomposition of the hydrazino group was achieved by bubbling air into an alkaline solution containing the hydrazine (190) to give 5-chloro-3-methylisoxazolo[5,4-*b*]pyridine (191) (82%) which upon treatment with sodium methoxide in refluxing methanol gave the 5-methoxy derivative (192) (Scheme 15). 3-Methylisoxazolo[5,4-*b*]pyridine (194) was prepared in two steps: hydrazinolysis of compound (191) to give the 5-hydrazino intermediate (193) which was oxidized, as above, to afford (194).



Scheme 15

Reaction of compound (194) with sodium hypochlorite or lead tetraacetate gave the 2-oxide (195) in 70 and 90% yields, respectively (Scheme 16) <87H(26)2921>. Treatment of the 2,4-oxide (196) with phosphorus trichloride in chloroform at reflux selectively deoxygenated compound (196) at the pyridine nitrogen and gave the 2-oxide (195) (63%).



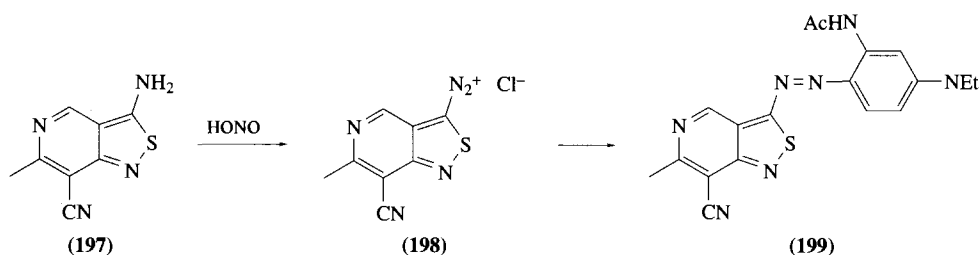
Scheme 16

7.08.5.11 Isothiazolo[4,3-*c*]pyridines

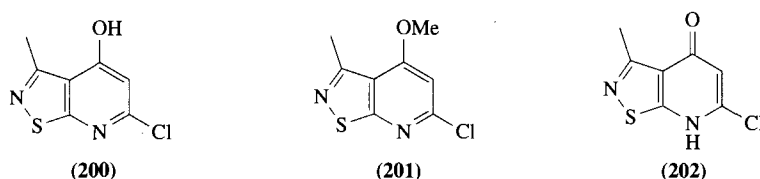
Diazotization of 3-aminoisothiazolo[4,3-*c*]pyridine (197) with HONO gave the 3-diazonium salt (198) in good yield. Compound (198) was coupled with aromatic amines to give the diazo dyes (199) (Scheme 17) <80BRP2074565>.

7.08.5.12 Isothiazolo[5,4-*b*]pyridines

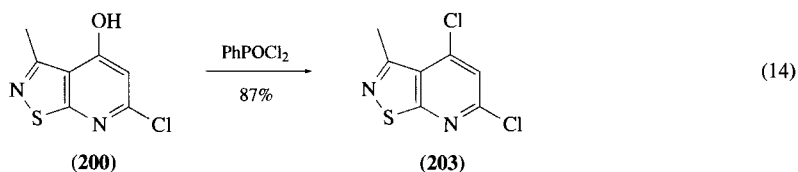
Methylation of 6-chloro-4-hydroxy-3-methylisothiazolo[5,4-*b*]pyridine (200) with ethereal diazo-methane for 13 h gave the 4-methoxy derivative (201) (93%) <90JCS(P1)1477>. None of the 7-methyl derivative was observed in the reaction, indicating that compound (200) exists almost exclusively as the 4-hydroxy tautomer and that the tautomeric 6-chloro-3-methylisothiazolo[5,4-*b*]pyridin-4-one (202) does not contribute significantly to the equilibrium.



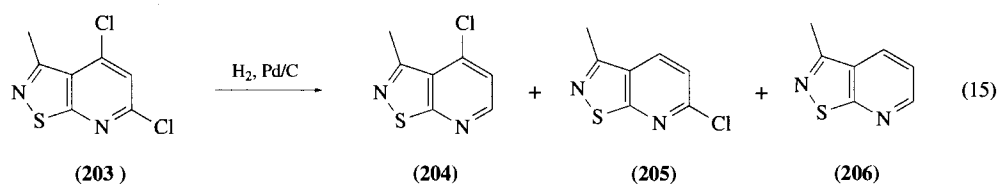
Scheme 17



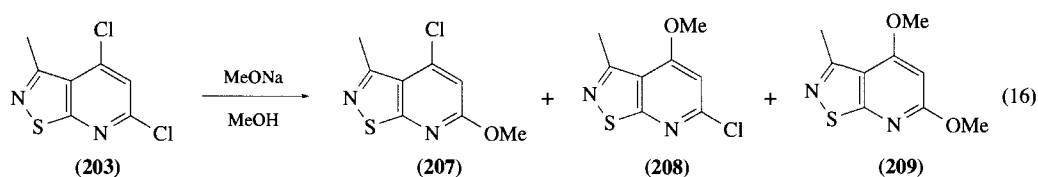
Chlorination of compound (200) to give 4,6-dichloro-3-methylisothiazolo[5,4-*b*]pyridine (203) has been accomplished by using phenylphosphonic dichloride (Equation 14) <90JCS(P1)1477>.



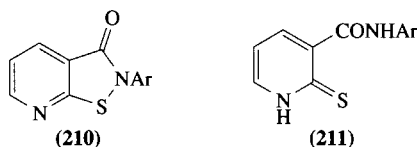
Hydrogenation of the product (203) using 10% palladium on carbon at 75 psi afforded a mixture of 4-chloro-3-methylisothiazolo[5,4-*b*]pyridine (204) (8%), 6-chloro-3-methylisothiazolo[5,4-*b*]pyridine (205) (53%) and 3-methylisothiazolo[5,4-*b*]pyridine (206) (11%) (Equation (15)) <90JCS(P1)1477>.



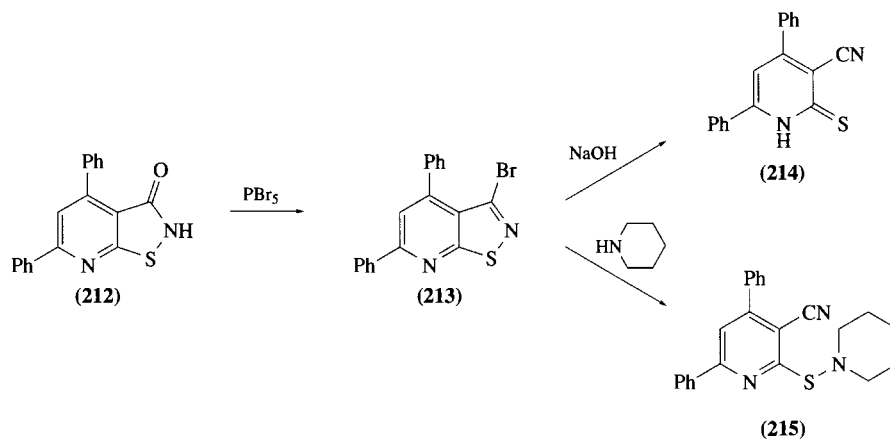
Treatment of compound (203) with nucleophiles has received limited study but it is apparent that there is little difference in selectivity between the 4- or 6-chloro groups toward nucleophiles <90JCS(P1)1477>. Mixtures of products were isolated from each reaction. Treatment with excess sodium methoxide in methanol at reflux for one hour gave a mixture of 4-chloro-6-methoxy-3-methylisothiazolo[5,4-*b*]pyridine (207) (7%), 6-chloro-4-methoxy-3-methylisothiazolo[5,4-*b*]pyridine (208) (18%) and 4,6-dimethoxy-3-methylisothiazolo[5,4-*b*]pyridine (209) (67%) (Equation (16)).



The treatment of a variety of 2-aryl substituted isothiazolo[5,4-*b*]pyridin-3-ones (**210**) with sodium hydroxide in refluxing ethanol for 15 min cleaved the isothiazole ring and gave the pyridines (**211**) in yields ranging from 60–70% [88JHC23].



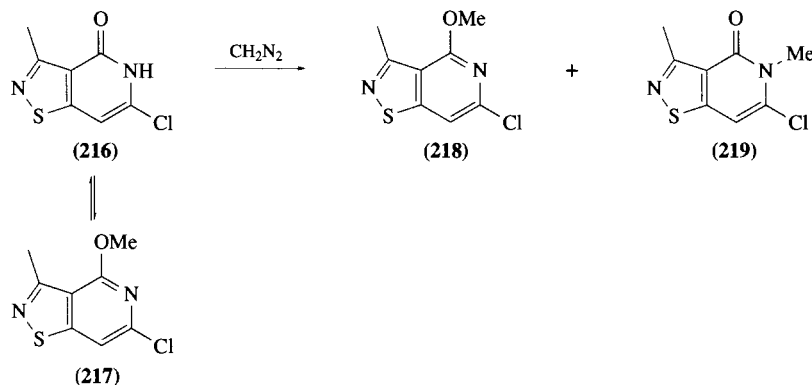
The bromination of 4,6-diphenylisothiazolo[5,4-*b*]pyridin-3-one (**212**) by treatment with phosphorus pentabromide at 100°C, gave 3-bromo-4,6-diphenylisothiazolo[5,4-*b*]pyridine (**213**) in 68% yield (Scheme 18) [88CHE385]. Treatment of this bromo derivative (**213**) with nucleophiles, i.e., sodium hydroxide or piperidine, gave ring-opened products. For example, heating with aqueous 3 M sodium hydroxide gave 3-cyano-4,6-diphenylpyridin-2-one (**214**) (15%) and reaction with piperidine in ethanol at reflux gave 2-piperidylthiol-3-cyano-4,6-diphenylpyridine (**215**) (48%). The structure (**215**) was established by IR, UV, and NMR analyses.



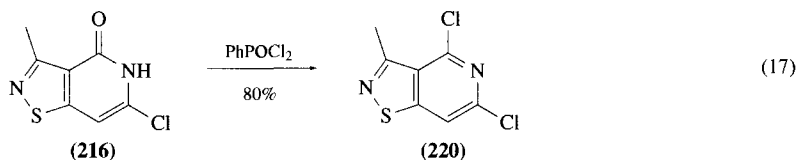
7.08.5.13 Isothiazolo[4,5-*c*]pyridines

Methylation of 6-chloro-3-methylisothiazolo[5,4-*c*]pyridin-4-one (**216**) with ethereal diazo-methane for 13 h gave a mixture of the 4-methoxy derivative (**218**) (25%) along with 6-chloro-3,5-dimethylisothiazolo[5,4-*c*]pyridin-4-one (**219**) (55%) (Scheme 19) [90JCS(P1)1477]. From these results it is apparent that the 4-hydroxy tautomer (**217**) exists in an equilibrium with the tautomeric 6-chloro-3-methylisothiazolo[5,4-*c*]pyridin-4-one (**216**).

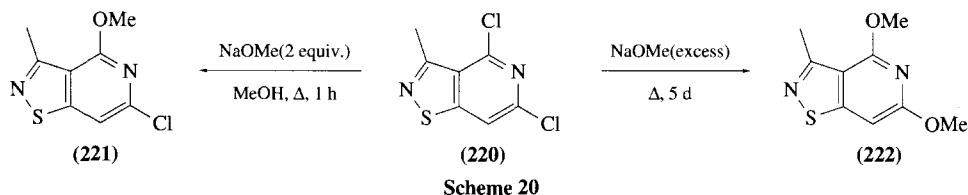
Chlorination of 6-chloro-3-methylisothiazolo[5,4-*c*]pyridin-4-one (**216**) to give 4,6-dichloro-3-



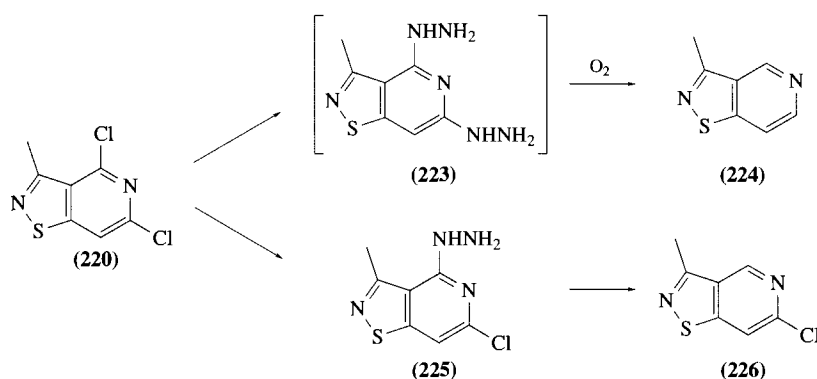
methylisothiazolo[4,5-*c*]pyridine (**220**) has been accomplished using phenylphosphonic dichloride (Equation (17)) <90JCS(P1)1477>. The dichloro derivative (**220**) was unaffected by catalytic hydrogenation in the presence of 10% palladium on carbon under a hydrogen atmosphere at 75 psi <90JCS(P1)1477>.



Treatment of compound (**220**) with nucleophiles has received limited study <90JCS(P1)1477>. Reaction with 2 equiv. of sodium methoxide in methanol at reflux for one hour gave solely 6-chloro-4-methoxy-3-methylisothiazolo[4,5-*c*]pyridine (**221**) (93%). If the reaction is carried out in the presence of excess sodium methoxide in methanol at reflux for 5 days, the major product is 4,6-dimethoxy-3-methylisothiazolo[4,5-*c*]pyridine (**222**) (67%) (Scheme 20).



When the dichloro derivative (**220**) was treated with anhydrous hydrazine at reflux for 1 h a mixture of hydrazino derivatives, which contained 4,6-dihydrazino-3-methylisothiazolo[4,5-*c*]pyridine (**223**) as the major component, was obtained. The crude mixture was subjected to oxidative removal of the hydrazino group by bubbling air through an alkaline solution for 3 d to afford 3-methylisothiazolo[4,5-*c*]pyridine (**224**) (23%) <90JCS(P1)1477>. Reacting compound (**220**) with hydrazine under milder reaction conditions, i.e. hydrazine hydrate in refluxing dioxane, gave 6-chloro-4-hydrazino-3-methylisothiazolo[4,5-*c*]pyridine (**225**) and subsequent oxidative dehydrazination gave 6-chloro-3-methylisothiazolo[4,5-*c*]pyridine (**226**) (Scheme 21).

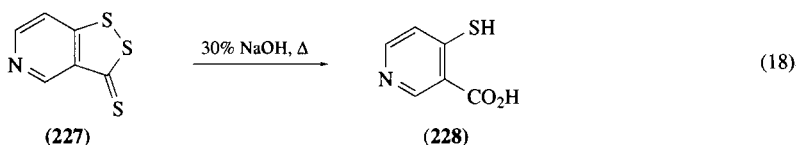


Scheme 21

7.08.5.14 3*H*-1,2-Dithiolo[4,3-*c*]pyridines

Compound (**227**) is remarkably stable to hydrolysis and is recovered unchanged after boiling in either 20% sodium hydroxide for 1 h or in concentrated HCl for 4 h. After heating compound (**227**)

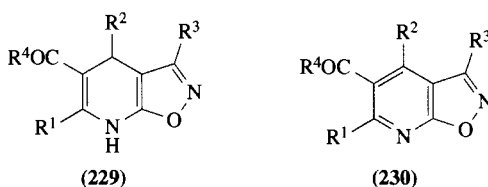
in 30% aqueous sodium hydroxide at reflux temperature for 16 h, 4-thionicotinic acid (**228**) was isolated upon neutralization (Equation (18)) <54JOC711>.



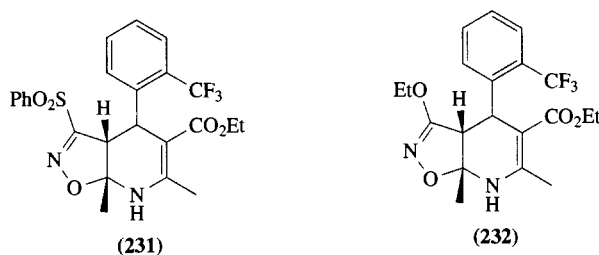
7.08.6 REACTIVITY OF NONCONJUGATED RINGS

7.08.6.1 Isoxazolo[5,4-*b*]pyridines

4,7-Dihydroisoxazolo[5,4-*b*]pyridines (**229**) are readily oxidized by sodium nitrite in acetic acid to give the derivatives (**230**) <85T913>.



The phenylsulfonyl group of compound (**231**) reacts directly with nucleophiles, such as sodium ethoxide, to give the modified C-3 derivative (**232**) <89JOC5585>.

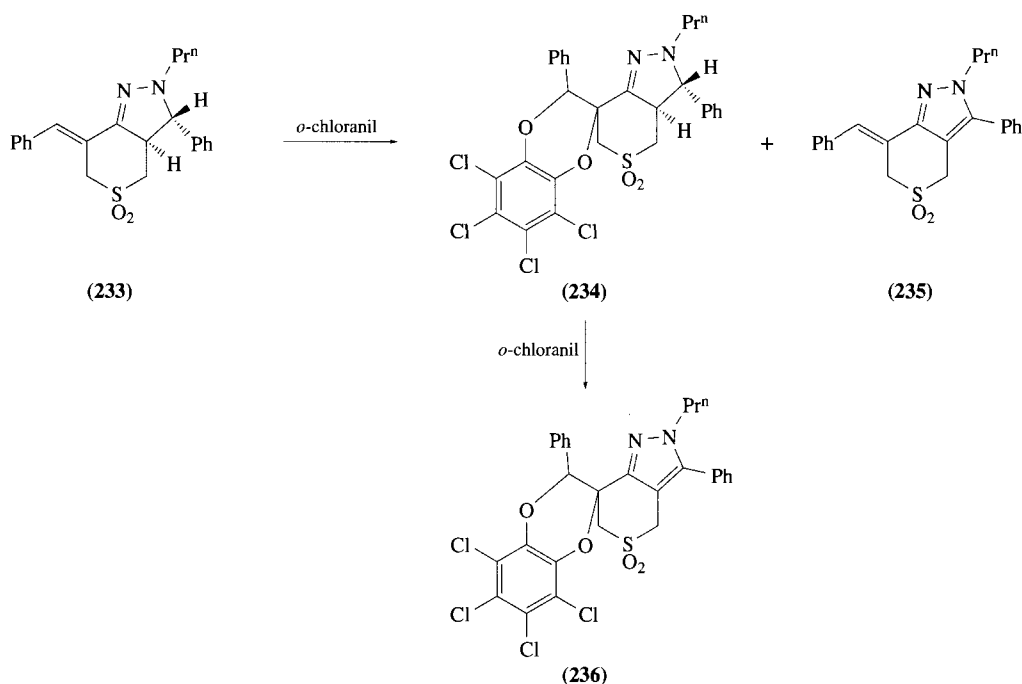


7.08.6.2 Thiopyrano[4,3-*c*]pyrazoles

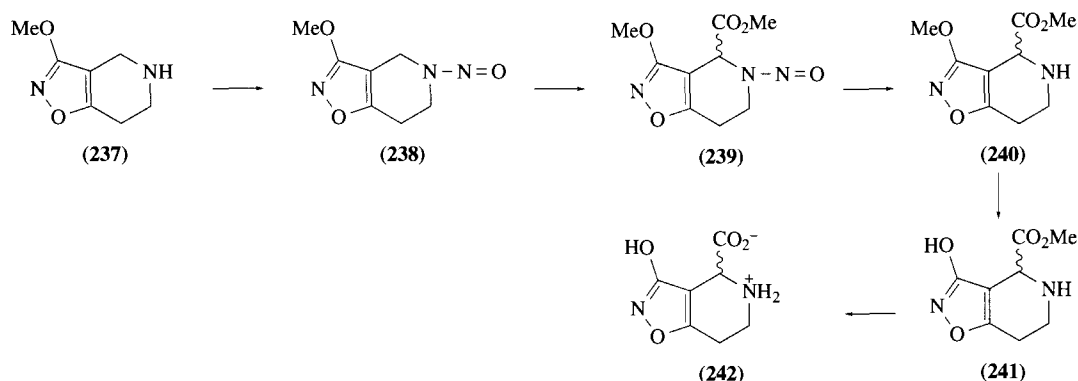
The oxidation of compound (**233**) with *o*-chloranil in CHCl₃ gave the benzodioxane adduct (**234**) along with a minor amount of the desired product (**235**). Extended treatment with *o*-chloranil or reaction of adduct (**234**) with *o*-chloranil gave compound (**236**) (Scheme 22) <79JOC2518>.

7.08.6.3 Isoxazolo[4,5-*c*]pyridines

Nitrosation at the 5-position of 3-methoxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (**237**) has been used as a method to block this basic nitrogen in the synthesis of compound (**242**) (Scheme 23), a conformationally restricted *N*-methyl-(*R*)-aspartic acid analogue, for evaluation as a potential excitator of neurotransmitters in the mammalian central nervous system <82MI 708-02, 86ACS(B)92>. Lithiation of the derivative (**238**) with *n*-butyllithium regioselectively at the 4-position followed by C-alkylation with the addition of methyl chloroformate gave the 4-methoxycarbonyl derivative (**239**), albeit in a low 16% yield. The remainder of the synthetic sequence involves a stepwise deprotection sequence (**239**)–(**242**).



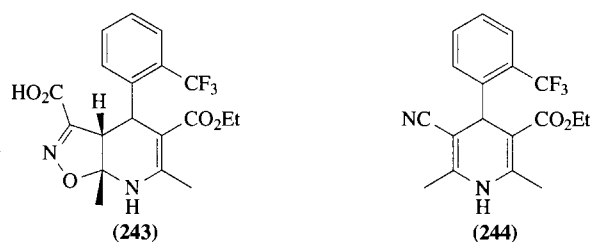
Scheme 22



Scheme 23

7.08.6.4 Isoxazolo[5,4-*b*]pyridines

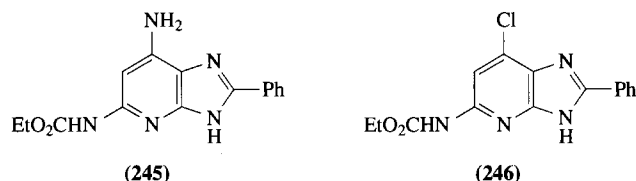
Saponification of the isoxazoline ring and subsequent decarboxylation of compound (243) afforded the 5-cyano-1,4-dihydropyridine-3-carboxylic acid ester (244) [89JOC5585]. If the acid (243) was first reesterified with (–)-menthol, the resulting diastereomeric esters were separable. Saponification of the individual enantiomers followed by decarboxylation afforded a method to prepare 3-cyano-1,4-dihydropyridines (244) stereospecifically.



7.08.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

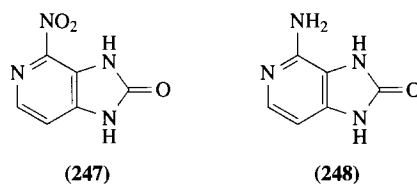
7.08.7.1 Imidazo[4,5-*b*]pyridines

Diazotization of the 4-aminoimidazo[4,5-*b*]pyridine (**245**) in concentrated hydrochloric acid furnishes the 4-chloro derivative (**246**) <87JMC1746>.



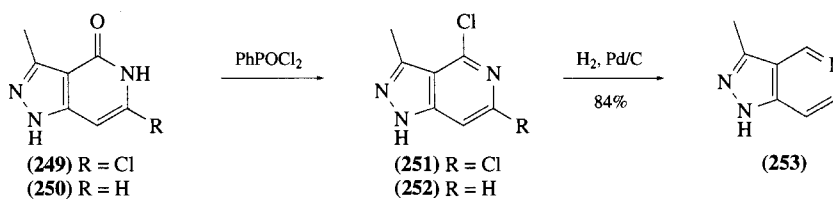
7.08.7.2 Imidazo[4,5-*c*]pyridines

4-Nitroimidazo[4,5-*c*]pyridin-2-one derivatives (**247**) have been reduced to their corresponding 4-amino derivatives (**248**) by iron, Na₂S, hydrazine, or hydroiodic acid in the presence of red phosphorus <86KGS97>.



7.08.7.3 Pyrazolo[4,3-*c*]pyridines

Chlorination of 6-chloro-3-methylpyrazolo[4,3-*c*]pyridin-4-one (**249**) or 3-methylpyrazolo[4,3-*c*]pyridin-4-one (**250**) with phenylphosphonic dichloride at 150°C gave 4,6-dichloro-3-methylpyrazolo[4,3-*c*]pyridine (**251**) and 4-chloro-3-methylpyrazolo[4,3-*c*]pyridine (**252**), respectively, in moderate yields <88H(27)1899>. Hydrogenation of the chloro derivatives (**251**) or (**252**) under a hydrogen pressure of 37 psi in the presence of 10% Pd/C gave 3-methylpyrazolo[4,3-*c*]pyridine (**253**) in good yield (Scheme 24).

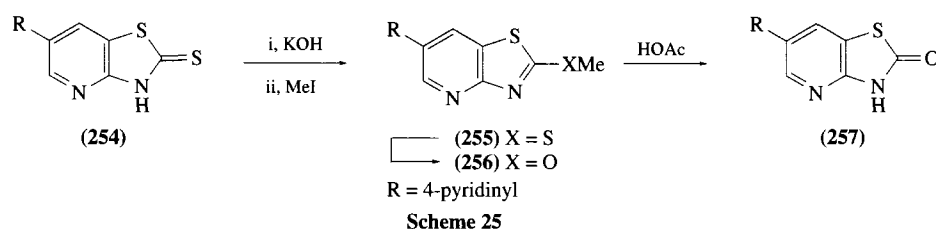


Scheme 24

7.08.7.4 Thiazolo[5,4-*b*]pyridines

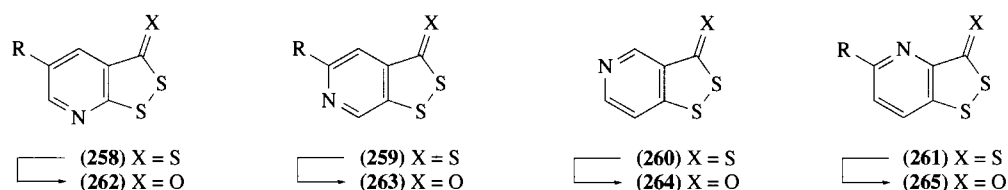
A two-step procedure has been developed to convert the 2-thione derivatives (**254**) into the 2-oxo derivatives (**257**) <93H(36)133, 94JMC248>. Methylation of the potassium salts of the derivatives (**254**)

with methyl iodide afforded the 2-methylthio derivatives (**255**) which were reacted with sodium methoxide. Without isolation of the 2-methoxy derivatives (**256**) the material was heated in an aqueous acetic acid mixture to give the 2-oxo compounds (**257**) in excellent yield (Scheme 25).



7.08.7.5 3H-1,2-Dithiopyridines

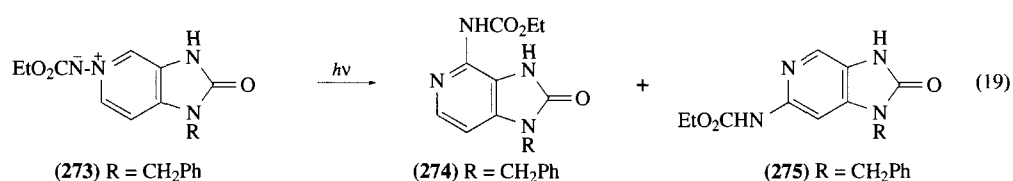
Treatment of 1,2-dithiolo[3,4-*b*]pyridine-3-thiones (**258**), 1,2-dithiolo[3,4-*c*]pyridine-3-thiones (**259**), 1,2-dithiolo[4,3-*c*]pyridine-3-thiones (**260**), or 1,2-dithiolo[4,3-*b*]pyridine-3-thiones (**261**), where R = H or phenyl, with mercuric acetate in glacial acetic acid yields the corresponding 1,2-dithiolo[3,4-*b*]pyridin-3-ones (**262**), 1,2-dithiolo[3,4-*c*]pyridin-3-ones (**263**), 1,2-dithiolo[4,3-*c*]pyridin-3-ones (**264**), or 1,2-dithiolo[4,3-*b*]pyridin-3-ones (**265**) in yields ranging from 93% for the 1,2-dithiolo[4,3-*c*]pyridin-3-ones (**264**) isomers to 63–80% for the other isomers <82JHC1393>.

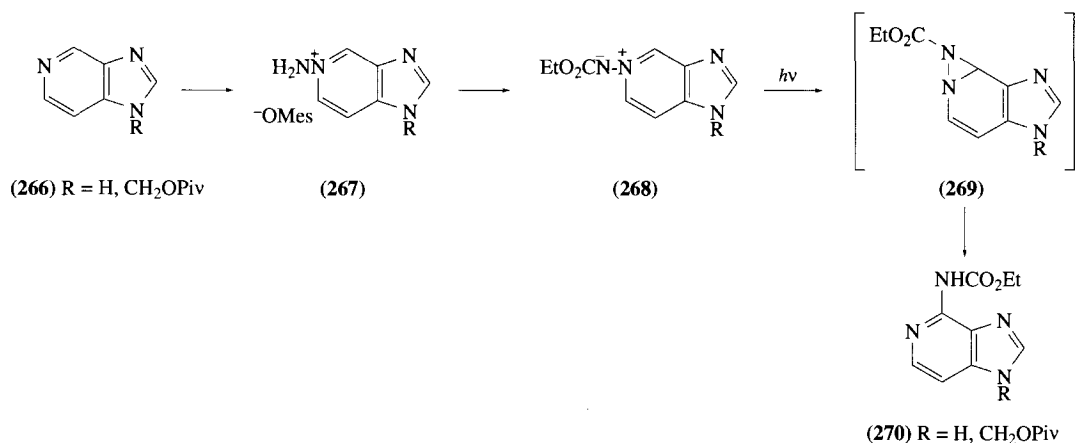


7.08.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

7.08.8.1 Imidazo[4,5-*c*]pyridines

The 4-ethoxycarbonylaminoimidazo[4,5-*c*]pyridines (**270**) have been prepared via intermediate 5-aminoimidazo[4,5-*c*]pyridines (**267**) <86T1511>. The *N*-amino compounds (**267**) were prepared by reaction of (**266**) with *O*-mesitylenesulfonylhydroxylamine in methanol and subsequent reaction of (**267**) with ethyl chloroformate furnished the ylides (**268**) in 16% overall yield. UV Irradiation of the ylides (**268**) in acetonitrile resulted in a photo-induced concerted electrocyclic ring closure to give a postulated diaziridine intermediate (**269**), which spontaneously undergoes an N—N bond fission to yield (**270**) (Scheme 26). The position of the substituent on the imidazole ring has little effect on the course of the reaction. The *N*-1 pivaloyloxymethyl derivative (**271**) when submitted to a similar reaction sequence gave regiospecifically 4-ethoxycarbonylamino-1-pivaloyloxymethyl-imidazo[4,5-*c*]pyridine (**272**) (25%). Irradiation of the imidazo[4,5-*c*]pyridin-2-one ylide (**273**) resulted in the formation of two isomeric N—N fission products, which were identified as 1-benzyl-4-ethoxycarbonylaminoimidazo[4,5-*c*]pyridin-2-one (**274**) and 1-benzyl-6-ethoxycarbonylaminoimidazo[4,5-*c*]pyridin-2-one (**275**), in a 1 : 1 ratio and in 54% overall yield (Equation 19).



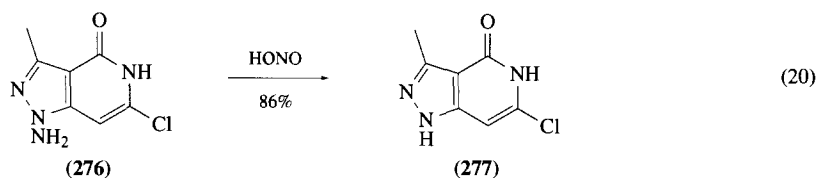


Scheme 26



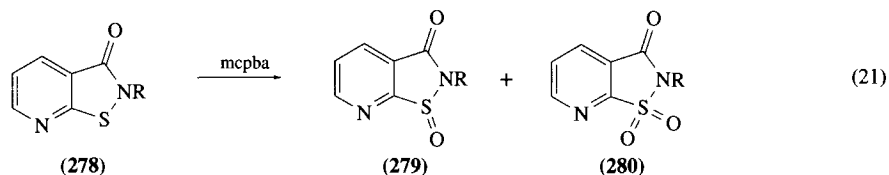
7.08.8.2 Pyrazolo[4,3-*c*]pyridines

Deamination of 1-amino-6-chloro-3-methylpyrazolo[4,3-*c*]pyridin-4-one (**276**) by treatment with sodium nitrite in 6 M hydrochloric acid gave compound (**277**) (Equation (20)) <88H(27)1899>.

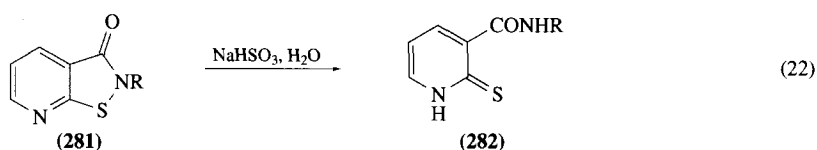


7.08.8.3 Isothiazolo[5,4-*b*]pyridines

Oxidation of the ring sulfur atom of the derivatives (**278**) with *m*-chloroperbenzoic acid in CHCl₃ at 0°C gives a mixture of the sulfoxides (**279**) and the sulfones (**280**) (Equation (21)) <85S861>.



Compounds (**281**) are easily reduced by sodium bisulfite in dilute HCl to give the amides (**282**) in about 90% yield (Equation (22)) <85JHC1353>.

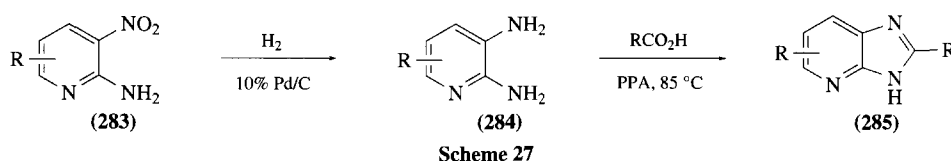


7.08.9 RING SYNTHESIS CLASSIFIED BY FORMATION OF THE SECOND HETEROCYCLIC RING

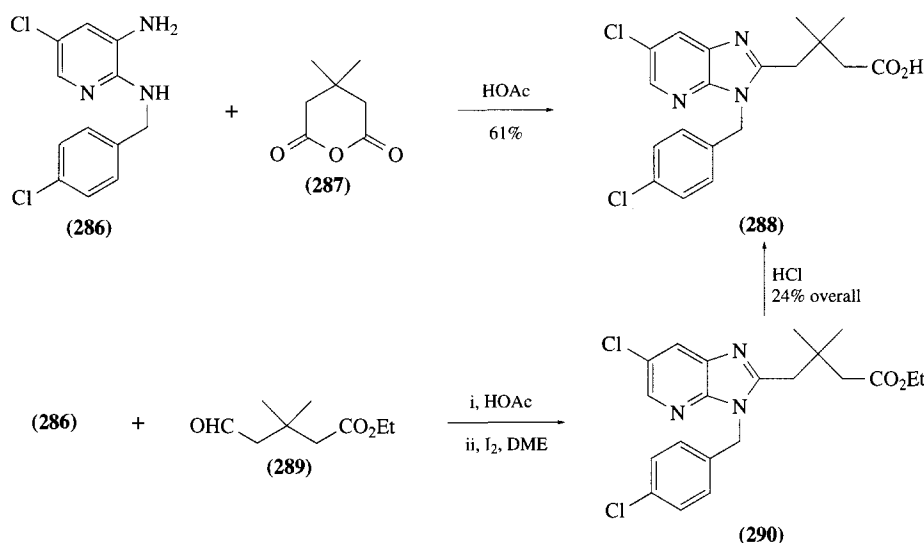
7.08.9.1 Imidazo[4,5-*b*]pyridines

7.08.9.1.1 Closure of the imidazole ring

2-Alkyl-imidazo[4,5-*b*]pyridines (**285**) have been prepared by reduction of 2-amino-3-nitropyridines (**283**) to the corresponding diaminopyridines (**284**) which were then condensed with an appropriate carboxylic acid in polyphosphoric acid (Scheme 27) <91JMC2919>. The cyclization of diamino compounds using acid chlorides and treating the intermediate amide with EtOH/HCl to promote cyclization is not always successful <93JMC1387>. However, the intermediate amides may be cyclized by heating with phosphorus oxychloride to give imidazo[4,5-*b*]pyridines <93JMC1387>.

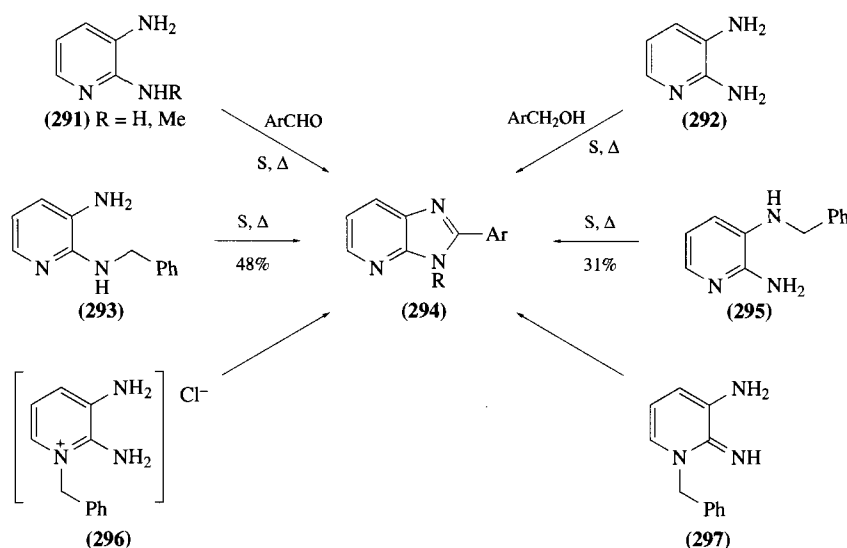


The condensation of the 2,3-diaminopyridine (**286**) with 3,3-dimethylglutaric anhydride (**287**) in refluxing acetic acid afforded the 2-substituted imidazo[4,5-*b*]pyridine (**288**) in good yield (Scheme 28) <94JHC73>. Compound (**288**) may also be prepared by the initial condensation of the pyridine (**286**) with the aldehyde (**289**) in the presence of acid to produce an intermediate Schiff base which on oxidation with iodine in 1,2-dimethoxyethane gives compound (**290**) which was hydrolyzed to the acid (**288**) <93JMC1175>. The yield in this reaction sequence was less than that from the condensation using the anhydride (**287**).



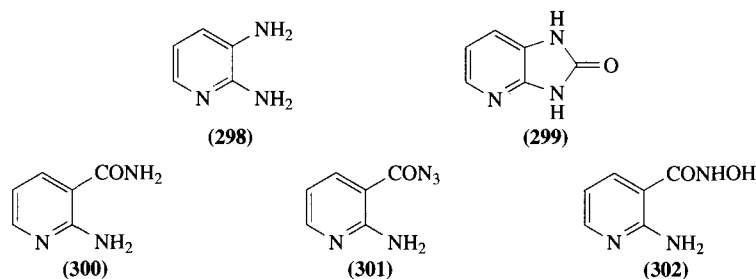
An improved procedure, which uses sulfur as an oxidizing agent, to prepare 2-aryl-imidazo[4,5-*b*]pyridines has been reported <87CHE529, 93JMC1387>. Heating equivalent amounts of 2-substituted amino-3-aminopyridines (**291**) with aryl aldehydes, or 2,3-diaminopyridine (**292**) with benzyl alcohol, in the presence of sulfur at 165–175°C or at reflux in the presence of sulfur in xylene or mesitylene as solvent, until hydrogen sulfide evolution ceased, gave 2-aryl-imidazo[4,5-*b*]pyridines (**294**) (Scheme 29). The condensation with aldehydes provided the products in high yields, while benzyl alcohols gave 2-aryl-imidazo[4,5-*b*]pyridines in somewhat lower yields. Oxidation of either a 3-amino-2-benzylaminopyridine (**293**) or a 2-amino-3-benzylaminopyridine (**295**) with sulfur also gave 2-aryl-imidazo[4,5-*b*]pyridines. Under Dimroth rearrangement conditions, compounds such as (**296**) or (**297**) also afforded 2-aryl-imidazo[4,5-*b*]pyridines (**294**).

The preparation of 1*H*,3*H*-imidazo[4,5-*b*]pyridin-2-one (**299**) and related compounds has been

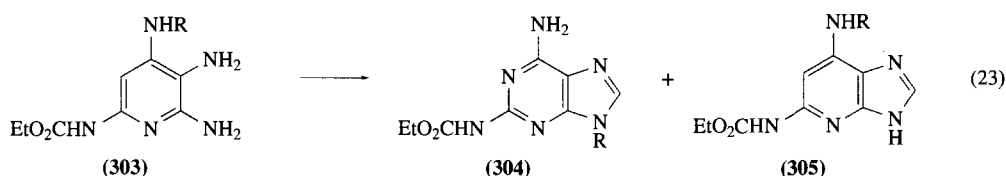


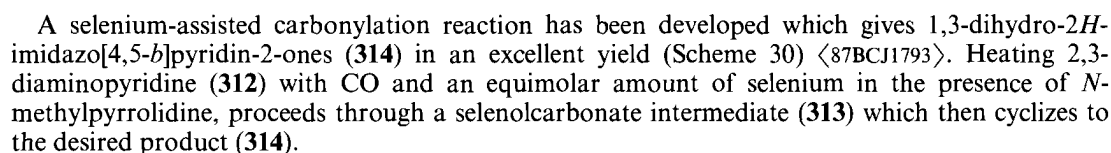
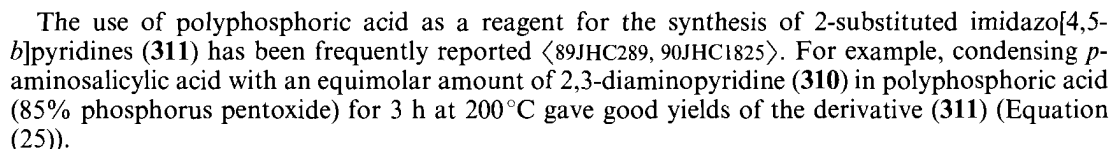
Scheme 29

accomplished in a number of ways. Cyclization of 2,3-diaminopyridine (298) with a variety of agents, for example, phosgene, urea, etc. is the main method of choice. Both the Hoffman rearrangement of 2-aminonicotinamides (300) <57AP(290)20, 58GEP1024974> and the Curtius rearrangement <59JCS3157> of 2-aminonicotinoyl azide (301) have been used to furnish compound (299). A modified Lossen rearrangement of compound (302) in the presence of benzenesulfonyl chloride gave the product (299) in excellent yield <68JOC2543>.



Reaction of the pyridine derivative (303; $\text{R} = \text{CH}(\text{Ph})_2$) with ethyl orthoformate afforded only the imidazo[4,5-*c*]pyridine (304) in good yield <73JMC292>. A later study <87JMC1746> has reported the isolation of mixtures of both imidazo[4,5-*c*]pyridines (304) and imidazo[4,5-*b*]pyridines (305) (Equation (23)) with the isomeric ratio being dependent on the steric bulk of the 4-amino substituent. When compound (303; $\text{R} = \text{phenyl}$) was cyclized with ethyl orthoformate a mixture of both isomers (304) and (305) was isolated in a 1 : 2 ratio. However, if compound (303; $\text{R} = \text{benzyl}$) is used a 1 : 10 ratio of the products (304) and (305) is obtained. When a phenethylamino group is positioned at C-4 only the isomer (304) is formed in the reaction. Interestingly, the reaction of the derivatives (306) or (308) with benzaldehyde at room temperature for 64 h furnished only modest yields of the products (307) and (309), respectively (Equation (24)). No imidazo[4,5-*c*]pyridine isomer was detected in these reactions.

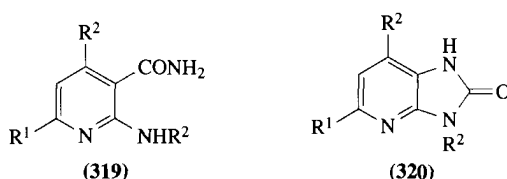


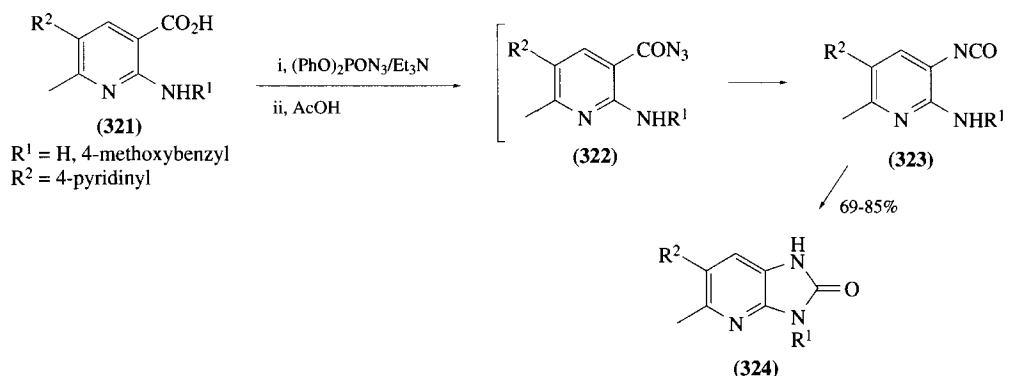


2-Aminoimidazo[4,5-*b*]pyridines (**317**) may be prepared in a two-step procedure (Scheme 31). Acylation of 2,3-diaminopyridine (**315**) with ethoxycarbonylisothiocyanate in the presence of triethylamine gives a mixture of 1-(2- and 3-methoxycarbonyl)-3-pyridinylthioureas (**316**) which upon treatment with DCC cyclize to give the 2-ethoxycarbonylamino derivative (**317**). The 2-aminoimidazo[4,5-*b*]pyridine (**318**) was prepared in 38% yield by the hydrolysis of the ester (**317**) with 4 M NaOH.



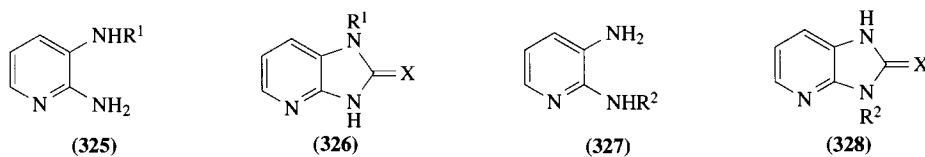
2-Alkylaminonicotinamides (**319**) undergo a Hofmann reaction with NaOBr–NaOH to give imidazo[4,5-*b*]pyridin-2-ones (**320**) in 60–90% yields $\langle 90\text{MI } 708-01 \rangle$. A Curtius rearrangement of the acyl azides (**322**) generated *in situ* by reacting the 2-aminonicotinic acids (**321**) with diphenyl phosphorazidate in triethylamine/dioxane produced the isocyanates (**323**) (Scheme 32) $\langle 94\text{JMC}248 \rangle$. These compounds underwent an intramolecular cyclization to form the imidazo[4,5-*b*]pyridin-2-ones (**324**).





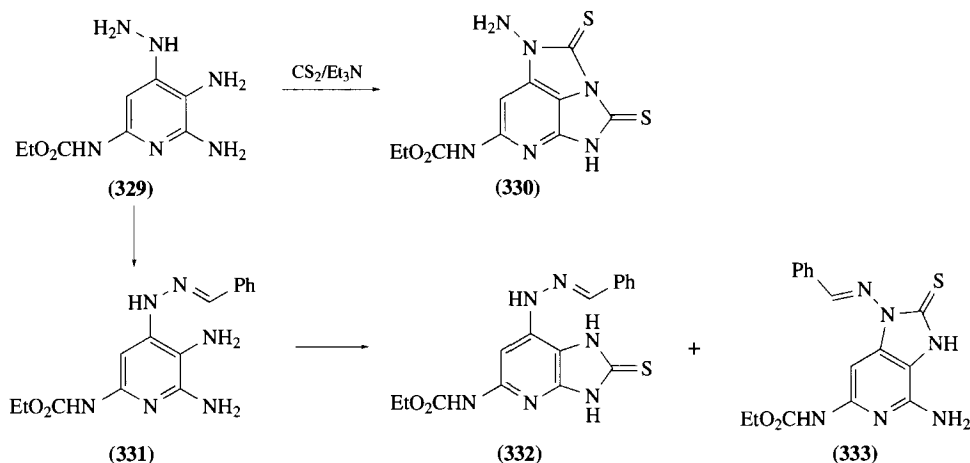
Scheme 32

Using more conventional and general procedures, the fusion of 3-alkylamino-2-aminopyridines (325) or 2-alkylamino-3-aminopyridines (327) with 3 equiv. of urea or thiourea <87JMC814, 88JAP63275582>, or by treatment with phosgene in the presence of triethylamine at 0°C , gives after work-up excellent yields of 1-substituted or 3-substituted 1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-ones (326; $\text{X} = \text{O}$) or (328; $\text{X} = \text{O}$). 1-Substituted or 3-substituted 1,3-dihydro-2H-imidazo[4,5-b]pyridine-2-thiones (326; $\text{X} = \text{S}$) or (328; $\text{X} = \text{S}$) are prepared in excellent yield by reacting the appropriate *o*-diaminopyridine (325) or (327) with potassium or sodium ethyl xanthate in pyridine- H_2O , or by refluxing in a mixture of carbon disulfide/pyridine <88CHE653>.



Where $\text{X} = \text{O}$ or S and $\text{R}^1, \text{R}^2 = \text{H}, \text{methyl}, \text{isopropyl}, \text{butyl}, \text{etc.}$

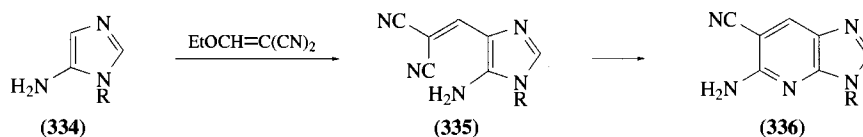
The reaction of the multisubstituted pyridine (329) with excess carbon disulfide in the presence of triethylamine at room temperature gave a product identified as the tricyclic compound (330) (Scheme 33) <90JMC656>. To block one mode of cyclization, the hydrazone (331) was prepared and condensed with one equivalent of carbon disulfide in the presence of triethylamine. In this case, no tricyclic product was formed but the products (332) and (333) were isolated in 15 and 36% yields, respectively.



Scheme 33

7.08.9.1.2 Closure of the pyridine ring

4-Unsubstituted-5-aminoimidazoles (**334**) have been shown, using AM1 MO calculations, to be *N,C*-ambident nucleophiles and that the orbital coefficient at C-4 favors addition of low energy LUMO (soft) electrophiles at this site to give the C-addition product $\langle 92\text{JCS(P1)2779, } 92\text{JCS(P1)2789, } 95\text{SL203} \rangle$. Thus the reaction of the amines (**334**) with a soft electrophile such as ethoxymethyl-enemalonitrile gives exclusively 5-amino-4-(2',2'-dicyanovinyl) derivatives (**335**) in good yields (Scheme 34). When these products (**335**) are heated in alcohol, in the presence of base, cyclization occurs to provide imidazo[4,5-*b*]pyridines (**336**). These α -aminocyanimidazo[4,5-*b*]pyridines have been proven useful intermediates for the preparation of a variety of tricyclic systems containing the imidazo[4,5-*b*]pyridine ring system.

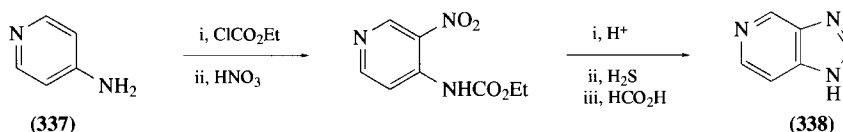


Scheme 34

7.08.9.2 Imidazo[4,5-*c*]pyridines

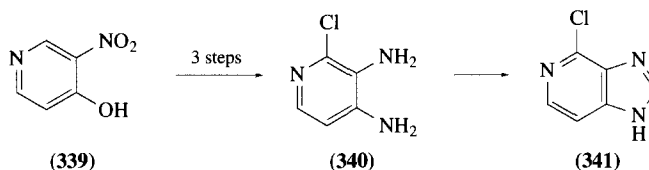
7.08.9.2.1 Closure of the imidazole ring

Starting with 4-aminopyridine (**337**), a total synthesis of the parent ring imidazo[4,5-*c*]pyridine (**338**) has been reported $\langle 86\text{T1511} \rangle$ in a 41% overall yield (Scheme 35).



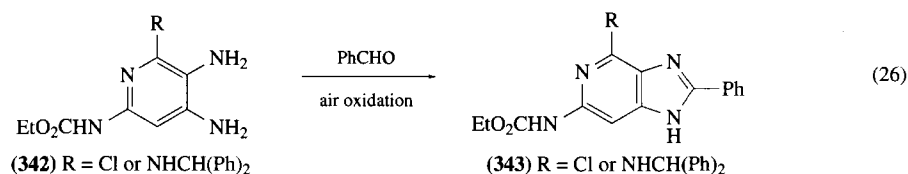
Scheme 35

Due to the interest in modified nucleosides, several improved syntheses of 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (**341**) have been reported $\langle 85\text{OPP409, } 85\text{JMC467, } 86\text{JHC669, } 89\text{JMC1442} \rangle$. In the latest procedure $\langle 89\text{JMC1442} \rangle$, which employs the best features of the previous syntheses, 4-hydroxy-3-nitropyridine (**339**) is converted into 2-chloro-3,4-diaminopyridine (**340**) which is then cyclized to compound (**341**) using trimethyl orthoformate and a catalytic amount of formic acid (Scheme 36).

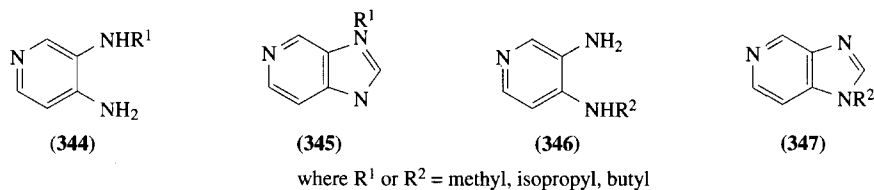


Scheme 36

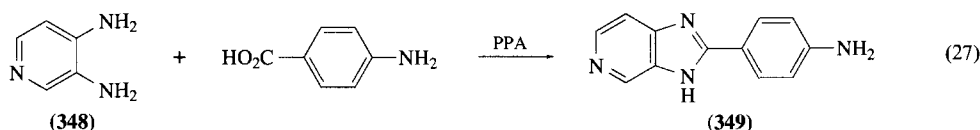
Oxidative cyclization of 3,4-diaminopyridines (**342**; $\text{R} = \text{Cl}$) with aryl aldehydes are illustrated by the formation of the derivative (**343**; $\text{R} = \text{Cl}$) (Equation (26)) $\langle 87\text{JMC1746} \rangle$. This type of reaction, which in this study used oxygen or bisulfite to oxidize the dihydro intermediate, is general for the formation of 2-aryl derivatives and has been carried out in the presence of several types of oxidizing agents, for example nitrobenzene $\langle 77\text{PIA(A)204} \rangle$, copper(II) salts $\langle 42\text{CB1936} \rangle$, and sulfur $\langle 87\text{CHE529} \rangle$. The application of this procedure to 2,3,4-triaminopyridines (**342**; $\text{R} = \text{NH}_2$) results in ring closure to give mixtures of imidazo[4,5-*c*]pyridines and imidazo[4,5-*b*]pyridines. However, if the 2-amino group is substituted with a sterically bulky group, such as a diphenylmethyl substituent, the reaction may be directed to afford exclusively the imidazo[4,5-*c*]pyridine isomer. For example, the derivative (**342**; $\text{R} = \text{NHCH}(\text{Ph})_2$) gave only the imidazo[4,5-*c*]pyridine when condensed with 4-methoxybenzaldehyde.



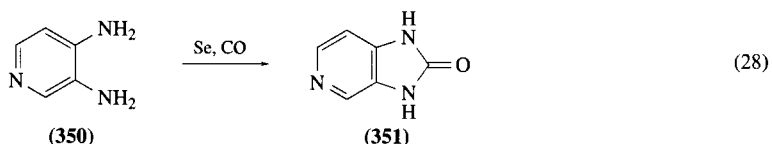
Heating a mixture of 3-alkylamino-4-aminopyridines (**344**), or 4-alkylamino-3-aminopyridines (**346**) at reflux in pentyl formate for 3–5 h gives N-1 and N-3 alkylimidazo[4,5-*c*]pyridines (**345**) and (**347**) in good yield <80URP717055, 88CHE653>.



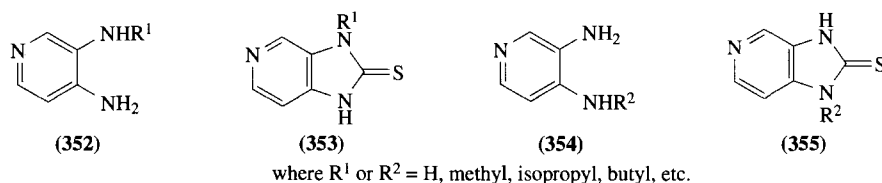
The application of polyphosphoric acid as a reagent for the synthesis of 2-substituted imidazo[4,5-*c*]pyridines (**349**) has been frequently used <89JHC289, 90JHC1825>. For example, the condensation of *p*-aminobenzoic acid with an equimolar amount of 3,4-diaminopyridine (**348**) in polyphosphoric acid (85% phosphorus pentoxide) gave a good yield of the highly colored imidazo[4,5-*c*]pyridine (**349**) (Equation (27)).



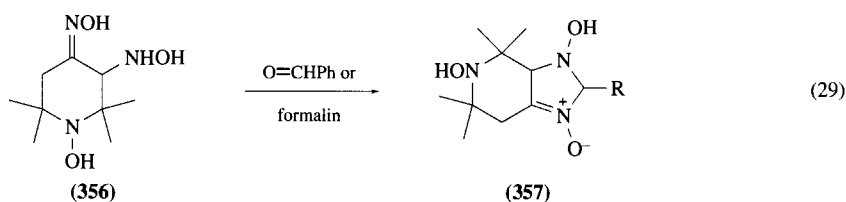
Treatment of 3,4-diaminopyridine (**350**) with carbon monoxide in the presence of selenium in *N*-methylpyrrolidine gives imidazo[4,5-*c*]pyridin-2-one (**351**) (96%) (Equation (28)) <87BCJ1793>. The selenium must be present in a stoichiometric or excess amount, or an acyclic urea formed via an intermolecular condensation of two 3,4-diaminopyridine moieties is the major product.



1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridine-2-thiones are prepared in excellent yield by reacting an *o*-diaminopyridine (**352**) or (**354**) with potassium or sodium ethyl xanthate in pyridine–H₂O, or refluxing in a mixture of carbon disulfide/pyridine to give the desired compounds (**353**) or (**355**) which are purified by base/acid reprecipitation <88CHE653>.



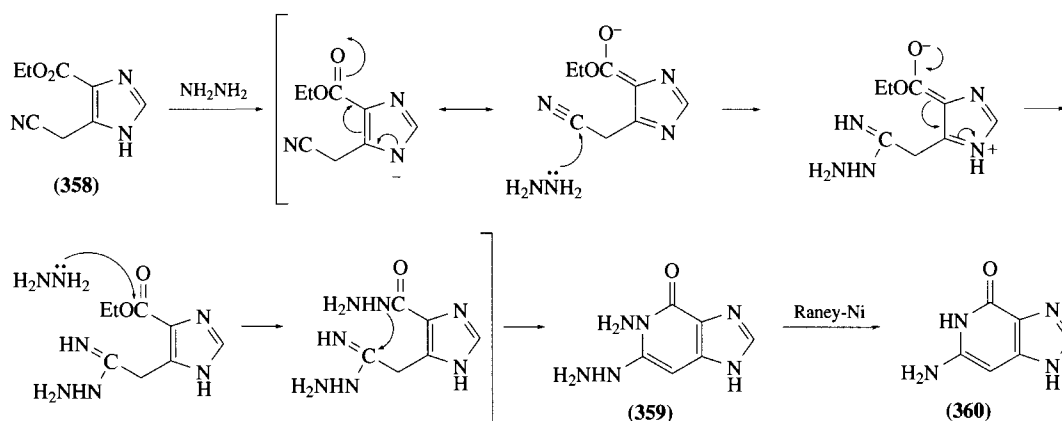
A derivative of the almost fully reduced imidazo[4,5-*c*]pyridine ring system, 3,3a,4,5,6,7-hexahydro-2*H*-imidazo[4,5-*c*]pyridine (**357**) has been prepared (Equation (29)) <88IZV409>. Cyclization of 1-hydroxy-3-hydroxyamino-2,2,6,6-tetramethyl-4-piperidone oxime acetate (**356**) with benzaldehyde or formalin at –20°C for 3 d gave the reduced bicyclic compound (**357**).



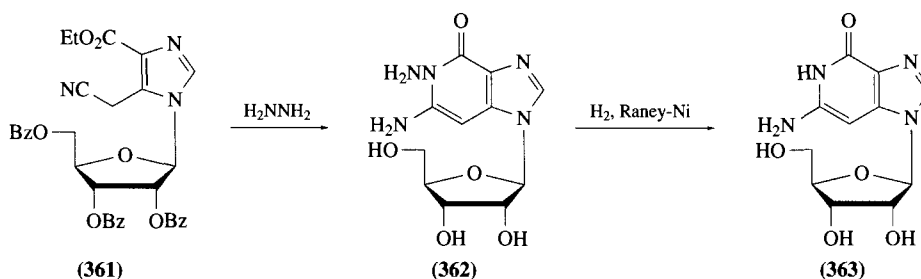
7.08.9.2.2 Closure of the pyridine ring

The antiviral and anticancer activities associated with 3-deazaguanine (**360**) and 3-deazaguanosine (**363**) prompted the development of a large-scale synthesis of these compounds (Scheme 37) <84JMC1389>. To accomplish this a base-catalyzed intramolecular cyclization of ethyl 5(4)-(cyanomethyl)imidazole-4(5)-carboxylate (**358**) and ethyl 5-(cyanomethyl)-1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazole-4-carboxylate (**361**) with hydrazine has been found to afford the target compounds in a 30% yield improvement over the previous methods <76JA1492, 79JHC1063>. The treatment of the ester (**358**) with hydrazine hydrate in ethanol at reflux for 15 h has been proposed to proceed as shown in Scheme 37 to afford the 5-amino-6-hydrazino derivative (**359**). The structure (**359**) was assigned on the basis of spectral and elemental analysis. Hydrogenation of this hydrazine (**359**) in the presence of Raney-nickel (W-4) catalyst gave 3-deazaguanine (**360**). A similar treatment of ethyl 5-(cyanomethyl)-1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazole-4-carboxylate (**361**), with ten equivalents of hydrazine hydrate gave the 5,6-diamino nucleoside (**362**) rather than the 5-amino-6-hydrazino intermediate. Hydrogenation of compound (**362**) in the presence of Raney-nickel gave 3-deazaguanosine (**363**) in good yield (Scheme 38). The reaction of ethyl 5-(cyanomethyl)-1-(3,5-di-*O*-toluoyl- β -D-erythro-pentofuranosyl)imidazole-4-carboxylate (**364**) with liquid ammonia at 100°C for 10 h gave 5-(cyanomethyl)-1-(β -D-erythro-pentofuranosyl)imidazole-4-carboxamide (**365**) (67%). Treatment with base was necessary to cyclize compound (**365**) to 2-deoxy-3-deazaguanosine (**366**) (Scheme 39). The structure (**365**) was confirmed by x-ray analysis.

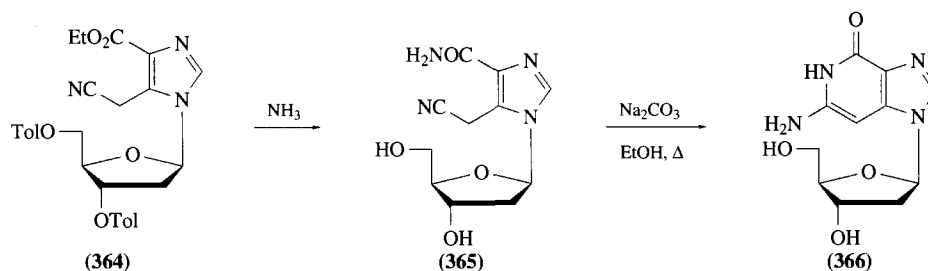
Thermal electrocyclic reactions of a series of 1-azahexatrienes (**367**), which contain a fused



Scheme 37

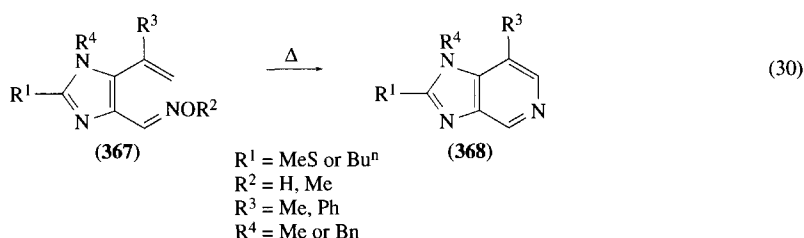


Scheme 38

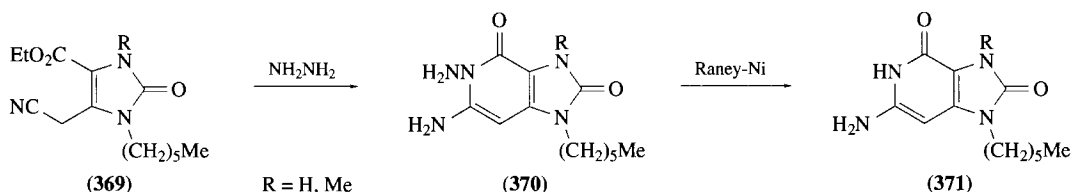


Scheme 39

imidazole ring, have been carried out and afford a new route to the imidazo[4,5-*c*]pyridines (368). In this reaction heating the oximes (367) at the reflux temperature of *o*-dichlorobenzene for 30–60 min gave, after purification by column chromatography using EtOAc as an eluent, the imidazo[4,5-*c*]pyridines (368) in good yield (Equation (30)) <95H(41)161>.



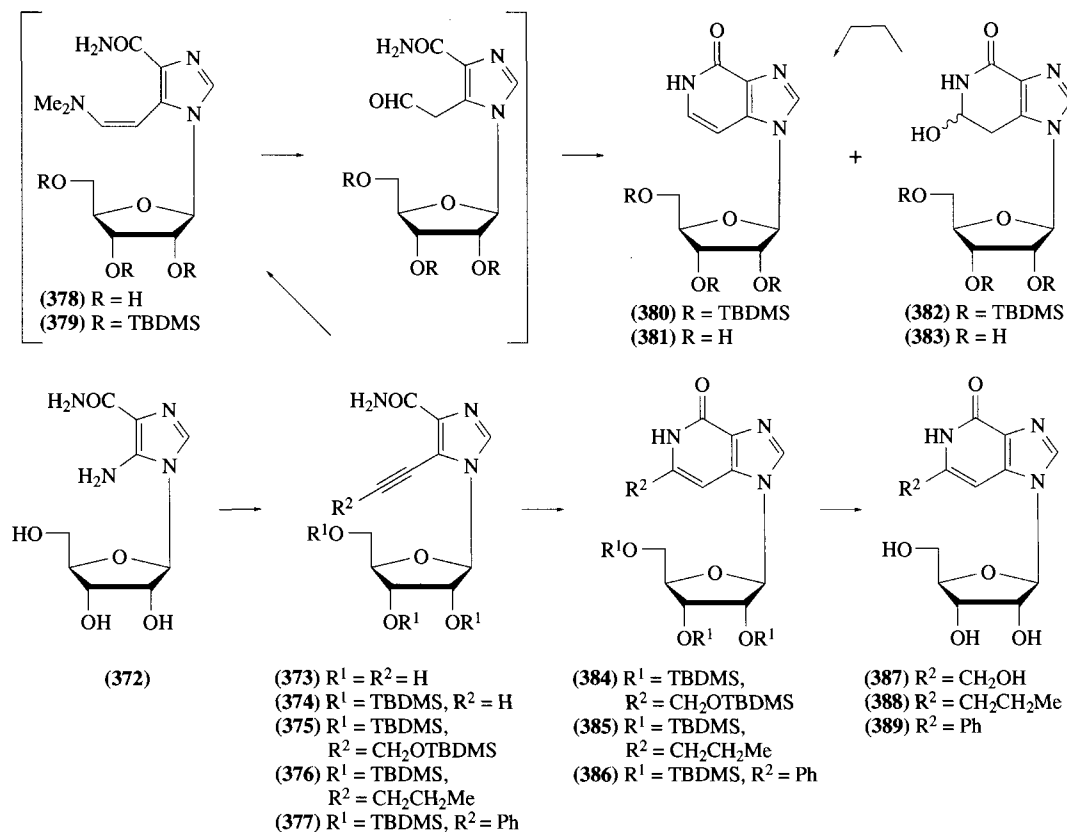
Annulation of the 1*H*,3*H*-imidazol-2-ones (369) <93JMC1341> has been accomplished by heating these compounds with hydrazine hydrate in ethanol at reflux temperature to give the derivatives (370) in good yield. Subsequent hydrogenation with a Raney-nickel catalyst provided the products (371) (Scheme 40).



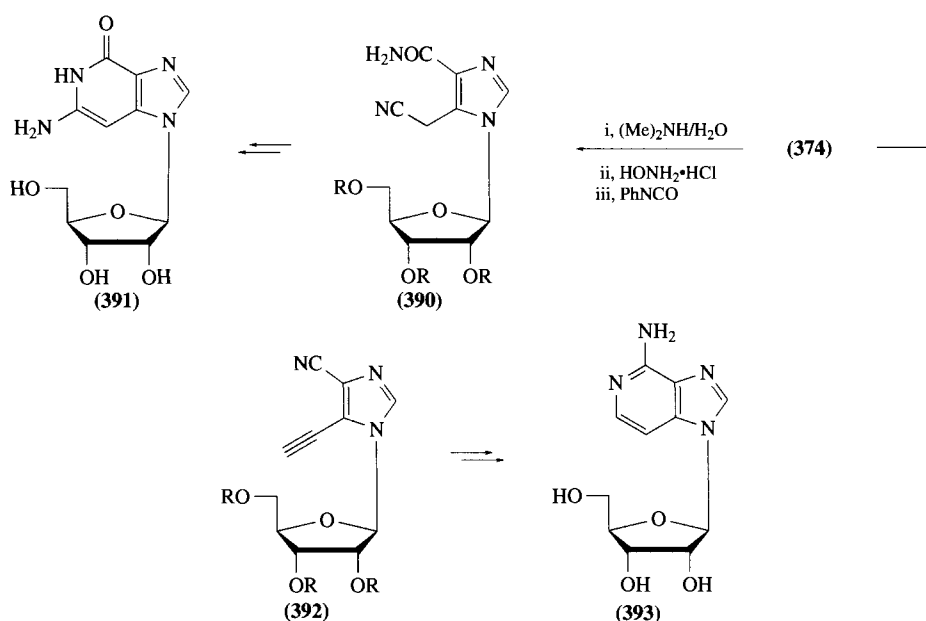
Scheme 40

5-Ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide (373), which is prepared from AICA-ribose (372) by a palladium-catalyzed cross-coupling reaction <88CPB2730, 91JMC778> has been cyclized by treatment with base to give the imidazo[4,5-*c*]pyridine nucleosides (381), (391), and (393) related to inosine, guanosine, and adenosine, respectively (Schemes 41 and 42) <93T557>. The preparation of the inosine analogue (381) involved treatment of the silylated derivative (374) with aqueous dimethylamine in EtOH at 80 °C in a sealed tube which afforded a 1:2 mixture of 1-(tri-*O*-*t*-butyldimethylsilyl)-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4-one (380) and a mixture of the epimers of compound (382) in 82% yield overall. Compound (382) could be converted to (383) in 87% overall yield by heating with 50% aqueous acetic acid in THF. Deprotection of compound (380) by treatment with TBAF afforded the 3-deazainosine analog (381) in excellent yield. A variety of 5-alkynyl imidazole-4-carboxamides (375)–(377), were also submitted to a similar reaction sequence, and although the desired imidazo[4,5-*c*]pyridine nucleosides (387)–(389) were isolated, the yields were low (14–45%). To prepare the guanosine analog (391), the 5-ethynyl group was converted to a cyanomethyl moiety. This was accomplished in a multistep reaction sequence (Scheme 42). First the alkyne (374) was treated with aqueous dimethylamine, then hydroxylamine hydrochloride in acetic acid. The resulting oxime was dehydrated by treatment with phenylisocyanate to give the key 5-cyanomethylimidazo-4-carboxamide riboside (390) (66%). Ring closure to the imidazo[4,5-*c*]pyridine system by heating (390) in 5% aqueous sodium carbonate–EtOH followed by deprotection of the sugar hydroxyl groups with TBAF afforded 3-deazaguanosine (391). To prepare the adenosine analogue (393), the carboxamide group of compound (374) was first

dehydrated to give 5-ethynyl-1-(β -D-ribofuranosyl)imidazole-4-carbonitrile (**392**) (Scheme 42). Deprotection of the sugar hydroxyl groups with TBAF followed by heating in methanolic ammonia at 120°C for 3 h caused an intramolecular cyclization to afford the desired product (**393**) in good yield.



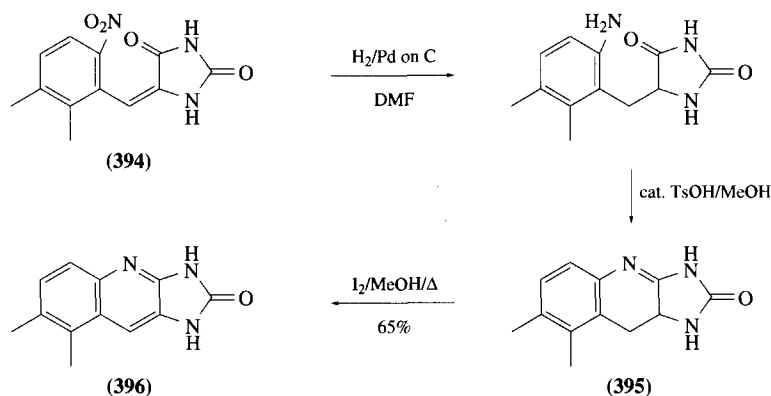
Scheme 41



Scheme 42

7.08.9.3 Imidazo[4,5-*b*]quinolin-2-ones

An improved method for the preparation of 2,3,9,9a-tetrahydro-2-oxoimidazo[4,5-*b*]quinolines (**395**) and imidazo[4,5-*b*]quinolin-2-ones (**396**) has been reported (Scheme 43) <30MI 708-01, 60JCS2994, 91JMC2906, 93JMC3251>. The method involves a closure of the central ring as the final synthetic step. The preparation of the intermediate 2-nitrobenzylidenehydantoins (**394**) is the key to these syntheses and improved methods <91JOC6897> provide these compounds in over 80% yield.

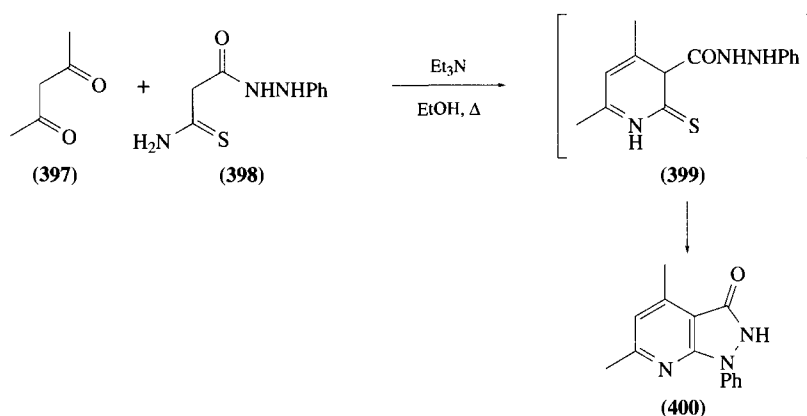


Scheme 43

7.08.9.4 Pyrazolo[3,4-*b*]pyridines

7.08.9.4.1 Closure of the pyrazole ring

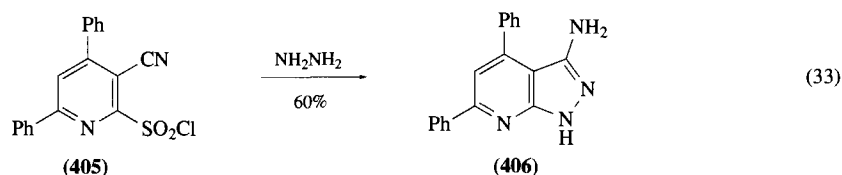
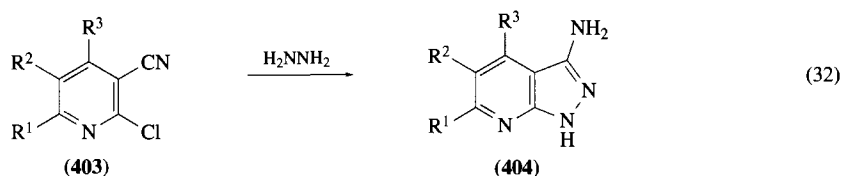
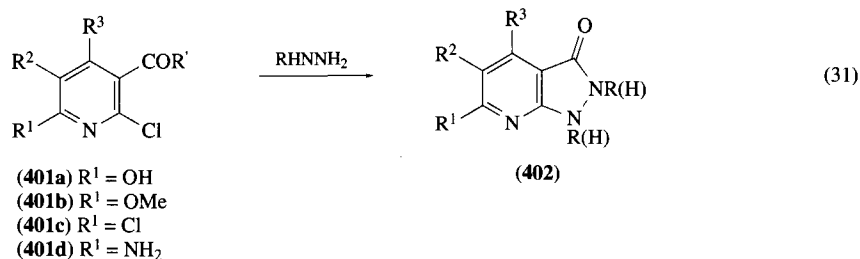
Monothiomalonic acid hydrazides (**398**), prepared by the reaction of cyanoacetohydrazides with H_2S , react with diketones (e.g. **(397)**) to give pyridine-2-thiono-3-carboxhydrazides (**399**) which cyclize with the loss of H_2S to give 1-substituted pyrazolo[3,4-*b*]pyridin-3-ones (e.g. **(400)**) (Scheme 44) <85S861>.



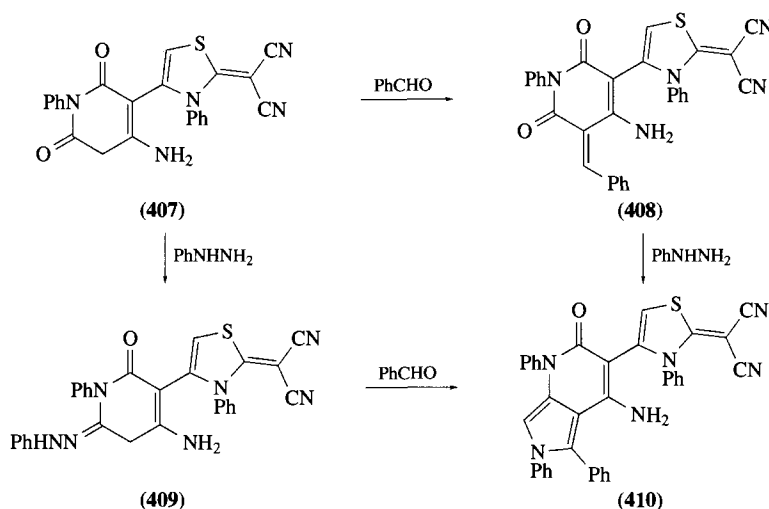
Scheme 44

Ring closure of the 2-chloronicotinic acid derivatives (**401a-d**) by reaction with hydrazine or substituted hydrazines has been used widely to prepare pyrazolo[3,4-*b*]pyridin-3-ones (**402**) (Equation (31)) <65AJC1267, 81USP4265895>. For example, 2-chloronicotinic acid (**401a**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$) reacted with hydrazine to afford an intermediate 2-hydrazinonicotinic acid, which upon heating in hydrochloric acid gave 1*H*-pyrazolo[3,4-*b*]pyridin-3-one (**402**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R} = \text{H}$) in good yield. Interestingly when 2-chloronicotinic acid was reacted with methylhydrazine only the 1-methyl derivative was obtained in 76% yield. In contrast, condensation with benzylhydrazine leads only to the 2-benzyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-one <71FES872>. Many additional 1*H*-pyrazolo[3,4-*b*]pyridin-3-ones and 1-substituted derivatives have been prepared by ring closure of the esters (**401b**) with hydrazine and substituted hydrazines <61AG15, 73JHC931>. The reaction of acid chlorides (**401c**)

with hydrazine give acid hydrazides which are subsequently cyclized to the bicyclic system <70AC(R)403, 71FES872>. The 3-carbamoyl derivatives (**401d**) also afford the corresponding 3-oxo derivatives (**402**) in good yields. The 2-chloro-3-cyanopyridines (**403**) have been reacted with hydrazines to give substituted 3-aminopyrazolo[3,4-*b*]pyridines (**404**) in high yield (Equation (32)) <65JHC192, 92KGS1218>. Treatment of 3-cyano-4,6-diphenylpyridine-2-sulfonyl chloride (**405**) with hydrazine provides an alternative procedure to prepare 3-amino-4,6-diphenylpyrazolo[3,4-*b*]pyridines (**406**) (Equation (33)) <90M281>.



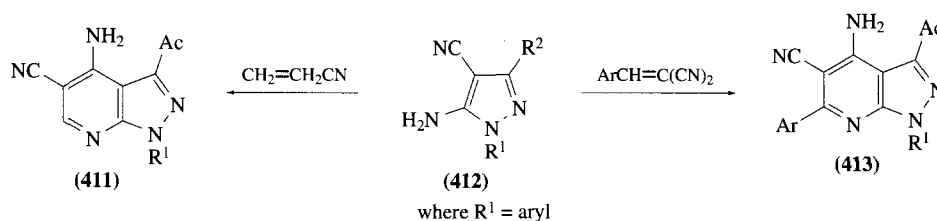
Compound (**408**), which was prepared by the condensation of the amine (**407**) with benzaldehyde in the presence of piperidine, upon treatment with phenylhydrazine afforded the orange pyrazolo[3,4-*b*]pyridin-2-one (**410**) (69%) (Scheme 45) <91PS(63)119>. The structure (**410**) was confirmed by an alternative synthesis involving a reversal of the reactants. In this case compound (**407**) was initially reacted with phenylhydrazine to give compound (**409**) and subsequent condensation with benzaldehyde gave the product (**410**).



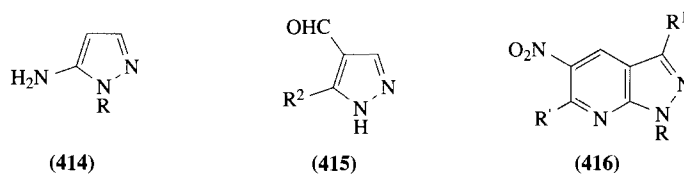
Scheme 45

7.08.9.4.2 Closure of the pyridine ring

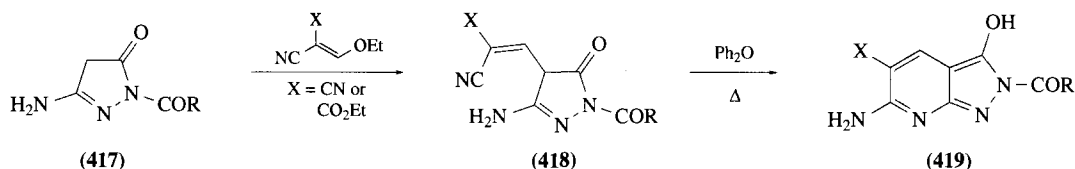
Ring closure of 5-amino-4-cyano-1,3-substituted pyrazoles (**412**) with acrylonitrile or α -cyano-cinnamitrile in dry pyridine produces the corresponding pyrazolo[3,4-*b*]pyridine derivatives (**411**) and (**413**), respectively (Scheme 46) <92JIC378>. *N*(1)-Unsubstituted, *N*(1)- or *N*(2)-substituted 5-nitropyrazolo[3,4-*b*]pyridines (**416**) are obtained in 40–90% yields by heating the amines (**414**) with the sodium salt of nitromalonic aldehyde in water or aqueous DMSO <92KGS1560>. The reaction of 3-amino-4-formylpyrazole (**415**) with nitroacetaldoxime, nitroacetone, or ethyl nitroacetate also affords 5-nitropyrazolo[3,4-*b*]pyridines. This is the method of choice to prepare 6-substituted derivatives. 1-Methyl- and 1-phenyl-5-nitropyrazolo[3,4-*b*]pyridines (**416**) have also been prepared by heating 1-substituted aminopyrazoles (**414**) with nitromalonic aldehyde in acetic or polyphosphoric acid <83KGS1471>.



Scheme 46



Treatment of 1-acyl-3-amino-5-pyrazolones (**417**) with an equimolar amount of an enol ether, such as ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile in DMSO at 70–80°C for 3 h furnishes pyrazoleacrylonitriles (**418**) in good yields. The use of other solvents decreases the yields considerably. Heating the intermediates (**418**) in diphenyl ether at 200°C promoted cyclization to give 2-acyl-6-amino-3-hydroxy-2*H*-pyrazolo[3,4-*b*]pyridines (**419**) (Scheme 47) <94JHC925>.

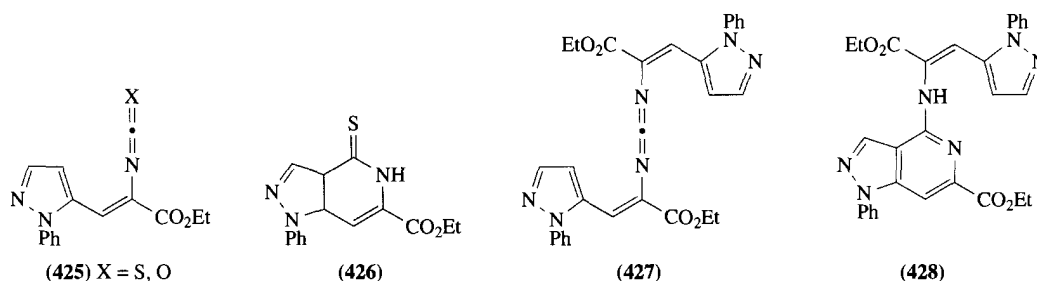
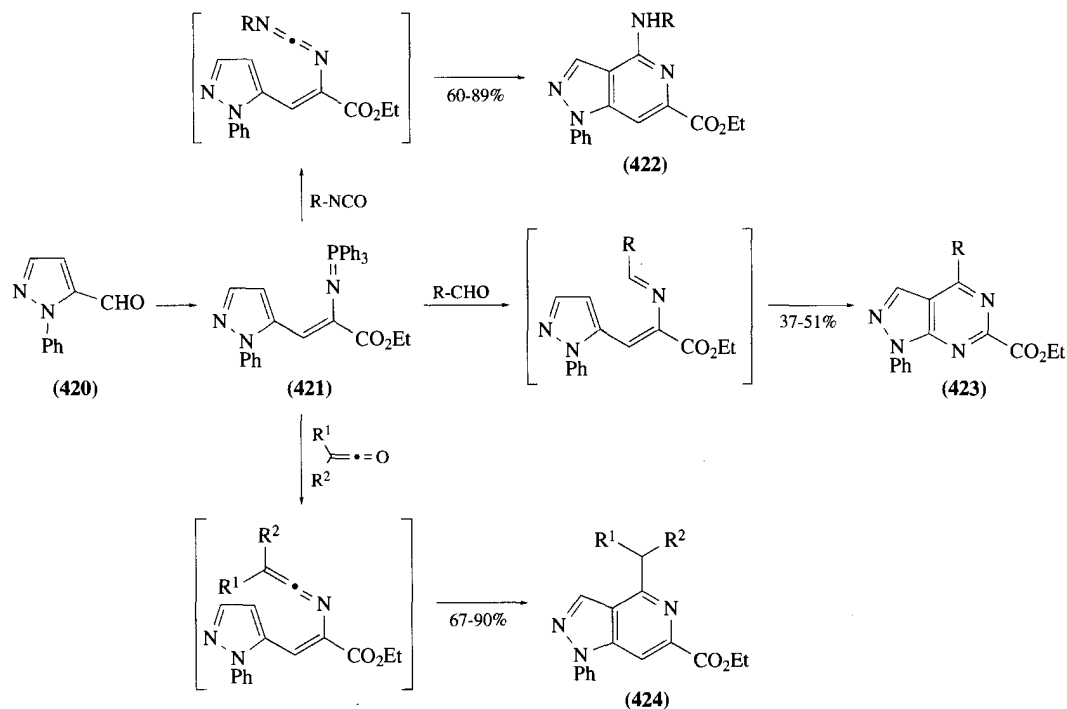


Scheme 47

7.08.9.5 Pyrazolo[4,3-*c*]pyridines

A new procedure for the preparation of pyrazolo[4,3-*c*]pyridines has been described using an aza Wittig-type reaction (Scheme 48) <91T6737>. The key iminophosphorane (**421**) is prepared from 5-formyl-1-phenylpyrazole (**420**) by a sequential treatment with ethyl azidoacetate and triphenylphosphine. Compound (**421**) reacts via a tandem aza Wittig-electrocyclic ring closure with isocyanates, ketenes, aldehydes, and carbon disulfide to give a variety of substituted pyrazolo[4,3-*c*]pyridines. The reaction of compound (**421**) with isocyanates and ketenes most probably involves an initial aza Wittig reaction to give a reactive intermediate which undergoes electrocyclic ring-closure followed by a [1,3] proton shift to give the 4-amino derivatives (**422**) and pyrazolo[4,3-*c*]pyridines (**424**). The reaction of the iminophosphorane (**421**) with aldehydes gives 4-alkyl(aryl)-6-ethoxycarbonyl-1-phenylpyrazolo[4,3-*c*]pyridines (**423**) in some what lower yields than the above reactions. If the reagent (**421**) is reacted with carbon disulfide in toluene at 120°C in a sealed tube, the intermediate isothiocyanate (**425**; X = S) can be isolated (73%). Raising the reaction temperature

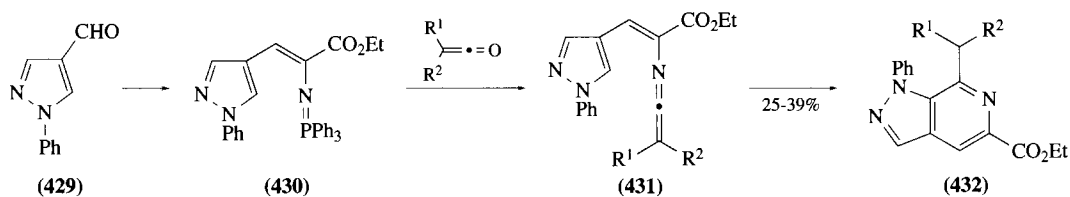
to 165°C gives the 4-thione derivative (**426**) (95%). Reaction with carbon dioxide at 120°C led to the formation of compound (**428**) (40%). This product (**428**) is most probably formed by ring closure of the carbodiimide (**427**) which was isolated, together with the isocyanate (**425**; X = O), when the reaction was performed at a lower temperature.



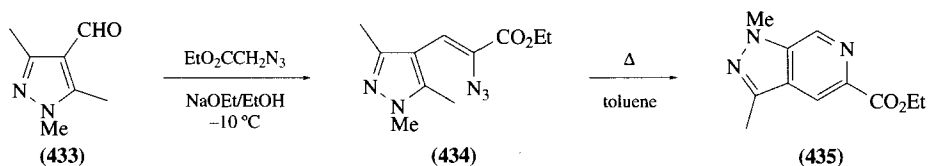
7.08.9.6 Pyrazolo[3,4-*c*]pyridines

Attempts to prepare pyrazolo[3,4-*c*]pyridines using a tandem aza Wittig-electrocyclic ring closure series of reactions were not as successful as for the formation of pyrazolo[4,3-*c*]pyridines <91T6737> (see Section 7.08.9.5). In this series the iminophosphorane (**430**), prepared from 4-formyl-1-phenylpyrazole (**429**) by a sequential treatment with ethyl azidoacetate and triphenylphosphine, reacted with isocyanates, aldehydes, and carbon disulfide to give the corresponding aldimines (Scheme 49). These compounds, due to the relative inactivity of the 3(5)-positions of the pyrazole ring system to electron-deficient dienophiles, failed to cyclize and no pyrazolo[3,4-*c*]pyridines were formed. However, the aldimines (**431**), prepared by the reaction of compound (**430**) with ketenes, gave the pyrazolo[3,4-*c*]pyridines (**432**) in low yield upon heating in toluene.

Thermolysis of the azide (**434**), prepared by treatment of the aldehyde (**433**) with ethyl azidoacetate in base, at reflux in xylene furnishes the pyrazolo[3,4-*c*]pyridine (**435**) (22%) along with the aldehyde (**433**) (Scheme 50) <84JCS(P1)2189>. Attempts to facilitate the reaction by addition of iodine did not increase the yield. These yields are somewhat lower than reported earlier <79CC627>.



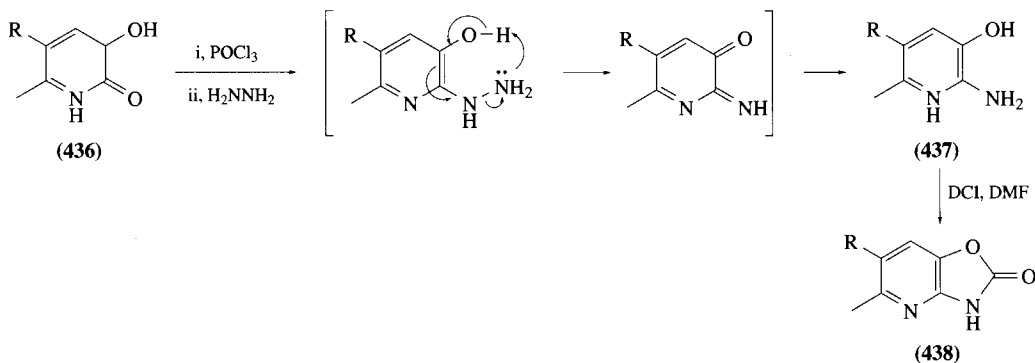
Scheme 49



Scheme 50

7.08.9.7 Oxazolo[4,5-*b*]pyridines

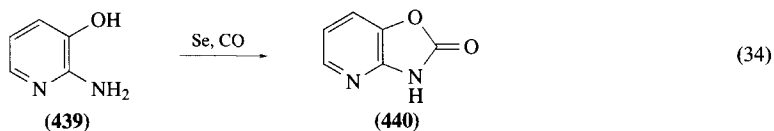
Chlorination of the pyridone (**436**; R = 4-pyridinyl) with phosphorus oxychloride followed by a reaction with hydrazine gave a low yield of the corresponding 2-amino-3-hydroxypyridine (**437**). Cyclization of this product was carried out by a reaction with 1,1'-carbonyldiimidazole in DMF at room temperature to give the oxazolo[4,5-*b*]pyridine (**438**; R = 4-pyridinyl) (Scheme 51) <94JMC248>.



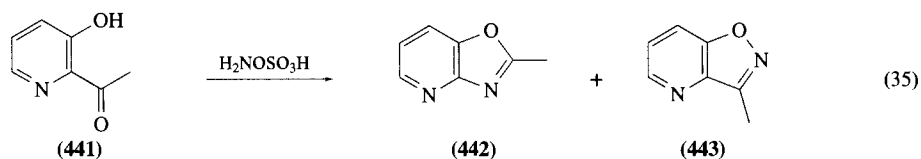
Scheme 51

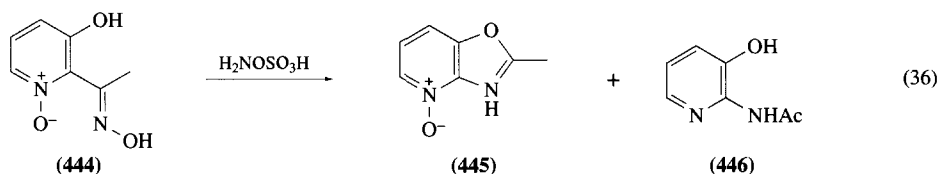
Treatment of 2-amino-3-hydroxypyridine (**439**) with carbon monoxide in the presence of selenium in *N*-methylpyrrolidine gives oxazolo[4,5-*b*]pyridin-2-one (**440**) (75%) (Equation (34)) <87BCJ1793>.

The selenium must be present in a stoichiometric or excess amount or an acyclic urea is the major product.



The reaction of 2-acetyl-3-hydroxypyridine (**441**) with hydroxylamine *O*-sulfonic acid afforded a 1:1 mixture of compound (**442**) and 2-methylisoxazolo[4,5-*b*]pyridine (**443**) (Equation (35)) <87H(26)2921>. The formation of the oxazolo[4,5-*b*]pyridine (**442**) results from a Beckmann rearrangement. The reaction of the oxime (**444**) with hydroxylamine *O*-sulfonic acid also gave Beckmann rearrangement products, such as (**445**) and (**446**) as a 1:1 mixture (Equation (36)).

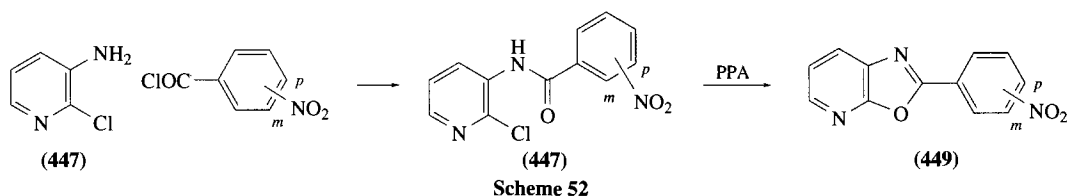




7.08.9.8 Oxazolo[5,4-*b*]pyridines

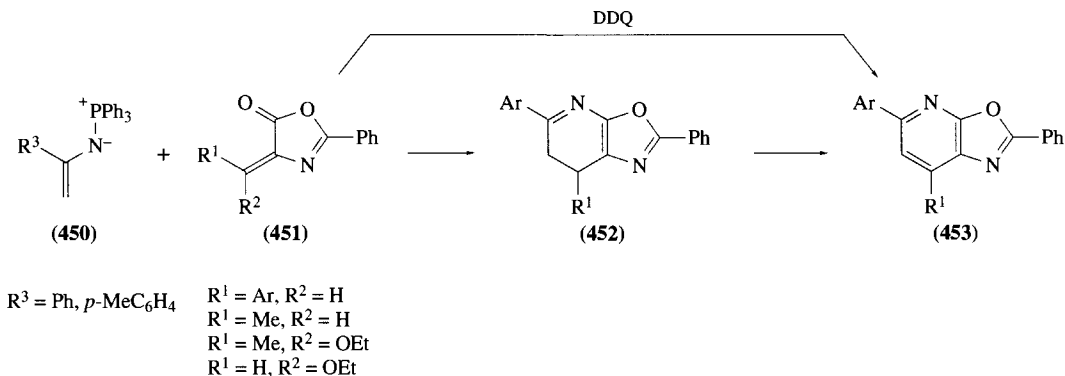
7.08.9.8.1 Closure of the oxazole ring

The use of polyphosphoric acid as a reagent for the synthesis of 2-substituted oxazolo[4,5-*b*]pyridines (**449**) has been reported (Scheme 52) (89JHC289, 90JHC1825). For example, acylating 2-chloro-3-aminopyridine (**447**) with *m*- or *p*-nitrobenzoyl chloride followed by heating of the intermediate (**448**) in polyphosphoric acid (85% phosphorus pentoxide) for 3 h at 200 °C gave good yields of the oxazolopyridines (**449**).



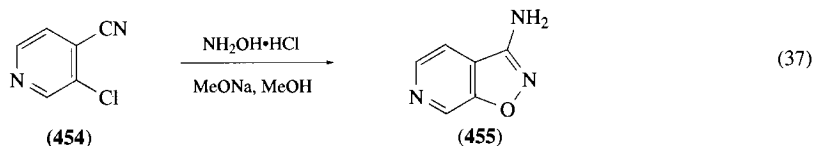
7.08.9.8.2 Closure of the pyridine ring

Oxazolo[5,4-*b*]pyridines have been prepared by the cyclocondensation of *N*-arylvinyliminophosphoranes with 4-alkylideneoxazol-5-ones (Scheme 53) (92JCS(P1)701). Heating the iminophosphoranes (**450**) with the alkylideneoxazol-5-ones (**451**) in refluxing benzene or anisole for 2–24 h gave the oxazolo[5,4-*b*]pyridines (**453**) as the major product together with the 6,7-dihydrooxazolo[5,4-*b*]pyridine (**452**). The 6,7-dihydro derivatives (**452**) are unstable (characterized by ¹H and ¹³C NMR) and undergo slow oxidation in air to give the products (**453**). By adding DDQ to the crude reaction mixture, to oxidize (**452**), the oxazolo[5,4-*b*]pyridines (**453**) were isolated in good yield. In this reaction the ambident nucleophile, vinyliminophosphorane (**450**), adds first to the exocyclic double bond and subsequent cyclization occurs through an aza-Wittig type reaction to give the 6,7-dihydro intermediate (**452**) which oxidizes to the aromatic oxazolo[5,4-*b*]pyridine. If derivatives (**451**; R² = EtO) are used in the initial step, then ethoxide ion is found to be eliminated after the nucleophilic addition of the iminophosphorane generating a double bond on the side chain: upon aza-Wittig cyclization the oxazolo[5,4-*b*]pyridine (**453**) was then formed directly.



7.08.9.9 Isoxazolo[5,4-*c*]pyridines

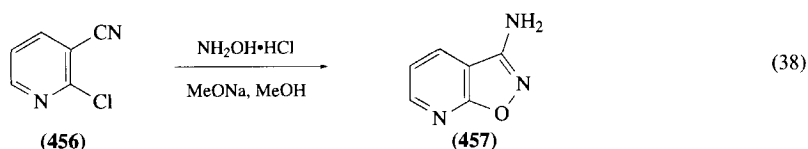
The treatment of 3-chloro-4-cyanopyridine (**454**) with hydroxyamine hydrochloride in methanol in the presence of sodium methoxide at 40°C for 10 min afforded 3-aminoisoxazolo[5,4-*c*]pyridine (**455**) (59%) (Equation (37)) <87ZC337>. This reaction did not proceed at 0°C.



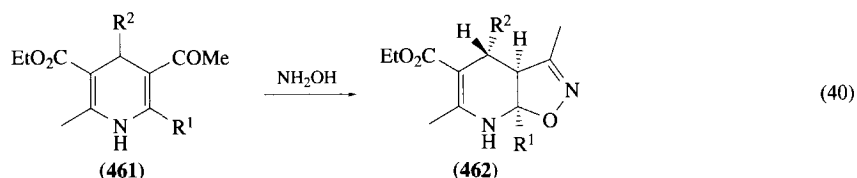
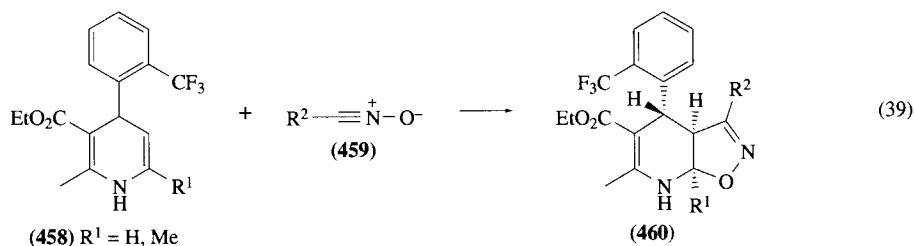
7.08.9.10 Isoxazolo[5,4-*b*]pyridines

7.08.9.10.1 Closure of the isoxazole ring

Treatment of 2-chloro-3-cyanopyridine (**456**) with hydroxyamine hydrochloride in methanol in the presence of sodium methoxide at 0°C for 10 min afforded 3-aminoisoxazolo[5,4-*b*]pyridine (**457**) (39%) (Equation (38)) <87ZC337>.



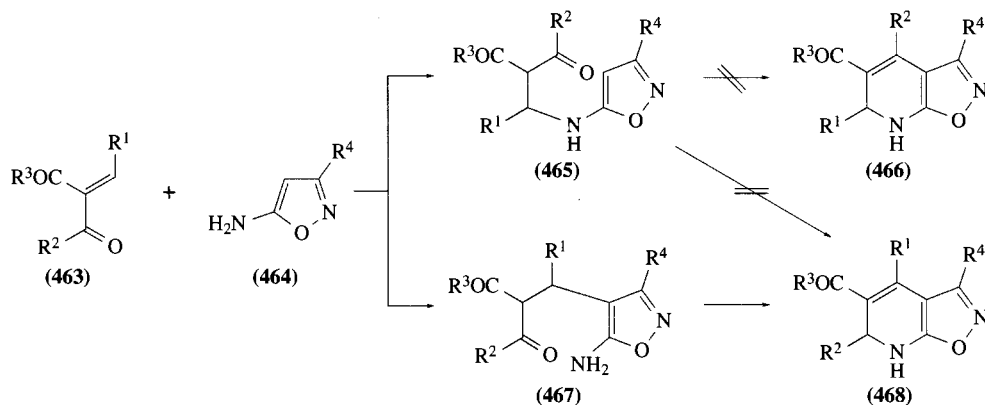
1,3-Dipolar cycloaddition of a variety of nitrile oxides with 5-unsubstituted 1,4-dihydropyridines (**458**) gives 3a,4,7,7a-tetrahydroisoxazolo[5,4-*b*]pyridines (Equation (39)). In this reaction the dihydropyridine (**458**) is treated with the nitrile oxide (**459**; R = carbethoxy, phenylsulfonyl, cyano, or phenylcarbonyl) in ether in the presence of triethylamine to give the adducts (**460**) in moderate to good yields <89JOC5585>. The stereochemistry at C-4 and C-3a in relationship to C-7a was established as *cis* by x-ray crystallography. Reacting 3-acetyl-1,4-dihydropyridines (**461**) with hydroxylamine hydrochloride in a mixture of pyridine and EtOH also gives 3a,4,7,7a-tetrahydroisoxazolo[5,4-*b*]pyridines (**462**) in moderate yield (Equation (40)) <86USP4593100>.



7.08.9.10.2 Closure of the pyridine ring

The treatment of 5-aminoisoxazoles (**464**) with α,β -unsaturated ketones (**463**), such as benzylidene-acetoacetate, ethylidene-acetoacetate derivatives, ethyl ethylidene-benzoylacetate, or 3-nitro-benzylideneacetylacetone, in *t*-butanol at reflux gives the 4,7-dihydroisoxazolo[5,4-*b*]pyridine deriva-

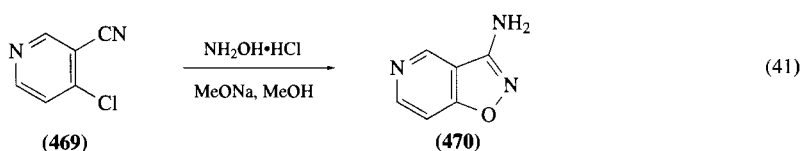
tives (**468**) in excellent yield (Scheme 54) <85T913>. If the reaction is carried out at room temperature in ethylene glycol, the amine adducts (**465**) are formed, which on heating give the derivatives (**468**) and not the isomers (**466**). This indicates that the amino adduct undergoes a retro-Michael reaction to regenerate the starting materials which then proceeds via Michael addition at the C-4 position of the amines (**464**) to give the intermediate (**467**) which ring closes subsequently to the observed products (**468**).



7.08.9.11 Isoxazolo[4,5-c]pyridines

7.08.9.11.1 Closure of the isoxazole ring

Treatment of 4-chloro-3-cyanopyridine (**469**) with hydroxyamine hydrochloride in methanol in the presence of sodium methoxide at 0 °C for 10 min afforded 3-aminoisoxazolo[4,5-c]pyridine (**470**) (18%) (Equation (41)) <87ZC337>.



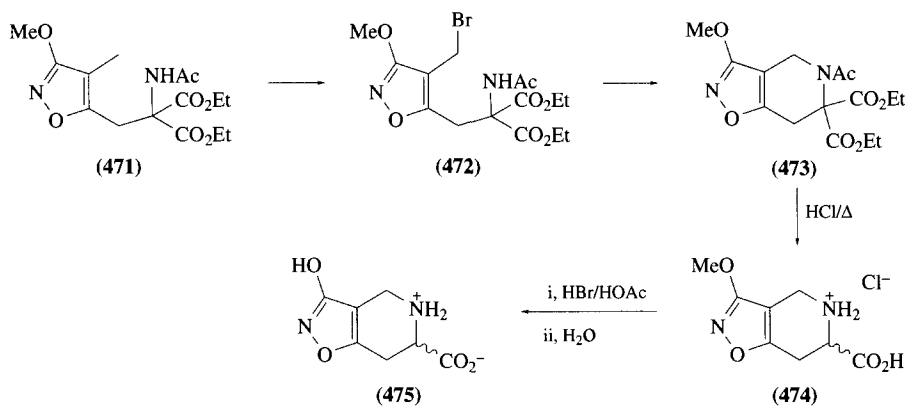
7.08.9.11.2 Closure of the pyridine ring

(*RS*)-3-Hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-6-carboxylic acid (**475**) has been prepared by a ring closure of the pyridine ring (Scheme 55) <86ACS(B)92>. Treatment of the diester (**471**) with an equimolar amount of NBS gave compound (**472**) along with a small amount of the 4-dibromomethyl derivative. Treatment of this product (**472**) with sodium hydride in DMF led to the cyclized compound (**473**) (65%) which upon acid hydrolysis and decarboxylation in boiling HCl, gave the acid (**474**). Compound (**474**) was treated with HBr to deblock the 3-methoxy group and gave the target tetrahydro derivative (**475**).

7.08.9.12 Isoxazolo[4,5-b]pyridines

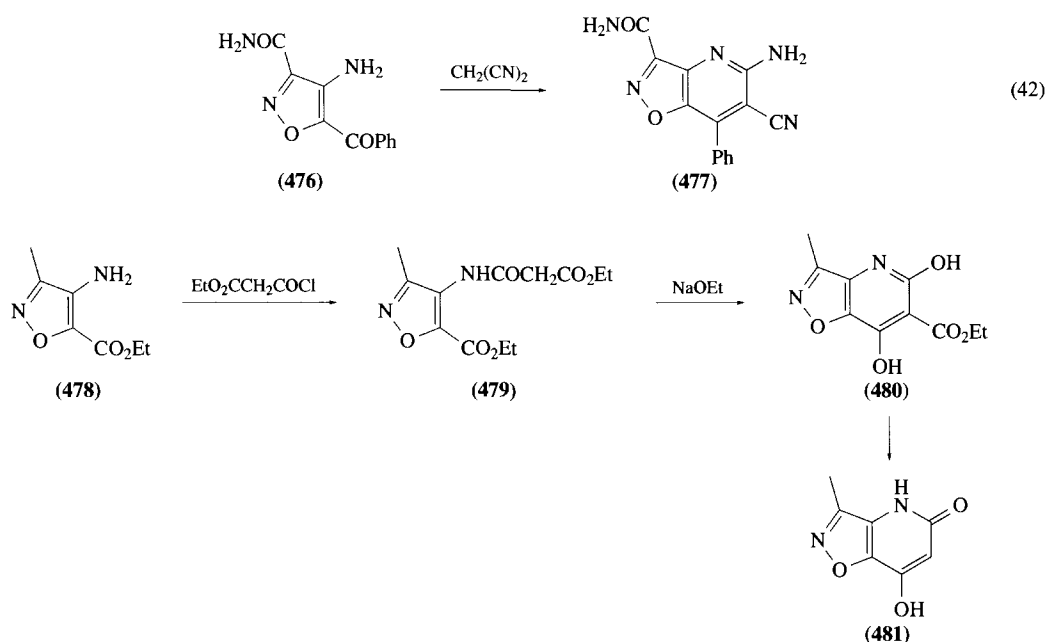
7.08.9.12.1 Closure of the pyridine ring

Condensation of 4-amino-5-benzoylisoxazole-3-carboxamide (**476**) with malononitrile in pyridine at reflux gave the first reported synthesis of an isoxazolo[4,5-*b*]pyridine derivative, namely 5-amino-6-cyano-7-phenylisoxazolo[4,5-*b*]pyridine-3-carboxamide (**477**) (62%) (Equation (42)) <80LA1623>.



Scheme 55

Using a two-step procedure, ethyl 4-amino-3-methylisoxazole-5-carboxylate (**478**) was condensed with ethyl malonyl chloride to afford the intermediate (**479**) which upon treatment with sodium ethoxide cyclized to the ester (**480**) in 82% overall yield <82JCS(P1)2391>. Compound (**480**) was decarboxylated to give the product (**481**) (Scheme 56).

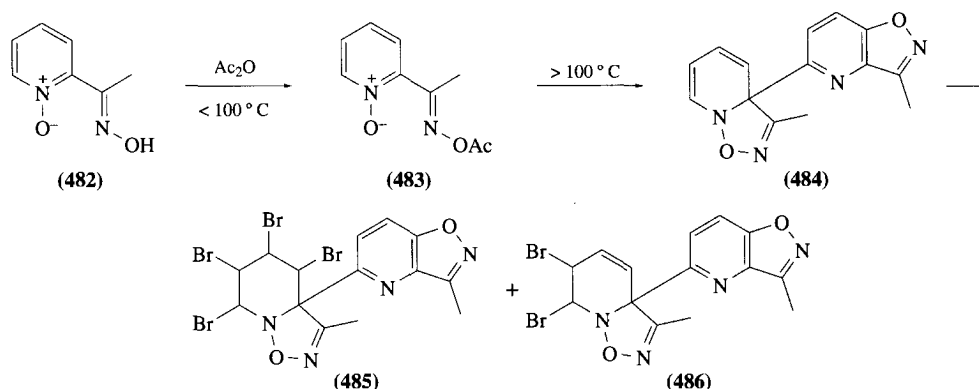


Scheme 56

7.08.9.12.2 Closure of the isoxazole ring

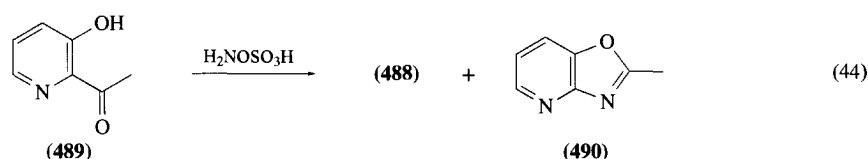
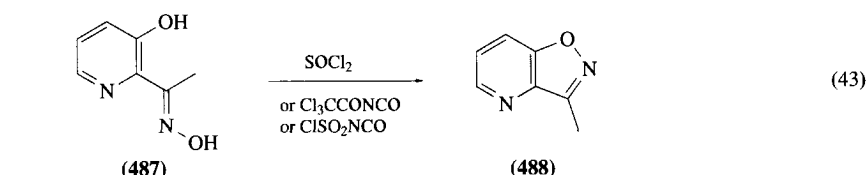
Heating (*E*)-methyl 1-oxide-2-pyridyl ketone oxime (**482**) in acetic anhydride at temperatures above 100°C initiated an exothermic reaction from which 3-methyl-3a-(3'-methylisoxazolo[4,5-*b*]pyridin-5'-yl)-3a*H*-[1,2,5]-oxadiazolo[2,3-*a*]pyridine (**484**) was isolated in 18% yield (Scheme 57) <86CPB4984>. If the reaction is carried out at a temperature less than 100°C , only the acetylated oxime (**483**) is isolated. Heating the (*Z*)-isomer in acetic anhydride at similar temperatures resulted only in the formation of the acetylated oxime. The structure of the product (**484**) was determined on the basis of two-dimensional COSY, DEPT, and 2D ^1H - ^{13}C chemical shift correlation experiments. The structure was also confirmed chemically via bromination which affords a mixture of the bromine adducts (**485**) and (**486**). Attempts to hydrolyze (**484**) under either acidic or basic conditions afforded only unchanged starting material. The formation of compound (**484**) from the *N*-oxide (**483**) proceeds via a radical mechanism. This mechanism was elucidated by a study of the reaction

in the presence of various radical scavengers and initiators. In the presence of the radical scavengers 1,1-diphenyl-2-picrylhydrazyl or Galvinoxyl, the compound (484) was formed in 44% or 58% yield, respectively, relative to a reaction containing no scavenger. Heating the acetylated oxime (483) in benzene effected no change but the addition of a radical initiator, such as benzoyl peroxide or 2,2'-azobisisobutyronitrile, to the solution caused the formation of the product (484) in each case in a 38% yield.

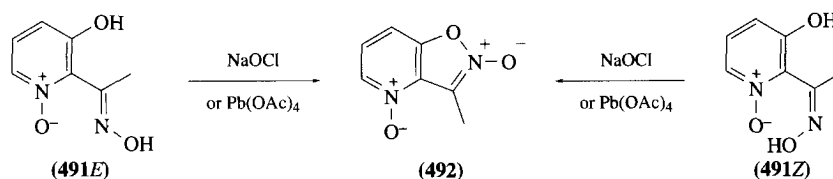


Scheme 57

The reaction of methyl (3-hydroxypyridin-2-yl)ketone oxime (487) with thionyl chloride, trichloroacetyl isocyanate or chlorosulfonyl isocyanate gave 3-methylisoxazolo[4,5-*b*]pyridine (488) in varying yields dependent upon the temperature and solvent (Equation (43)) <87H(26)2921>. Trichloroacetyl isocyanate was particularly effective in the formation of compound (488) in either diethyl ether or tetrahydrofuran, at ambient temperature or at reflux, affording 60–78% yields. The treatment of 2-acetyl-3-hydroxypyridine (489) with hydroxylamine *O*-sulfonic acid afforded a 1 : 1 mixture of compound (488) and 2-methyloxazolo[4,5-*b*]pyridine (490) (Equation (44)). The formation of the isomer (490) results from a Beckmann rearrangement.

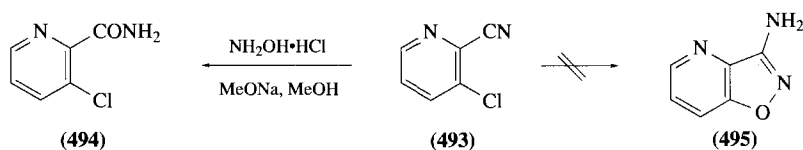


The reaction of (491(*E*)) or (491(*Z*)) with sodium hypochlorite or lead tetraacetate gave 3-methylisoxazolo[4,5-*b*]pyridine 2,4-dioxide (492) in low yield <87H(26)2921> due to the low solubility of the oximes (Scheme 58).



Scheme 58

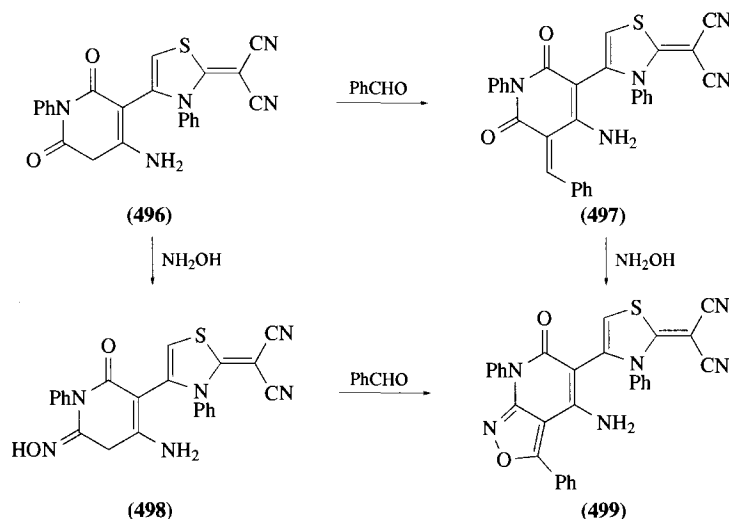
Treatment of 3-chloro-2-cyanopyridine (493) with hydroxylamine hydrochloride in methanol in the presence of sodium methoxide gave 3-chloro-2-carboxamide (494) rather than the expected 3-aminoisoxazolo[4,5-*b*]pyridine (495) (Scheme 59) <87ZC337>.



Scheme 59

7.08.9.13 Isoxazolo[3,4-*b*]pyridines

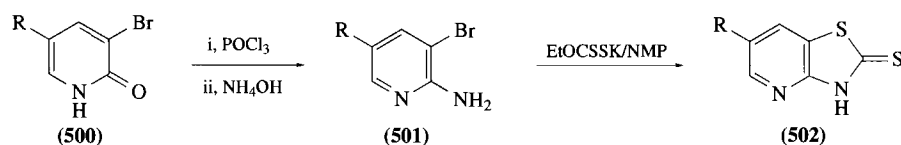
Compound (497), prepared by the condensation of the amine (496) with benzaldehyde in the presence of piperidine, upon treatment with hydroxylamine afforded the orange oxazolo[3,4-*b*]pyridin-2-one (499) (69%) (Scheme 60) <91PS(63)119>. The structure (499) was confirmed by an alternative synthesis involving a reversal of the reactants to compound (496). In this case compound (496) was initially reacted with hydroxylamine to give (498). Subsequent condensation of (498) with benzaldehyde gave (499).



Scheme 60

7.08.9.14 Thiazolo[4,5-*b*]pyridines

Chlorination of the derivatives (500) with phosphorus oxychloride followed by reaction with ammonia, gives the 2-amino-3-bromopyridines (501). Cyclization of (501; R = 4-pyridyl) was accomplished by heating with ethyl potassium xanthate in 1-methyl-2-pyrrolidinone at 160–165°C to give the thiazolo[4,5-*b*]pyridine (502; R = 4-pyridyl) in near quantitative yield (Scheme 61) <94JMC248>.

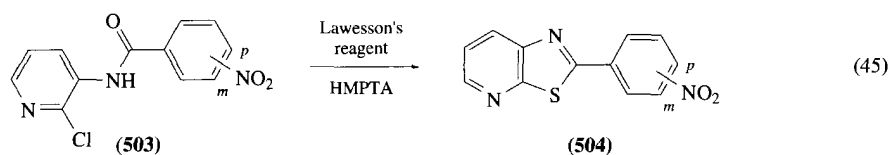


Scheme 61

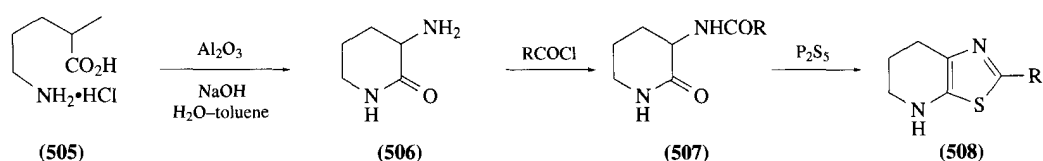
7.08.9.15 Thiazolo[5,4-*b*]pyridines

The use of Lawesson's reagent to cyclize 2-chloro-3-acylamidopyridines (503) furnishes 2-substituted thiazolo[5,4-*b*]pyridines (504) (Equation (45)) <89JHC289, 90JHC1825>. Heating compounds

(503) with Lawesson's reagent in HMPT for 3 h at 140 °C gave good yields of the thiazolopyridines (504).



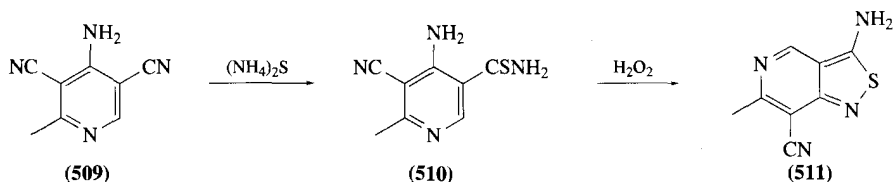
A variety of 2-substituted 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines have been prepared from 3-aminopiperidin-2-one (506), synthesized by lactamization of ornithine (505) (Scheme 62). After acylation at the exocyclic amine group, the amides (507) were reacted with phosphorus pentasulfide (or Lawesson's reagent) in pyridine to give 2-substituted 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines (508) in moderate yield (94JHC877).



Scheme 62

7.08.9.16 Isothiazolo[4,3-*c*]pyridines

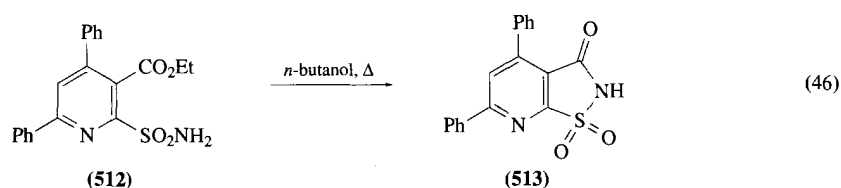
Treatment of 4-amino-3,5-dicyano-2-methylpyridine (509) with ammonium sulfide at 45 °C for 10 h gave only 4-amino-3-cyano-2-methyl-5-thiocarbamoylpyridine (510). Oxidation of this thioamide (510) with hydrogen peroxide gave the 3-aminoisothiazolo[4,3-*c*]pyridine (511) in good yield (Scheme 63) (80BRP2074565).

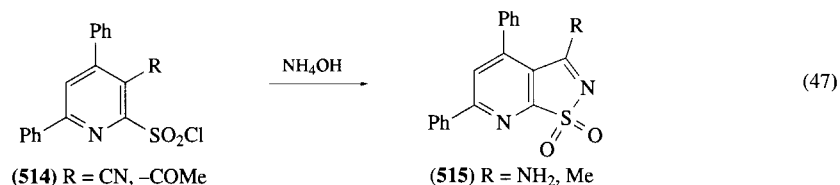


Scheme 63

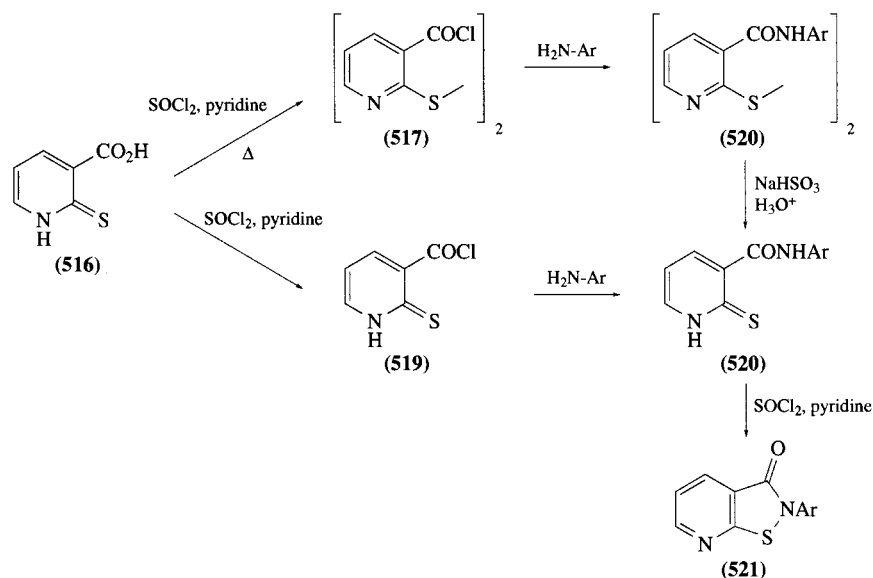
7.08.9.17 Isothiazolo[5,4-*b*]pyridines

Isothiazolo[5,4-*b*]pyridine-1,1-dioxides (513) have been prepared by a direct synthesis (Equation 46) (90M281). 3-Carboethoxy-4,6-diphenylpyridine-2-sulfonamide (512) cyclizes in butanol at reflux temperature to give 3-oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-*b*]pyridine-1,1-dioxide (513) (50%). Similarly, the reaction of 3-cyano- and 3-acetyl-4,6-diphenyl-2-pyridinesulfonyl chlorides (514) with ammonia afforded the corresponding 3-amino- and 3-methylisothiazolo[5,4-*b*]pyridine-1,1-dioxides (515) (Equation 47).



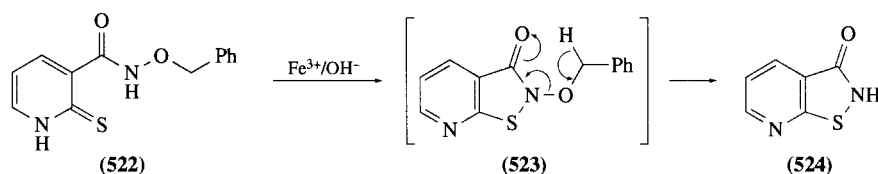


The synthesis of 2-substituted isothiazolo[5,4-*b*]pyridin-3-ones has been extensively investigated in view of their biological activity <85FRP2555450, 85JHC1353, 86EUP178697, 86FES124, 87MI 708-01, 88EUP342105, 90MI 708-02, 94H(38)333>. Reported derivatives substituted at the 4–6 positions include 5-amino <94H(38)333>, 5-nitro <94H(38)333>, 4-methyl <85S861>, 4-phenyl <82JHC1393>, 4,6-dimethyl <86FES124>, or 4,6-diphenyl <90M281>, and 5-amino-6-carbamoyl <87MI 708-01> derivatives. Starting with pyridine-2-thione-3-carboxylic acid (**516**), two different routes have been used to prepare *N*-substituted pyridine-2-thione-3-carboxamides (**520**), which are subsequently cyclized to the bicyclic system (**521**) (Scheme 64). The reaction of the acid (**516**) with thionyl chloride at room temperature gives pyridine-2-thione-3-carbonyl chloride (**519**). Carrying out the reaction at reflux in either pyridine <85JHC1353, 88JHC23>, or toluene <94H(38)333> leads to 2,2'-dithio-bis(pyridine-3-carbonyl chloride) (**517**). The treatment of either (**517**) or (**519**) with amines leads to the pyridine-3-carboxamides (**518**) and (**520**) respectively. Oxidation of the amides (**520**) with thionyl chloride in pyridine/chloroform at room temperature, potassium hexacyanoferrate(III) <85S861> or iodine <85S861> gives the isothiazolo[5,4-*b*]pyridin-3-ones (**521**) directly in 77–92% yields. The 2,2'-dithio-bis(pyridine-3-carboxamides) (**518**) were reduced with sodium bisulfite <85JHC1353> and then cyclized or spontaneously disproportionated <94H(38)333> upon a reaction with amines to give the products (**521**).



Scheme 64

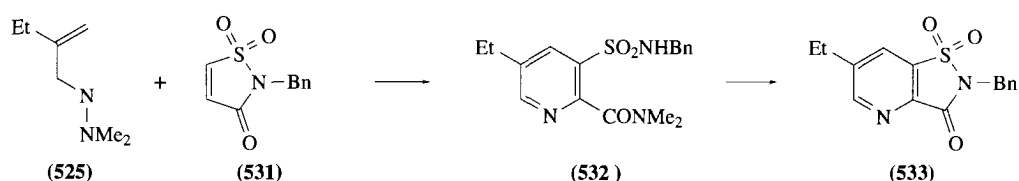
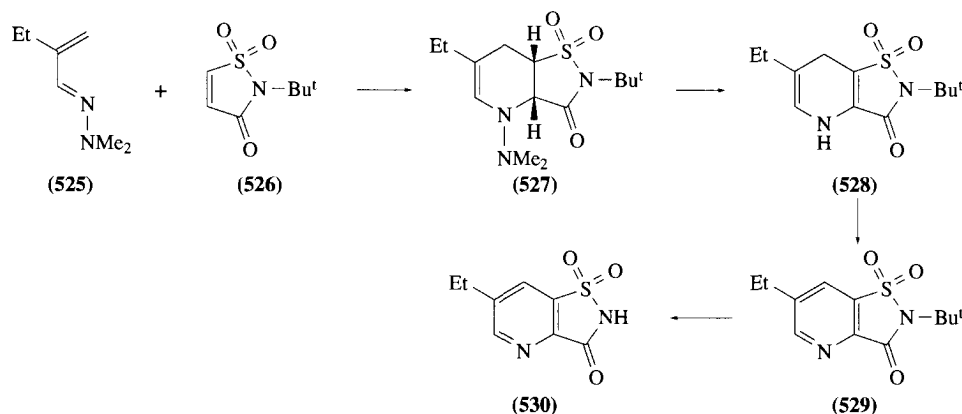
The *N*-(benzyloxy)carboxamide (**522**) upon oxidation cyclizes to furnish an intermediate 2-benzyloxy derivative (**523**) which under basic conditions eliminates benzaldehyde to give the *N*-unsubstituted derivative (**524**) (Scheme 65) <85S861>.



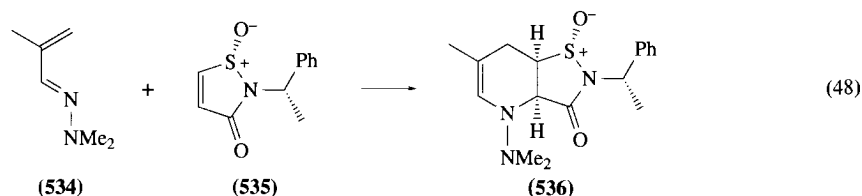
Scheme 65

7.08.9.18 Isothiazolo[4,5-*b*]pyridines

With an interest in preparing aza analogues of saccharin, isothiazol-3(2*H*)-one 1,1-dioxide derivatives (e.g. (526)) have been developed as dienophiles to be used in [4 + 2] cycloaddition reactions (Scheme 66). Condensing these isothiazol-3(2*H*)-on-1,1-dioxides with α,β -unsaturated hydrazones in a Diels–Alder fashion has furnished a method to prepare isothiazolo[4,5-*b*]pyridine analogs of saccharin <89HCA1435, 89TL3061>. For example, [4 + 2] cycloaddition of 1-dimethylamino-1-azabutadiene (525) with the 2-(*t*-butyl)isothiazol-3-one 1,1-dioxide (526) in either acetonitrile or ethanol at 80 °C proceeded with regioselectivity, due mainly to the electronic effects of the 3-oxo substituent, to give 2-(*t*-butyl)-4-dimethylamino-6-ethyl-3a,4,7,7a-tetrahydroisothiazolo[4,5-*b*]pyridin-3-one 1,1-dioxide (527) (79%). Partial oxidation of the adduct (527) by treatment with silica gel in refluxing toluene gave the dihydro derivative (528) (73%). Compound (528) upon reaction with manganese dioxide in acetic acid at 80 °C gave 2-(*t*-butyl)-6-ethylisothiazolo[4,5-*b*]pyridin-3-one 1,1-dioxide (529) (93%). Cleavage of the *t*-butyl group was accomplished by heating (529) in TFA at reflux to afford compound (530). If 2-(benzyl)isothiazol-3-one 1,1-dioxide (531) is used as the dienophile and the solvent is changed to DMSO, *N*²-benzyl-2-(*N,N*-dimethylcarbamoyl)-5-ethylpyridin-3-sulfonamide (532) is the major product (Scheme 67). Compound (532) may be cyclized to the 6-ethylisothiazolo[4,5-*b*]pyridin-3-one 1,1-dioxide (533) by treatment with a mixture of acetic acid and sulfuric acid at 100 °C.

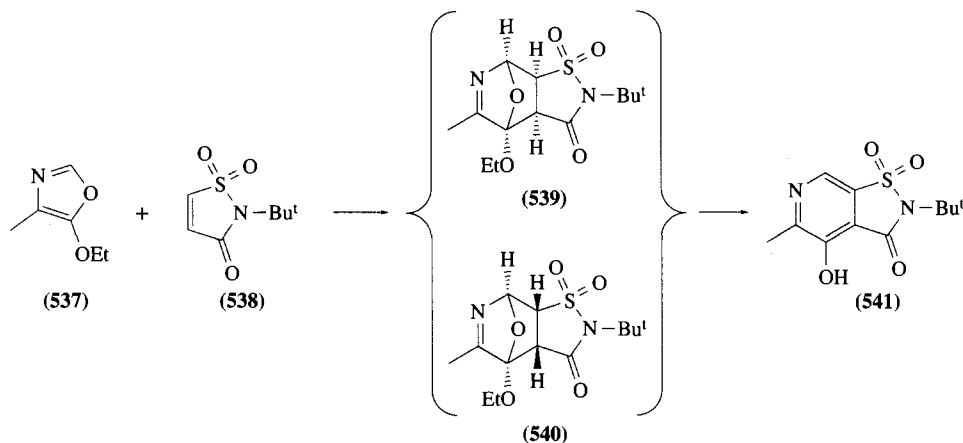


The Diels–Alder [4 + 2] cycloaddition of the homochiral dienophile 2-((*S*)-1-phenylethyl)-1,2-thiazolin-3-one-(*S*)-1-oxide (535) with 1.1 equiv. of 1-dimethylamino-1-azabutadiene (534) in acetonitrile at 70 °C proceeded with regioselectivity and with greater than 98% diastereoselectivity to give the adduct (536) in 85% yield (Equation (48)) <89TL3061>. In this reaction the regiochemistry is controlled by the acrylate substructure while the sulfinyl group inductively activates the C=C double bond.



7.08.9.19 Isothiazolo[5,4-*c*]pyridines

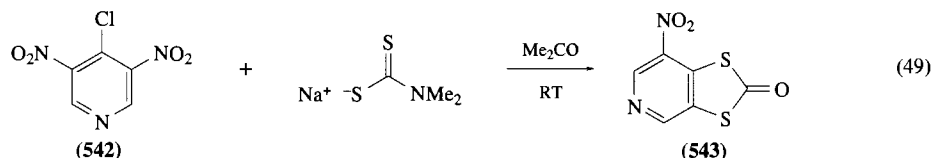
Isothiazolo[5,4-*c*]pyridines have been prepared by a Diels–Alder reaction (Scheme 68) (90HCA69). The regioselective [4 + 2] addition of the dienophile 2-(*t*-butyl)isothiazol-3-one 1,1-dioxide (538) with 5-ethoxy-4-methyloxazole (537) in benzene at room temperature gave a 5:3 mixture of the *exo* to *endo* adducts (539) and (540) in an overall 85% yield. The two adducts (539) and (540) were surprisingly stable and separable by fractional crystallization from a methylene chloride/hexane mixture. Bubbling a stream of anhydrous hydrochloric acid into an ethanolic solution of these adducts (539) and (540) gave the isothiazolo[5,4-*c*]pyridine (541) as its hydrochloride in 63% yield.



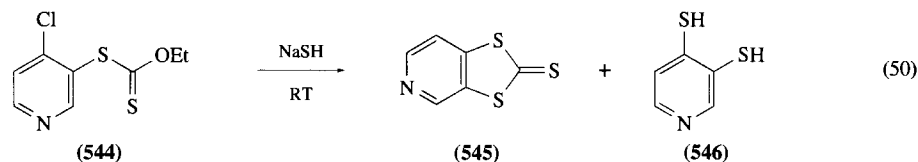
Scheme 68

7.08.9.20 1,3-Dithiolo[4,5-*c*]pyridines

The 1,3-dithiolo[4,5-*c*]pyridine ring system has been prepared by the reaction of 4-chloro-3,5-dinitropyridine (542) with sodium dimethyldithiocarbamate at 10–20°C in acetone which furnished 7-nitro-1,3-dithiolo[4,5-*c*]pyridin-2-one (543) (45%) (Equation (49)) (81JHC1581).

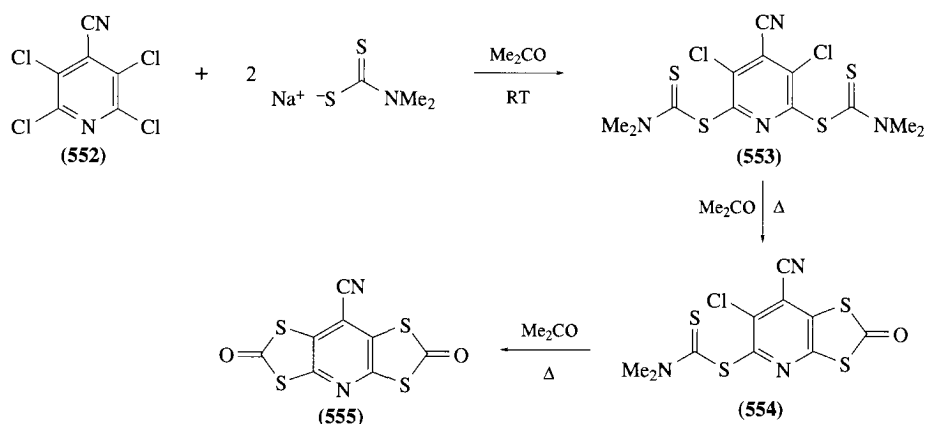
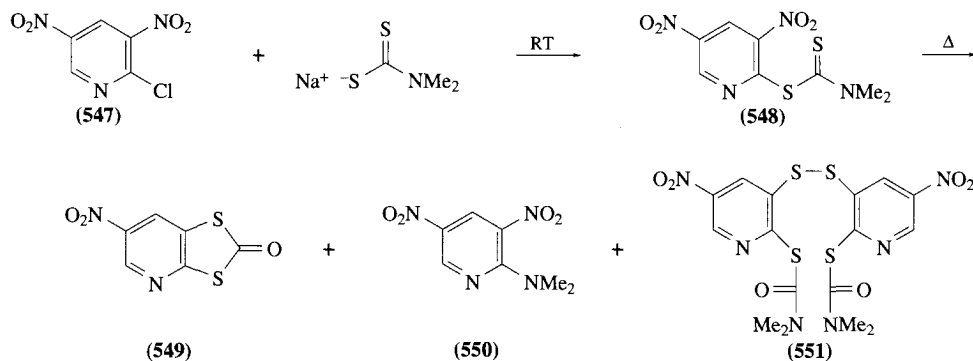


The reaction of ethyl (*S*)-(4-chloro-3-pyridyl)xanthate (544) with sodium hydrosulfide gave 1,3-dithiolo[4,5-*c*]pyridine-2-thione (545) along with 3,4-dithiopyridine (546) (Equation (50)) (77RZC2435).

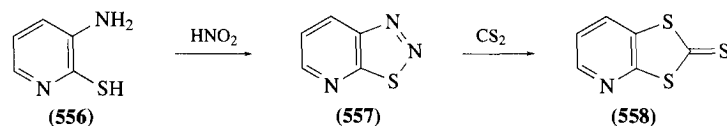
7.08.9.21 1,3-Dithiolo[4,5-*b*]pyridines

The 1,3-dithiolo[4,5-*b*]pyridin-2-one (549) has been prepared in a two-step procedure (Scheme 69) (81JHC1581). Treatment of 2-chloro-3,5-dinitropyridine (547) with sodium dimethyldithiocarbamate in anhydrous acetone at 25°C overnight afforded 3,5-dinitropyridyl-2-dimethyldithiocarbamate (548) (82%) as a stable crystalline solid. Heating (548) at reflux in acetone afforded a mixture of compounds from which 6-nitro-1,3-dithiolo[4,5-*b*]pyridin-2-one (549) (7%), 2-dimethyl-

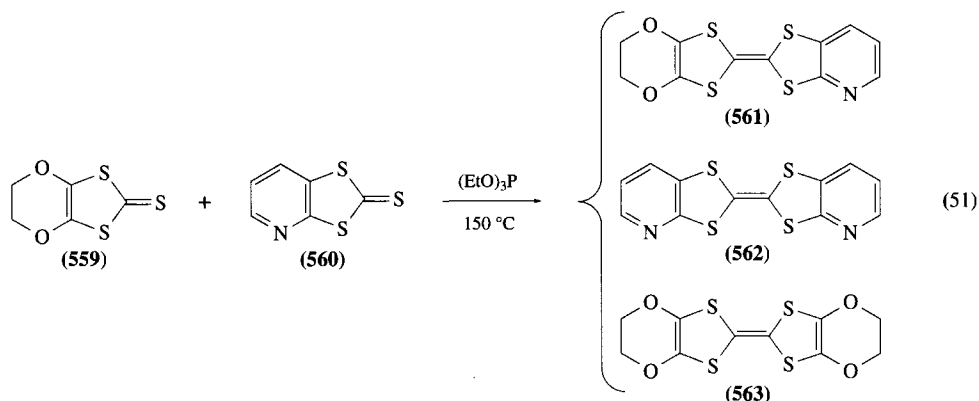
amino-3,5-dinitropyridine (**550**) (3%) and (*S,S'*)-[2,2'-dithiobis(nitropyridyl)]bis(*N,N*-dimethylcarbamothioate) (**551**) (23%) were isolated. Treatment of the disulfide (**551**) with sodium hydrosulfide in DMSO at room temperature gave 6-nitro-1,3-dithiolo[4,5-*b*]pyridin-2-one (**549**) (31%). Using similar reaction conditions <90DOK(312)147> the reaction of 4-cyano-2,3,5,6-tetrachloropyridine (**552**) with 2 equiv. of sodium dimethyl dithiocarbamate in acetone at room temperature for 3 h gave the disubstituted pyridine derivative (**553**) (Scheme 70). Heating (**553**) at reflux in acetone promoted conversion to the 1,3-dithiolo[4,5-*b*]pyridin-2-one (**554**) and 8-cyano-bis(1,3-dithiolo[4,5-*b*:4',5'-*e*])pyridine-2,6-dione (**555**) in 10% and 50% yields, respectively.



Diazotization of 3-amino-2-thiopyridine (**556**) gave thiadiazolo[5,4-*b*]pyridine (**557**) which on treatment with carbon disulfide at 220°C furnished 1,3-dithiolo[4,5-*b*]pyridine-2-thione (**558**) (46%) (Scheme 71) <78PJC2039>.

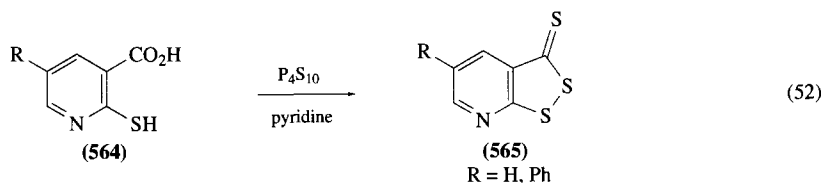


Ethylenedioxy-pyridino[4,5-*b*]tetrathiafulvalene (**561**) has been prepared as an example of an unsymmetrical π -donor capable of electron conduction. The compound (**561**) was prepared via cross-coupling 1,3-dithiolo[4,5-*b*]pyridin-2-one (**560**) with 4,5-ethylenedithio-3,1-dithiol-2-thione (**559**) by heating in triethylphosphite at 150°C for 5 h (Equation (51)). The reaction afforded the desired product (**561**) (6%) together with the self-coupled products (**562**) and (**563**) <90ZN(B)1216>.

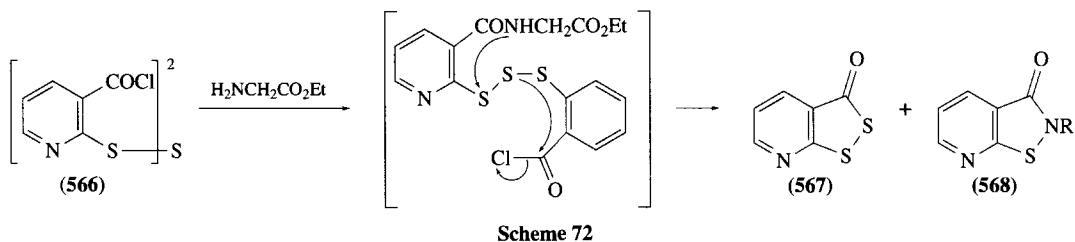


7.08.9.22 3H-1,2-Dithiolo[3,4-b]pyridines

2-Thiopyridin-3-carboxylic acid (**564**) or 5-substituted derivatives on treatment with phosphorus pentasulfide in refluxing pyridine furnished 1,2-dithiolo[3,4-b]pyridines (**565**) in moderate yields (Equation (52)) <82JHC1393>.

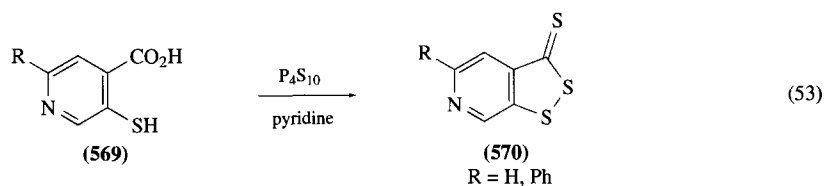


Treatment of compound (**566**) with ethyl glycinate gave 1,2-dithiolo[3,4-b]pyridin-3-one (**567**) in low yield along with the isothiazolo[5,4-b]pyridin-3-one (**568**). This reaction occurs most probably via the mechanism shown in Scheme 72 <94H(38)333>.



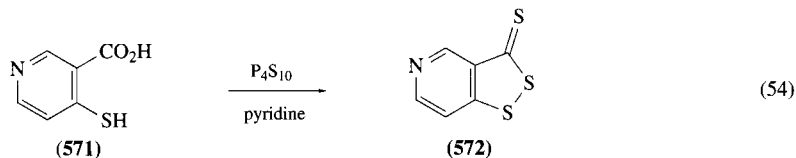
7.08.9.23 3H-1,2-Dithiolo[3,4-c]pyridines

3-Thiopyridine-4-carboxylic acid (**569**) or related 5-substituted derivatives on treatment with phosphorus pentasulfide in refluxing pyridine give 1,2-dithiolo[3,4-c]pyridines (**570**) in moderate yields (Equation (53)) <82JHC1393>.

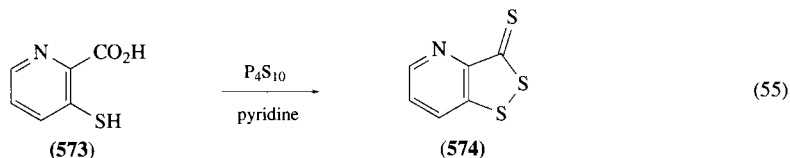


7.08.9.24 3*H*-1,2-Dithiolo[4,3-*c*]pyridines

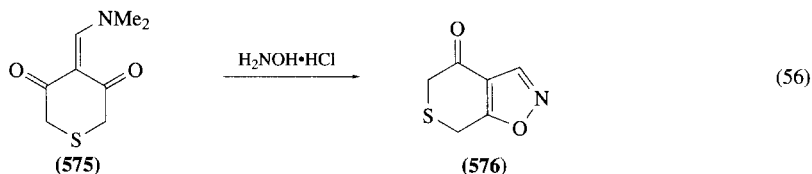
4-Thiopyridine-3-carboxylic acid (**571**) on treatment with phosphorus pentasulfide in refluxing pyridine gives 1,2-dithiolo[4,3-*c*]pyridine (**572**) in moderate yield (Equation (54)) <82JHC1393>.

**7.08.9.25 3*H*-1,2-Dithiolo[4,3-*b*]pyridines**

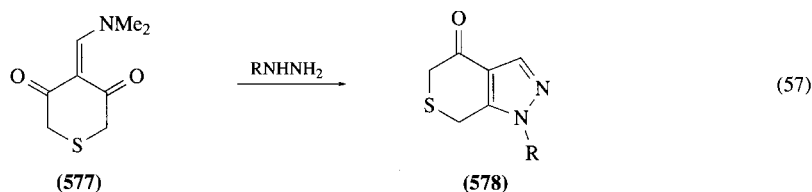
3-Thiopyridin-2-carboxylic acid (**573**) on treatment with phosphorus pentasulfide in refluxing pyridine gives 1,2-dithiolo[4,3-*b*]pyridine (**574**) in moderate yield (Equation (55)) <82JHC1393>.

**7.08.9.26 Thiopyrano[4,3-*d*]isoxazoles**

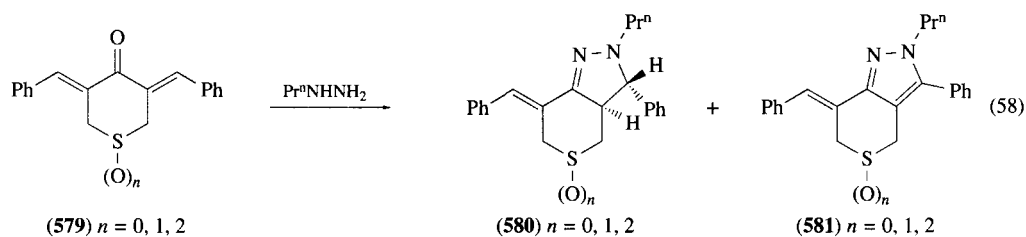
Treatment of 4-dimethylaminomethylene-2*H*-thiopyran-3,5-(4*H*,6*H*)-dione (**575**) with hydroxylamine hydrochloride in refluxing MeOH gives compound (**576**) in good yield (Equation (56)) <84JHC1437>.

**7.08.9.27 Thiopyrano[3,4-*c*]pyrazoles**

The 5,7-dihydro compounds can be prepared by treatment of the enamine (**577**) with substituted hydrazines to produce the derivatives (**578**) (Equation (57)) <84JHC1437>. The cyclization proceeds in two steps, i.e. an initial nucleophilic displacement of dimethylamine by hydrazine, followed by cyclization.

**7.08.9.28 Thiopyrano[4,3-*c*]pyrazoles**

Reaction of the ketones (**579**) with *n*-propylhydrazine in refluxing MeOH gave a mixture of 2,3,3a,4,6,7-hexahydrothiopyrano[4,3-*c*]pyrazoles (**580**) (19–65%) together with the tetrahydrothiopyrano[4,3-*c*]pyrazoles (**581**) (3–26%) (Equation (58)) <79JOC2513, 79JOC2518, 82JMC1482>.

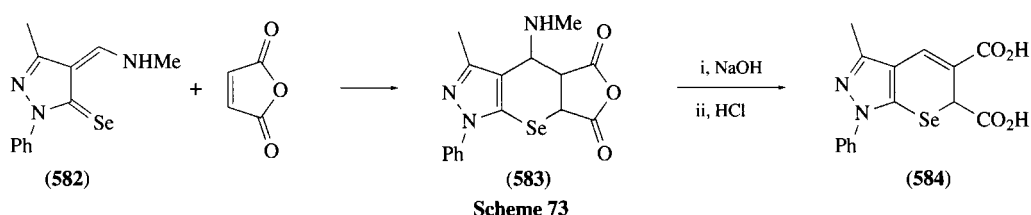


7.08.9.29 Thiopyrano[2,3-*c*]pyrazoles

Thiopyrano[2,3-*c*]pyrazoles have been prepared by the condensation of maleic anhydride with pyrazol-5-thiones in a manner similar to the preparation of the selenopyrano[2,3-*c*]pyrazoles described in Section 7.08.9.30 <79KGS527>.

7.08.9.30 Selenopyrano[2,3-*c*]pyrazoles

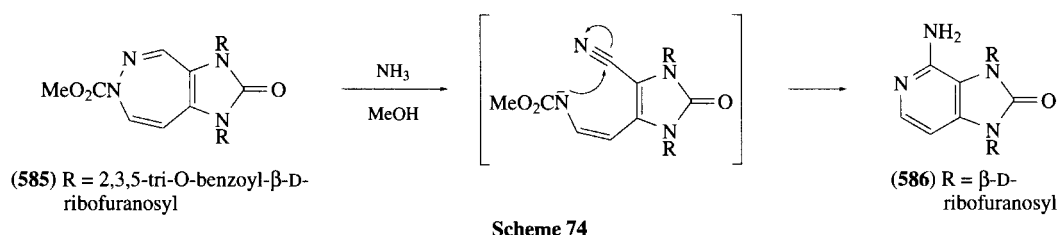
The cycloaddition of maleic anhydride to 3-methyl-4-methylaminopyrazol-5-selenone (582) in dioxane gave 4,5,6-tetrahydroselenopyrano[2,3-*c*]pyrazole-5,6-dicarboxylic acid anhydride (583) (75%). Treatment of this adduct (583) with base promoted the elimination of methylamine giving the diacid (584) (Scheme 73) <79KGS527>.



7.08.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER BICYCLIC RING SYSTEM

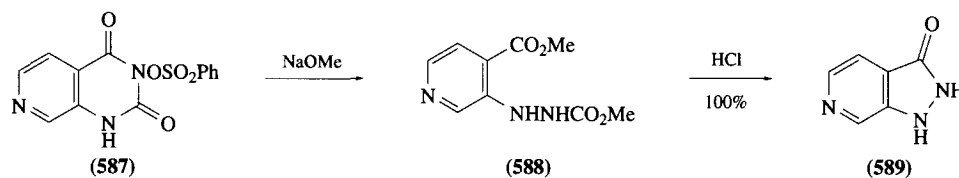
7.08.10.1 Imidazo[4,5-*c*]pyridines

The imidazo[4,5-*d*][1,2]diazepine diribonucleoside (585) upon treatment with methanolic ammonia at room temperature undergoes a base-catalyzed ring contraction of the diazepine ring to give 4-amino-1,3-dihydro-1,3-bis(β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-2-one (586) (58%) (Scheme 74) <86T1511>.



7.08.10.2 Pyrazolo[3,4-*c*]pyridines

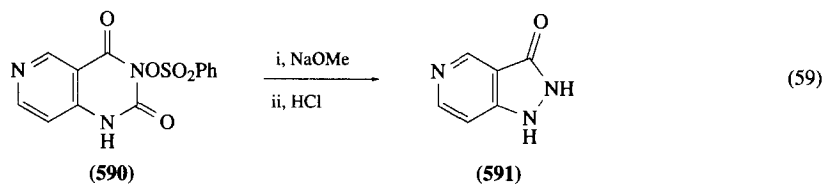
Ring opening of 3-(phenylsulfonyloxy)pyrido[3,4-*d*]pyrimidine-2,4-dione (**587**) with sodium methoxide, followed by a Lossen rearrangement gave the hydrazinopyridine ester (**588**) which in refluxing acid yielded 1*H*-pyrazolo[3,4-*c*]pyridin-3-one (**589**) (Scheme 75) <74JHC163>.



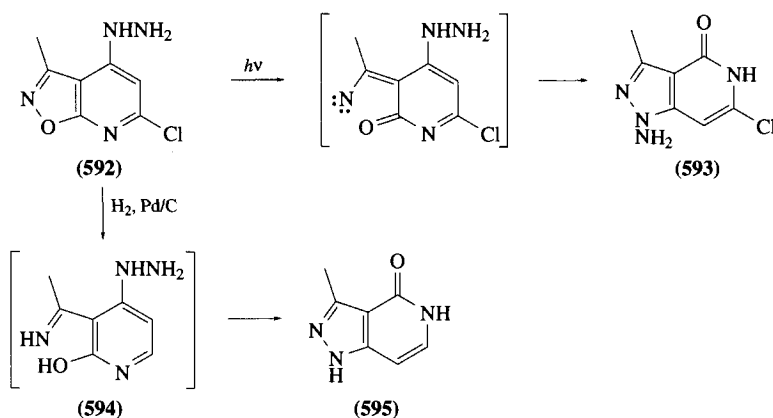
Scheme 75

7.08.10.3 Pyrazolo[4,3-*c*]pyridines

Using the general method described in Section 7.08.10.2 <74JHC163> 3-(phenylsulfonyloxy)pyrido[4,3-*d*]pyrimidine-2,4-dione (**590**) ring opens with sodium methoxide and rearranges to a hydrazinopyridine ester, which in refluxing acid yields 1*H*-pyrazolo[4,3-*c*]pyridin-3-one (**591**) (Equation (59)).



Photochemical irradiation of 4-hydrazinoisoxazolo[5,4-*b*]pyridines affords pyrazolo[4,3-*c*]pyridines via cleavage of the N—O bond to give nitrene intermediates which then evolve into the final products by an intramolecular attack of the hydrazine group <88H(27)1899>. For example, irradiation of 6-chloro-4-hydrazino-3-methylisoxazolo[5,4-*b*]pyridine (**592**) with a water-cooled low-pressure mercury immersion lamp (6W) gave 1-amino-6-chloro-3-methylpyrazolo[4,3-*c*]pyridin-4-one (**593**) (60%) (Scheme 76).

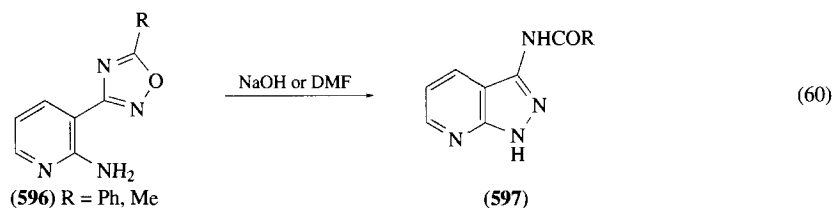


Scheme 76

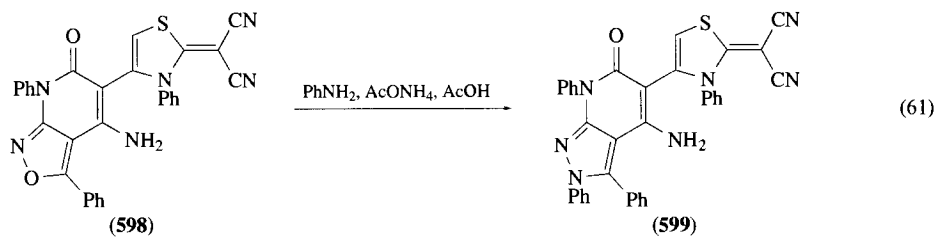
In a related reaction, catalytic hydrogenation of compound (**592**) reductively ring opens the isoxazole ring to give the intermediate (**594**), and a subsequent intramolecular attack by the adjacent hydrazino group on the resulting 1-iminoethyl group followed by dehydrochlorination gives 3-methylpyrazolo[4,3-*c*]pyridin-4-one (**595**).

7.08.10.4 Pyrazolo[3,4-*b*]pyridines

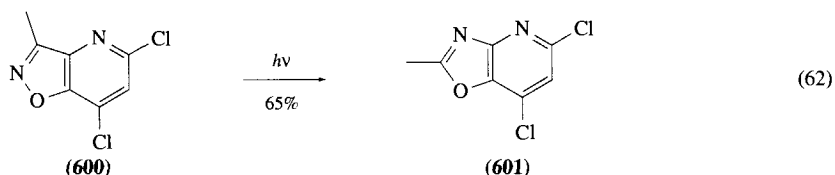
Mononuclear heterocyclic rearrangement of 3-(2-aminopyridinyl)-1,2,4-oxadiazoles (**596**) has been accomplished by heating in DMF with or without the presence of base affording 3-(acylamino)pyrazolo[3,4-*b*]pyridines (**597**) in excellent yield (Equation (60)) <82JCS(P1)759>. Electron-attracting groups (R) at the 5-position of the oxadiazole ring system accelerate the rearrangement.



In an interesting reaction, the oxazolo[3,4-*b*]pyridine (**598**) was converted to the pyrazolo[3,4-*b*]pyridine (**599**) (70%) by heating at reflux in a mixture of aniline, ammonium acetate, and glacial acetic acid for 2 h <91PS(63)119>. The authors propose that the reaction proceeds by ring opening of the isoxazole ring by aniline with the formation of a phenylhydrazino intermediate which then cyclizes (Equation (61)).

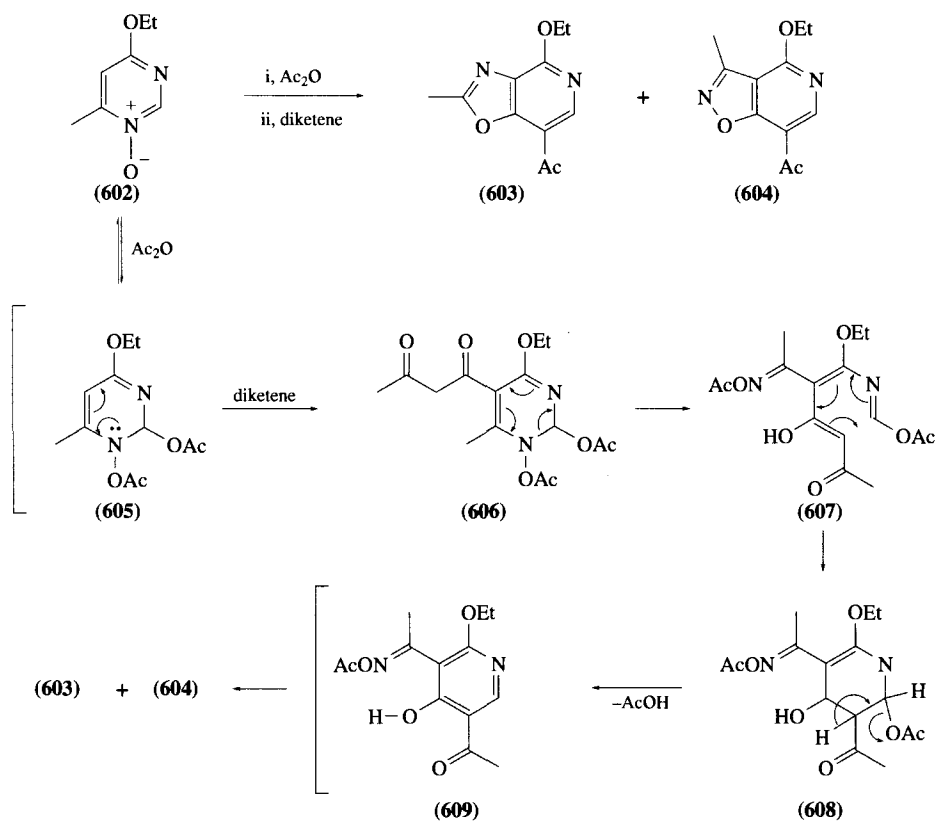
7.08.10.5 Oxazolo[4,5-*b*]pyridines

Photorearrangements of isoxazolopyridines to the corresponding oxazolopyridines are quite general <88H(27)1899>. Irradiation of 5,7-dichloro-3-methylisoxazolo[4,5-*b*]pyridine (**600**) gave 5,7-dichloro-2-methyloxazolo[4,5-*b*]pyridine (**601**) (Equation (62)).

7.08.10.6 Oxazolo[4,5-*c*]pyridines

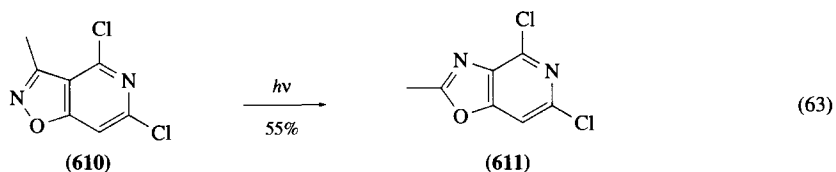
Treatment of 4-ethoxy-6-methylpyrimidine-1-oxide (**602**) with acetic anhydride at 25–35°C in chloroform followed by the addition of diketene at <20°C caused an exothermic reaction from which was isolated 7-acetyl-4-ethoxy-2-methyloxazolo[4,5-*c*]pyridine (**603**) (22%) and 7-acetyl-4-ethoxy-3-methylisoxazolo[4,5-*c*]pyridine (**604**) (8%) <88CPB168>. A plausible mechanism for the formation of the isomers (**603**) and (**604**) is shown in Scheme 77. Acetylation with acetic anhydride furnishes an initial intermediate, 1,2-diacetoxy-1,2-dihydropyrimidine (**605**). Electrophilic attack by diketene at C-5 then yields an acetoacetyl intermediate (**606**). Ring-opening and recyclization of (**606**) then gives via intermediates (**607**) and (**608**) the pyridine (**609**). Compound (**609**), which is not

isolated in the reaction, then either undergoes a Beckmann rearrangement and subsequent cyclization to give compound (603), or will cyclize directly to afford the isomer (604).



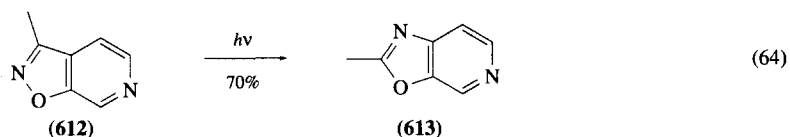
Scheme 77

Irradiation of 5,7-dichloro-3-methylisoxazolo[4,5-*c*]pyridine (610) gives 5,7-dichloro-2-methyl-oxazolo[4,5-*c*]pyridine (611) (Equation (63)) <81TL2121, 88H(27)1899>.



7.08.10.7 Oxazolo[5,4-*c*]pyridines

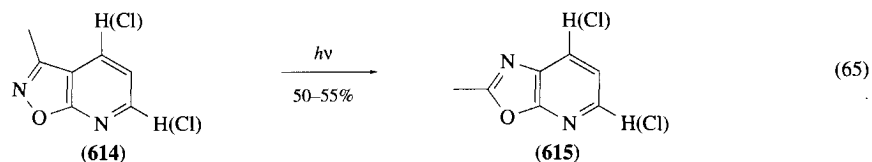
Irradiation of 3-methylisoxazolo[5,4-*c*]pyridine (612) gives 2-methyloxazolo[5,4-*c*]pyridine (613) (Equation (64)) <88H(27)1899>.



7.08.10.8 Oxazolo[5,4-*b*]pyridines

Irradiation of the 3-methylisoxazolo[5,4-*b*]pyridines (614) gives the 2-methyloxazolo[5,4-*b*]pyridines (615) (Equation (65)) <88H(27)1899, 90JPC5271>. In a flash photolysis study it was found that a

ketenimine and a spiroazirine intermediate most probably account for the final products. Acid catalysis plays an important part in the formation of the 2-methyloxazolo[5,4-*b*]pyridine (**615**) from the intermediate spiroazirine.

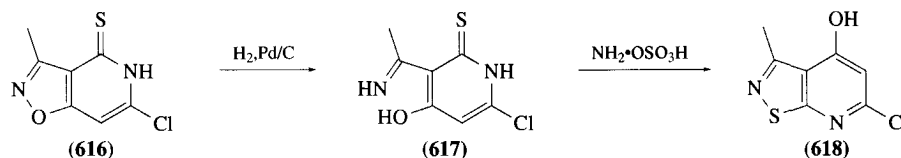


7.08.10.9 Isoxazolo[4,5-*c*]pyridines

Treatment of 4-ethoxy-6-methylpyrimidine 1-oxide (**602**) with acetic anhydride at 25–35°C in chloroform followed by the addition of diketene at <20°C caused an exothermic reaction from which was isolated 7-acetyl-4-ethoxy-3-methylisoxazolo[4,5-*c*]pyridine (**604**) (8%) and 7-acetyl-4-ethoxy-2-methyloxazolo[4,5-*c*]pyridine (**603**) (22%) <88CPB168>. A plausible mechanism for the formation of both isomers (**604**) and (**603**) is described in Section 7.08.10.6.

7.08.10.10 Thiazolo[5,4-*b*]pyridines

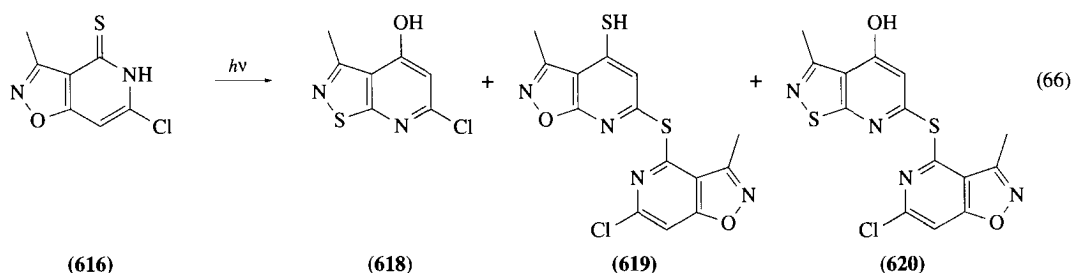
Isoxazolo[4,5-*c*]pyridines have been converted into thiazolo[5,4-*b*]pyridines by three methods. Catalytic hydrogenation of compound (**616**) using palladium on carbon (10%) in aqueous sodium hydroxide at 50 psi followed by neutralization with HCl to selectively cleave the isoxazole ring afforded 6-chloro-3-(1-iminoethyl)-4-hydroxypyridine-2-thione (**617**) (57%) <90JCS(P1)1477>. Amination of the thione moiety of the imine (**617**) with hydroxylamine-*O*-sulfonic acid and subsequent cyclization affords 6-chloro-4-hydroxy-3-methylisothiazolo[5,4-*b*]pyridine (**618**) (57%) (Scheme 78).

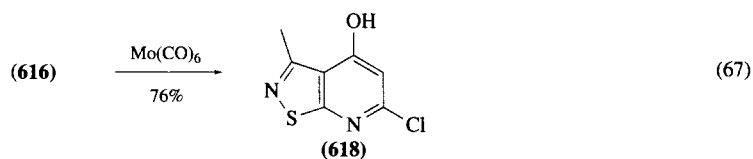


Scheme 78

Irradiation of compound (**616**) with a medium-pressure mercury immersion lamp cooled with a copper(II) sulfate solution (≥ 300 nm) for 3 h gave, after work-up, the isothiazolo[5,4-*b*]pyridine (**618**) in 30% yield along with the side products (**619**) (11%) and (**620**) (22%) (Equation (66)) <90JCS(P1)1477>. The photolysis most probably proceeds via an initial isoxazole cleavage to give a reactive nitrene intermediate. Intramolecular attack of the SH group gives the cyclized isothiazolo[5,4-*b*]pyridine system. The structures of the by-products were unequivocally substantiated by alternative syntheses involving heating the potassium salt of compound (**616**) with an equimolar quantity of either (**616**) or (**618**) in DMF.

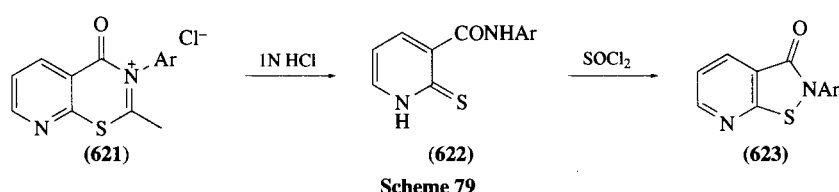
The thermal N—O cleavage of isoxazoles to nitrene intermediates by heating the isoxazole in the presence of hexacarbonylmolybdenum has been reported <85JCS(P1)1401>. Heating the isoxazolo[4,5-*c*]pyridine (**616**) in the presence of an equimolar amount of hexacarbonylmolybdenum in methanol produced a smooth transformation of compound (**616**) into the thiazolo[5,4-*b*]pyridine (**618**) in high yield (Equation (67)) <90JCS(P1)1477>.



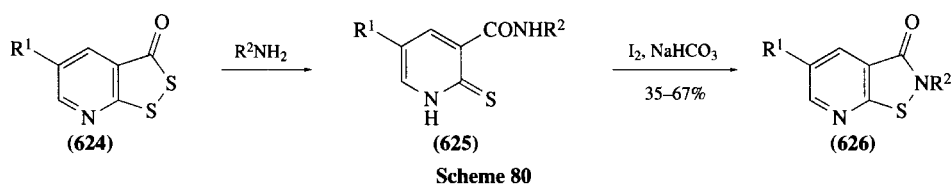


7.08.10.11 Isothiazolo[5,4-*b*]pyridines

In a two-step process, pyrido[3,2-*e*]thiazines (621) have been converted into isothiazolo[5,4-*b*]pyridin-3-ones (Scheme 79). In the first step, the salts (621) are hydrolyzed by treatment with 1 N HCl at room temperature for 12 h to give the amides (622). Subsequent oxidation with SOCl_2 (<85JHC1353> effects closure of the isothiazole ring to give the products (623) in good yield.

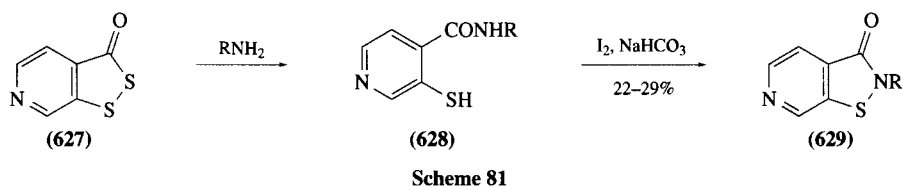


1,2-Dithiolo[3,4-*b*]pyridin-3-ones (624; $\text{R}^1 = \text{H, Ph}$) undergo nucleophilic ring opening upon reaction with amines to give the intermediate 3-carboxamidopyridine-2-thiones (625). Oxidation of the SH group with iodine in the presence of NaCO_3 gives the isothiazolo[5,4-*b*]pyridin-3-ones (626) in variable yields (Scheme 80) (<82JHC1393, 93JAP70469>).



7.08.10.12 Isothiazolo[5,4-*c*]pyridines

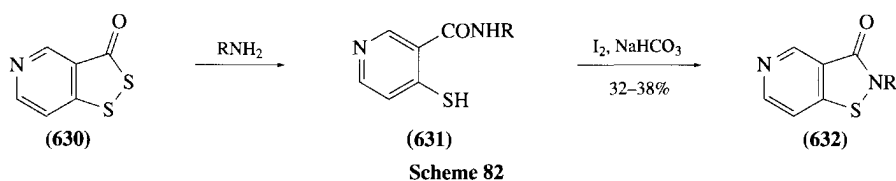
In a reaction similar to that described in Section 7.08.10.11, 1,2-dithiolo[3,4-*c*]pyridin-3-one (627) undergoes nucleophilic ring opening upon reaction with amines to give pyridinecarboxamides (628). Subsequent ring closure via oxidation of the SH group with iodine in the presence of NaHCO_3 gives isothiazolo[5,4-*c*]pyridin-3-ones (629) in variable yields (Scheme 81) (<82JHC1393>).



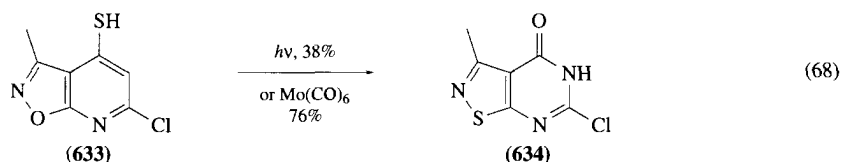
7.08.10.13 Isothiazolo[4,5-*c*]pyridines

There are relatively few reported syntheses of isothiazolo[4,5-*c*]pyridines. The first report involved the transformation of 1,2-dithiolo[4,3-*c*]pyridin-3-ones (630) into isothiazolo[4,5-*c*]pyridin-3-ones (632) (<82JHC1393> via a nucleophilic ring opening to pyridinecarboxamides (631). Subsequent ring

closure via oxidation of the SH group with iodine in the presence of NaHCO_3 gave isothiazolo[5,4-*c*]pyridin-3-ones (**632**) in variable yields (Scheme 82).



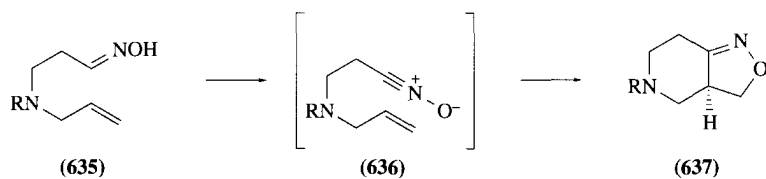
A report in 1990 <90JCS(P1)1477> described two syntheses based on the cleavage of the N—O bond in an isoxazolo[5,4-*b*]pyridine-4-thiol to form a reactive nitrene intermediate which cyclizes to give isothiazolo[4,5-*c*]pyridin-4-ones (Equation (68)). This transformation was carried out by irradiating compound (**633**) with a medium-pressure mercury immersion lamp cooled with copper(II) sulfate solution (≥ 300 nm) for 3 h to give the isothiazolo[4,5-*c*]pyridine (**634**) (38%). Alternatively, heating the isoxazolo[5,4-*c*]pyridine (**633**) in the presence of an equimolar amount of hexacarbonylmolybdenum in methanol produced a thermal N—O cleavage of the isoxazole ring and formed a nitrene-metal intermediate. N—S bond formation by attack of the adjacent SH group on the nitrene resulted in a smooth transformation into the isothiazolo[4,5-*c*]pyridine (**634**) in high yield.



7.08.11 SYNTHESIS FROM ACYCLIC PRECURSORS

7.08.11.1 Isoxazolo[4,3-*c*]pyridines

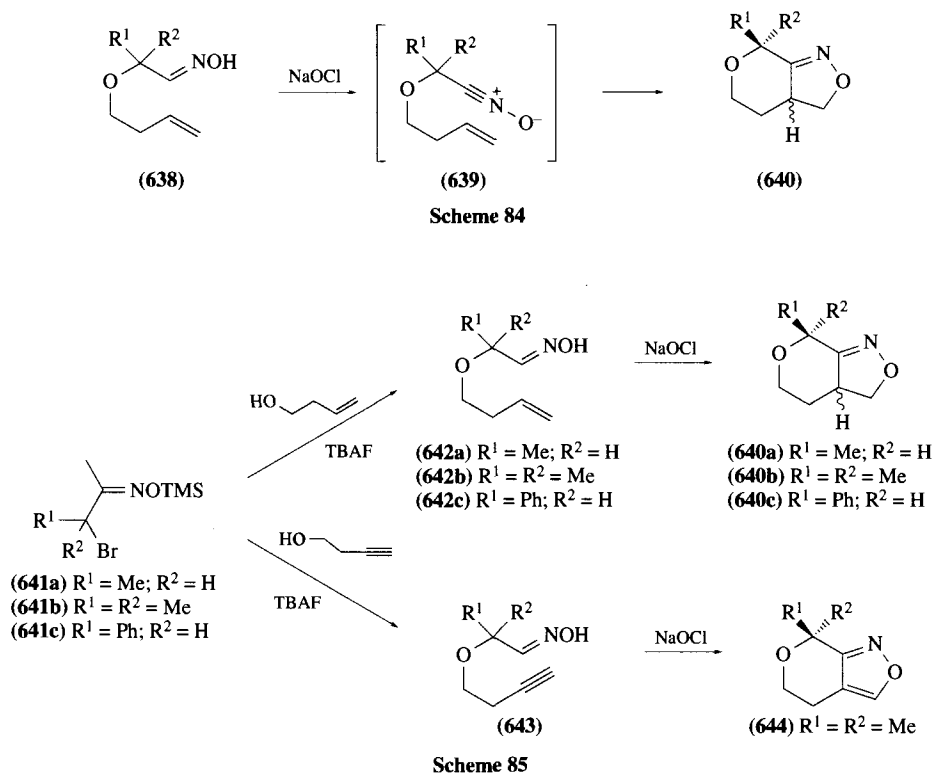
Conversion of the oximes (**635**) to nitrile oxides (**636**) by treatment with chloramine-T led to an intramolecular nitrile oxide-alkene cycloaddition and formation of the derivatives (**637**) (Scheme 83) <88TL5313>.



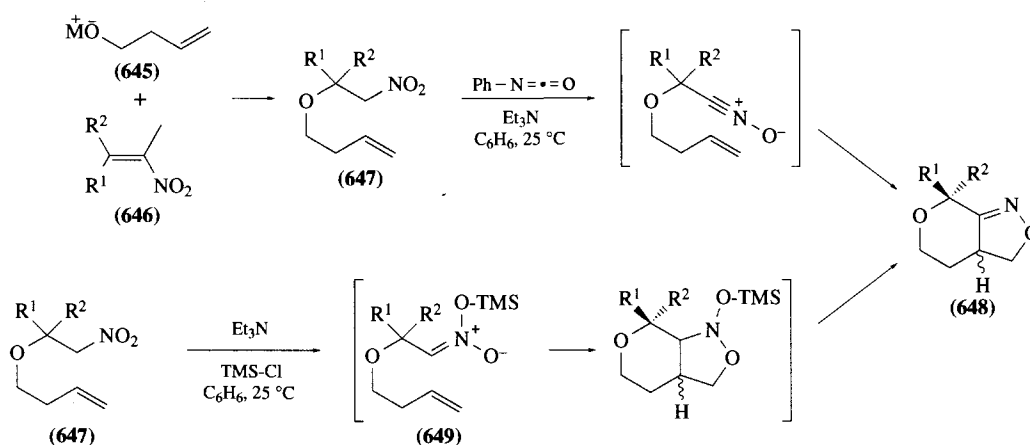
7.08.11.2 4*H*-Pyrano[3,4-*c*]isoxazoles

Studies on the intramolecular 1,3-dipolar cycloaddition of nitrile oxides (INOC) <87TL683, 87TL4097, 89JOC5277, 91TL3605, 91TL4259>, as shown by the oximes (**638**) (Scheme 84) proceeding to (**639**), or silyl nitronates (ISOC) have been extended to include the preparation of 7-substituted-3,3a,4,5-tetrahydro-7*H*-pyrano[3,4-*c*]isoxazoles (**640**) and 7-substituted-4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (**644**) <94JHC797>. By introducing a 1-butenyl ether into the nitrile oxide system, the reaction proceeds to provide the derivatives (**640**) while nitrile oxides containing a propargyl ether undergo cycloaddition to afford 7-substituted-4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (**644**) (Scheme 85). Two approaches have been used to generate the desired cycloadduct precursors (**642**) and (**643**). The reaction of α -bromopropanal *O*-(trimethylsilyl)oximes (**641a-c**) with 1-buten-4-ol in the presence of tetrabutylammonium fluoride gave the oximes (**642a-c**) (56%). Subsequent reaction with sodium hypochlorite gave the nitrile oxides (**639**) which were trapped *in situ* by an intra-

molecular cycloaddition to give the adducts (**640a–c**) as mixtures of stereoisomers with the *cis* isomer predominating. Substituting propargyl alcohol in the reaction gave the oximes (**643**) which upon treatment with sodium hypochlorite led to the fused tetrahydropyrano[3,4-*c*]isoxazoles (**644**).



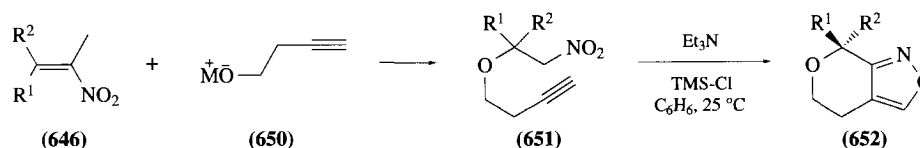
Nitroalkenes have also been used as cycloadduct precursors in the INOC reaction (Scheme 86). The nitroalkene (**647**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{COEt}$) was prepared by the addition of an unsaturated alkoxide (**645**) to the β -nitroenone (**646**). Formation of the required nitrile oxide was accomplished by dehydration of the primary nitromethyl group with phenyl isocyanate and triethylamine. The resulting nitrile oxide underwent cycloaddition and gave the adduct (**648**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{COEt}$).



Scheme 86

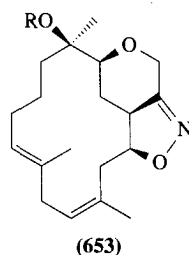
In the ISOC process alkenic silyl nitronates (**649**) are the reactive intermediates which undergo cycloaddition. This species is generated by reacting the nitroalkene (**647**) (Scheme 86) or nitroalkyne (**651**) (Scheme 87) with triethylamine and trimethylchlorosilane in benzene at room temperature for 48 h to give the fused isoxazole systems (**648**) or (**652**). A *cis* relationship between the less bulky C-7 and the hydrogen at C-3a in the products (**648**) is preferred. The yields of the reactions average

88%. The INOC method appears to be more general in nature and can be used to prepare a variety of 7-substituted-3,3a,4,5-tetrahydro-7*H*-pyrano[3,4-*c*]isoxazoles (**640**).



Scheme 87

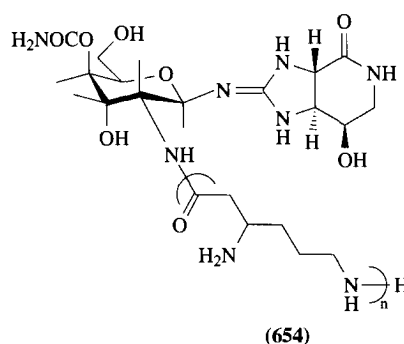
Using the INOC procedure, compound (**653**; $\text{R} = \text{Si}(\text{Me})_2\text{Bu}^t$) was prepared in good yield (<91TL3605>).



7.08.12 IMPORTANT COMPOUNDS AND APPLICATIONS

7.08.12.1 Natural Products

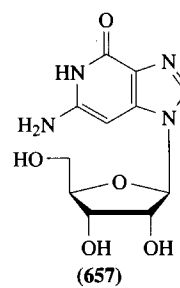
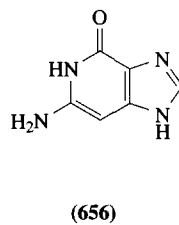
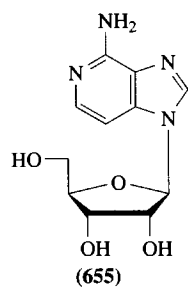
A group of soil actinomycete *Streptomycesnojiriensis* have been identified as producing derivatives of streptothricin antibiotics of the general structure (**654**) which incorporates a hexahydroimidazo[4,5-*c*]pyridine system into the molecule (<87JAN1140>). The total synthesis of streptothricin F has been reported (<82TL2961>).



7.08.12.2 Nucleosides

A number of imidazo[4,5-*c*]pyridine nucleosides (3-deazapurine nucleosides) are of special interest because of their biological properties. 3-Deazaadenosine (**655**) inhibits biochemical methylations by acting as either an inhibitor or substrate of (*S*)-adenosylhomocysteine hydrolase (<79BP1897>). Compound (**655**) has antiviral (<78BBR(82)417>) and antimalarial activities (<80MI 708-01>). 3-Deaz-

aguanine (**656**) and 3-deazaguanosine (**657**) have both shown potent antiviral and antitumor activity
 (76MI 708-01, 77MI 708-01).



7.09

Bicyclic 5-6 Systems: Four Heteroatoms 1 : 3

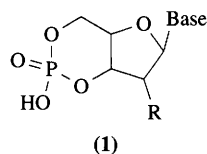
STEPHEN T. MULLINS
Brunel University, Uxbridge, UK

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7.09.1 INTRODUCTION

There have been relatively few reports concerning the chemistry of fused 5–6 bicyclic systems with one heteroatom in the five-membered ring and three in the six-membered ring, so this is a field of chemistry which is very open to new research. The only classes of compounds which have been widely reported are the 3',5'-nucleoside cyclic phosphates (**1**) and their analogues. Many thousands of papers have been written concerning these molecules in contrast to the very small number

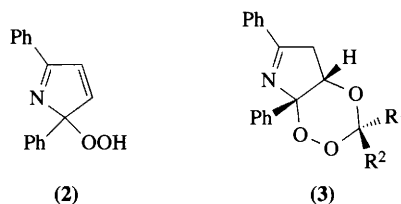
concerned with non-nucleoside molecules. The majority deal with the biochemistry of these important molecules and the effects of their analogues on biological systems; they are not discussed in this chapter.



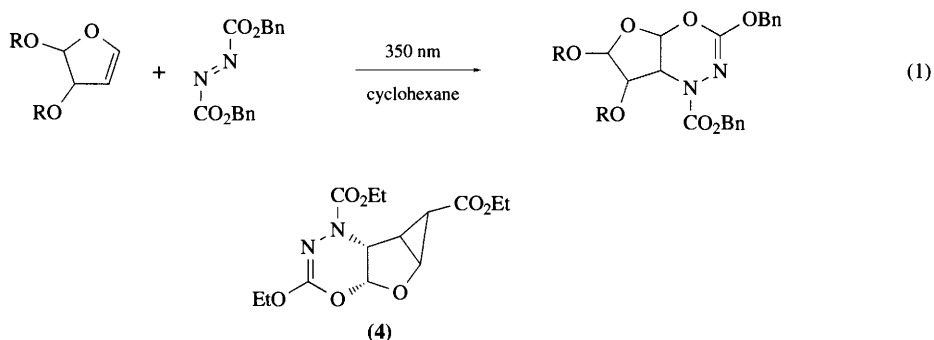
7.09.2 EXPERIMENTAL AND STRUCTURAL METHODS

7.09.2.1 X-ray Diffraction

X-ray diffraction techniques are now widely available and are almost routinely used to determine the structure and absolute stereochemistry of molecules. The structure of a series of 1,2,4-trioxanes has been determined by x-ray crystallography and configurations of the trioxanes assigned by comparison of the x-ray results with spectral properties $\langle 84\text{HCA}2254 \rangle$. 2,5-Diphenyl-2-hydroperoxypyrrole (2) condenses with acetaldehyde or pivalaldehyde to yield the corresponding trioxanes (3; $\text{R}^1 = \text{Me}$, Bu^t , $\text{R}^2 = \text{H}$). Two diastereomers are possible but only the *cis*-isomer is observed, probably due to the presence of the bulky phenyl group at the ring junction disfavoring the orientation of the aldehyde which leads to *trans* ring fusion.

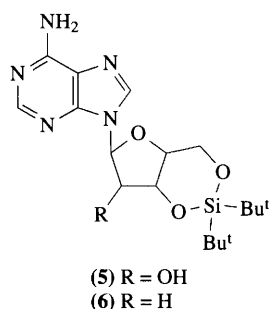


The $[4 + 2]$ cycloaddition reaction of dibenzyl azodicarboxylate and glycals allows the stereoselective introduction of an amino group at the C-2 of a carbohydrate, the key step in the reaction is shown in Equation (1) $\langle 89\text{JA}2295 \rangle$. The nature of the products was determined by x-ray crystallography; NMR and IR data proved insufficient as the two possible products from $[4 + 2]$ and $[2 + 2]$ addition are so similar. X-ray analysis confirmed that the reaction of diethyl azodicarboxylate with cyclopropylfuran gives compound (4), by a $[4 + 2]$ addition, in 94% yield. Further comparison of the NMR and IR data for all the adducts with spectral data of compound (4) confirmed that $[4 + 2]$ adducts were formed consistently.



A major area of research in bio-organic chemistry is the synthesis of analogues of nucleoside cyclic phosphates. The bond lengths and bond angles in the furanose ring of 3',5'-*O*-(di-*t*-butyl-

silanediyl)adenosine (**5**) and its 2'-deoxy analogue (**6**) are confirmed, by x-ray crystallography, to be in good agreement with those determined for cyclic adenosine monophosphate <90AX(C)1509>.

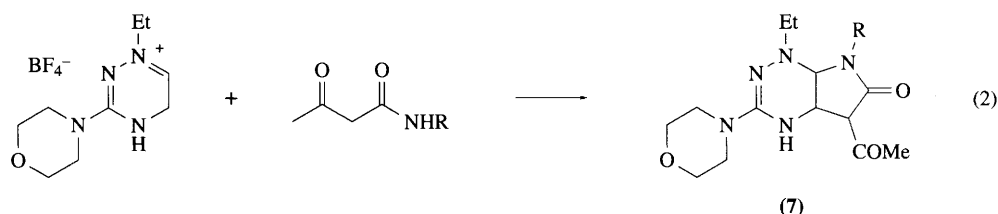


Conformational analysis of silicon analogues of cyclic phosphates, such as (**5**) and (**6**), reveal that they have restricted conformations analogous to those observed for 3',5'-cyclic nucleotides <90CL97>. The pseudorotation angle (P) obtained for compound (**5**) is 43.4° . This indicates that the twist conformation ${}_4T^3$ is in good agreement with the mean value (45°) obtained for 3',5'-cyclic nucleotides.

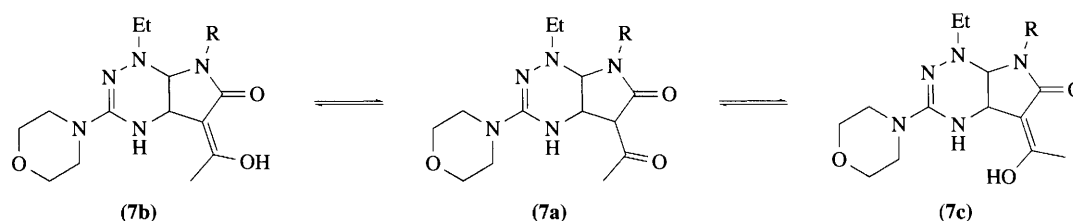
7.09.2.2 NMR Studies

Reports of all new compounds are now almost always accompanied by ^1H NMR spectral details providing evidence of molecular structure, and often conformational and stereochemical information. Thus this section deals only with compounds whose NMR has some particular merit or where NMR has been explicitly used to determine structure.

Reaction of 1,2,4-triazinium salts with amides of acetoacetic acid results in 1,4,4a,5,7,7a-hexahydro-6*H*-pyrrolo[3,2-*e*]-1,2,4-triazin-6-ones via the diaddition of bifunctional nucleophiles at the C-5 and C-6 positions of the 1,2,4-triazine ring (Equation (2)) <88TL1431>.



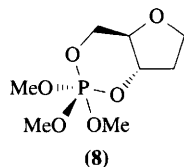
The structures of the adducts were confirmed by ^1H NMR. The regio-orientation of the pyrrole ring in compound (**7**) is apparent from the chemical shifts and splitting patterns of resonances due to the H-4a and H-7a protons. The doublet for H-7a is at a lower field than that for H-4a which appears as a multiplet due to spin-spin coupling with the H-5a, H-7a and H-4 (NH) protons. Proton NMR studies also reveal that there are two enolic forms of the ketone function in (**7**) but the major tautomer is the keto form (**7a**) (Scheme 1).



Scheme 1

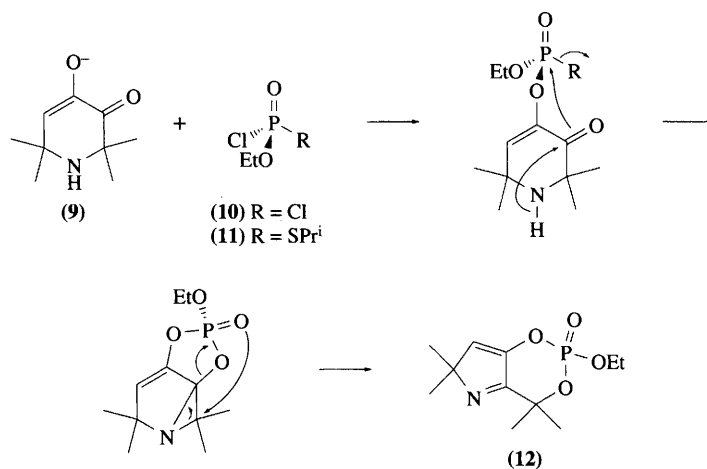
Results from ^1H and ^{13}C NMR studies of cyclic phosphate (**8**) indicate that the 1,3,2-dioxaphosphorinane ring is attached apical/equatorial to phosphorus and in a twist rather than a chair conformation <90JOC3444>. Cyclic pentavalent phosphorus(V) adducts are proposed as inter-

mediates both in the phosphodiesterase-catalyzed hydrolysis <83MI 709-01> of cyclic AMP (AMP = adenosine monophosphate) to 5'-AMP and in the activation by cyclic AMP of protein kinases <84RTC119>. Thus, in an attempt to understand the mechanisms involved in the biological systems, simple model compounds such as compound (8) have been prepared and examined.



Carbon-13 NMR spectra for the cyclic phosphate (8) over a temperature range of 25°C to -113°C show that a slow exchange limit is reached at which the low-field signals due to equatorial methoxy carbons are twice as intense as the resonances at higher field due to the apical methoxy group. This means the 1,3,2-dioxaphosphorinane ring is attached apical/equatorial and not diequatorial.

Phosphorylation of the potassium salt of 2,2,6,6-tetramethylpiperi-3,4-dione (9) by chlorophosphates (10) and (11) leads to the cyclic phosphate derivative (12) (Scheme 2) <85JOC2091>. This unusual product is formed due to intramolecular nitrogen participation and was characterized by ¹³C and ³¹P NMR. There are no resonances in the ¹³C NMR spectra which would indicate the presence of an SPr group in the product and the ³¹P NMR has a resonance at an unusual upfield shift indicating a cyclic phosphate. Structure (12) is consistent with these findings and with the extensive phosphorus-carbon and phosphorus-hydrogen coupling seen in its NMR spectra.



Scheme 2

7.09.2.3 Mass Spectrometry

Molecular ions have been reported for a number of novel 5,6-bicyclic systems discussed in this chapter, but no detailed analysis of mass spectral information has been reported.

7.09.2.4 Infrared Spectroscopy

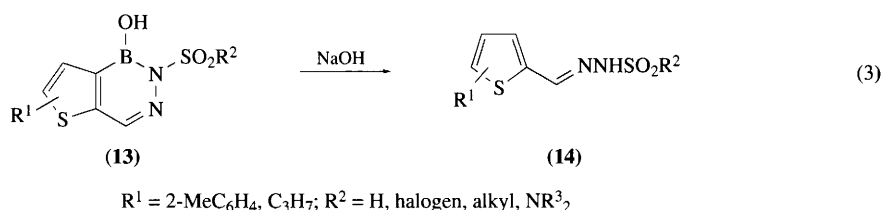
Little use of IR has been made in the structural determination of the compounds discussed in this chapter.

7.09.3 THERMODYNAMIC ASPECTS

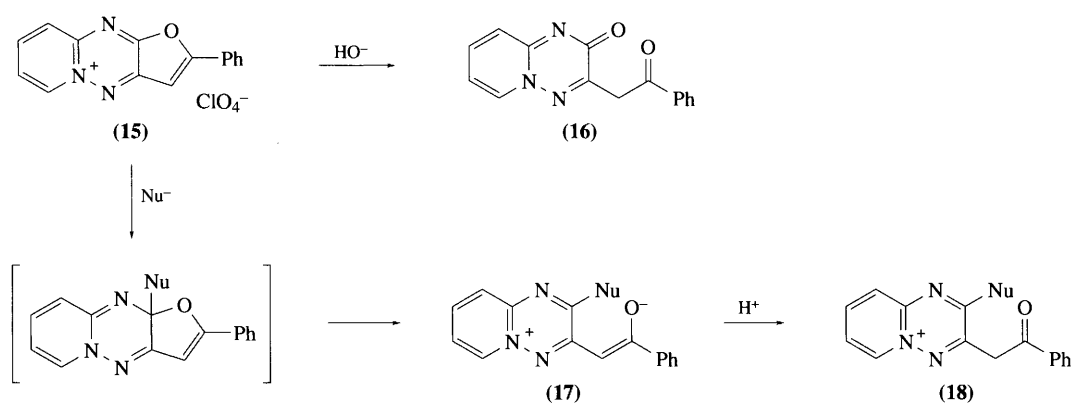
Little has been reported specifically concerning the thermodynamic properties of 5,6-bicyclic systems discussed in this chapter. Where new compounds have been reported, melting points are quoted and thermodynamic properties are discussed in the section on preparative methods.

7.09.4 REACTIVITY OF FULLY CONJUGATED RINGS

1,2-Dihydro-1-hydroxy-thieno[3,2-*d*][1,2,3]diazaborines (**13**) ring open when treated with aqueous 2 M sodium hydroxide at 100 °C to give 2-thiophenecarboxaldehyde organosulfonylhydrazones (**14**) (Equation (3)) <85LA683>.

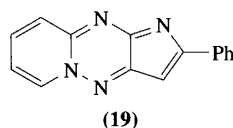


The reaction of the tricyclic furo[2,3-*e*]pyrido[1,2-*b*]-*as*-triazinium salt (**15**) with a variety of nucleophiles has been studied (Scheme 3) <89CB1935>. Compound (**15**) shows a high reactivity towards nucleophiles as do other related bridgehead nitrogen-containing heteroaromatics <87JOC2017>. It reacts readily with aqueous base to yield the ring-opened product (**16**) via attack of a hydroxide ion at the C-10a atom with subsequent opening of the furan ring. Reaction of the salt (**15**) with other nucleophiles such as methoxide or secondary amines also results in opening of the furan ring but zwitterionic products (**17**) are formed. Structure (**17**) is supported by the downfield shift of the C-6 hydrogens adjacent to the positively charged nitrogen, and by the significant negative solvatochromy found in the UV spectrum. Treatment of the mesomeric betaines (**17**) with acid results in formation of the pyrido[1,2-*b*]-*as*-triazinium salts (**18**).

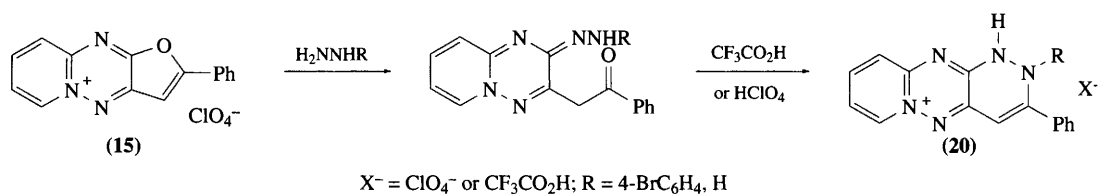


Scheme 3

A novel pyrido[1,2-*b*]pyrrolo[2,3-*e*]-*as*-triazine (**19**) is produced when compound (**15**) is treated with ammonia; ammonia attacks the C-10a carbon and causes ring opening to give the triazinium derivative (**18**; Nu = NH₂) and the amine substituent is then able to react with the carbonyl group of the benzoyl substituent to give the cyclized product (**19**) in high yield.



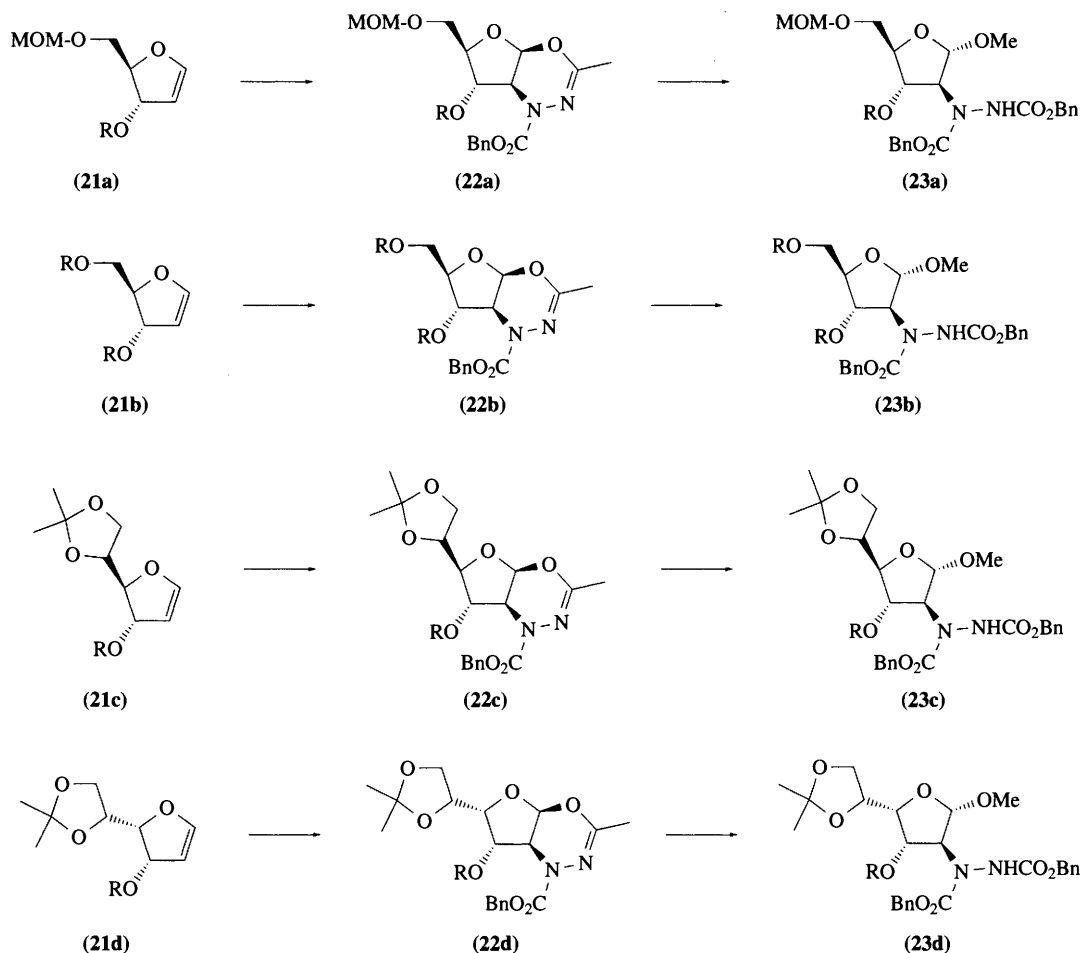
Expansion of the furan ring is achieved by reacting compound **(15)** with hydrazine derivatives to give pyrido[1,2-*b*]pyridazino[3,4-*e*]-*as*-triazinium salts **(20)** (Scheme 4) <90CB1415>.



Scheme 4

7.09.5 REACTIVITY OF NONCONJUGATED RINGS

The cycloaddition of glycols **(21a–d)** and dibenzylazidocarboxylate gives compounds **(22a–d)** in yields greater than 70% (Scheme 5) <87JA285>. These [4 + 2] adducts are useful intermediates in the preparation of 2-amino-2-deoxy carbohydrates <89JA2295>. The cycloaddition is stereospecific and is controlled by the stereochemistry at the C-3 position: stereochemistry has been assigned by nuclear Overhauser enhancement (NOE) studies.

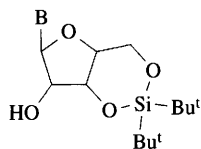


Scheme 5

Treatment of the adducts with catalytic amounts of *p*-toluene sulfonic acid in methanol results in formation of the corresponding methylglycosides **(23a–d)** arising from inversion at C-1. Hydrogenolysis of compounds **(23a–d)** then yields the 2-amino glycosides.

7.09.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Ribonucleosides react with di-*t*-butylsilyl diester (the ditriflate, dinitrate, and diperchlorate have been used) in DMF to give selectively 3',5'-*O*-(di-*t*-butylsilylanediyl)ribonucleosides (**24**) <90CL97>. Conformational analysis using ¹H NMR and x-ray crystallography show that the derivatives of (**24**) have a restricted conformation analogous to 3',5'-cyclic nucleotides. A variety of protecting groups can be introduced at the 2' position, for example, acetyl, tetrahydropyranyl, methoxytetrahydropyranyl and *t*-butyldimethylsilyl. Removal of the di-*t*-butylsilylanediyl group from the derivatives of (**24**) and their 2'-protected analogues is achieved by reaction with tributylamine hydrofluoride under very mild conditions <89CL509>.

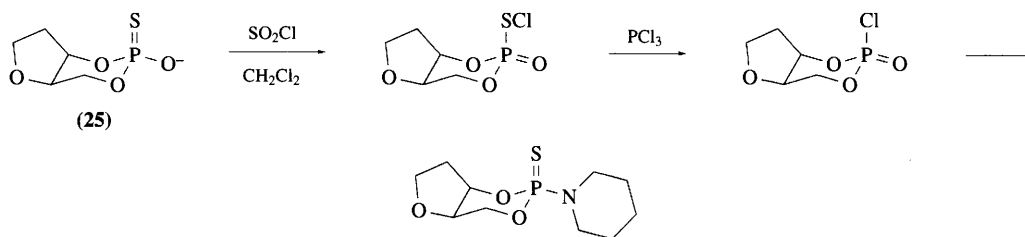


(24)

B	Yield (%)
Uracil	94
Cytosine	90
Adenine	95
Guanine	95

7.09.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The sulfur substituent in the cyclic phosphorothioate (**25**) can readily be converted into a sulphenylchloride by reaction with sulfuryl chloride. This reaction occurs with retention of configuration about the phosphorus atom <85TL443>. Subsequent reaction of the sulphenyl chlorides with phosphorus trichloride leads to stereospecific formation of chlorophosphates (Scheme 6). The stereochemical assignments of the chlorophosphates have been confirmed by converting them into phosphoramidates, by reaction with piperidine, which are readily isolated and purified. Analysis of ³¹P and ¹H NMR spectra of the phosphoramidates then allows assignment of configuration and comparison with the starting chlorophosphates.



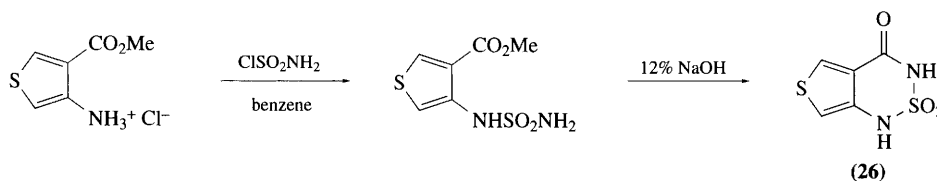
Scheme 6

7.09.8 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

7.09.8.1 Synthesis of the Six-Membered Ring

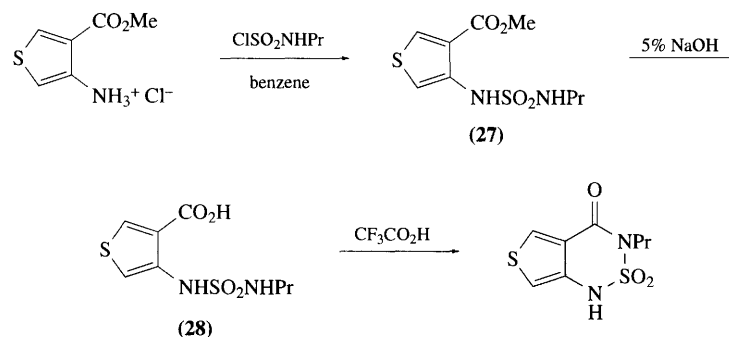
7.09.8.1.1 From [6 + 0] atom fragments

4-Oxo-3,4-dihydro-1*H*-thieno[3,4-*c*][1,2,6]thiadiazine 2,2-dioxide (**26**) is prepared by a two step procedure from 3-amino-4-methoxycarbonylthiophene involving sulfamoylation of the 3-amino group followed by ring closure (Scheme 7) <89S280>.



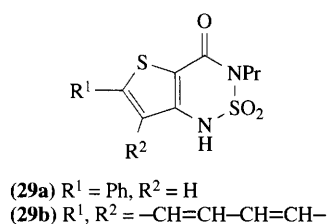
Scheme 7

The cyclization is carried out under basic conditions in most cases. However if the sulfamoyl residue bears a branched alkyl group, as in compound (27), then the cyclization is effected by first isolating the carboxylic acid intermediate (28) and carrying out the cyclization under acidic conditions using trifluoroacetic acid and trifluoroacetic anhydride (Scheme 8).



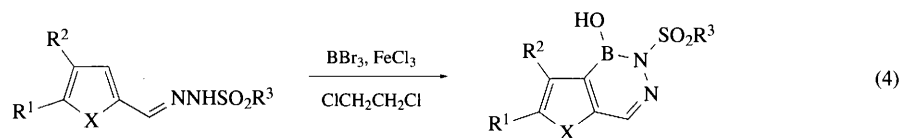
Scheme 8

This methodology has been extended to the synthesis of new thieno[3,2-*c*][1,2,6]thiadiazine 2,2-dioxides bearing substituents on the thiophene ring, for example compounds (29a) and (29b).



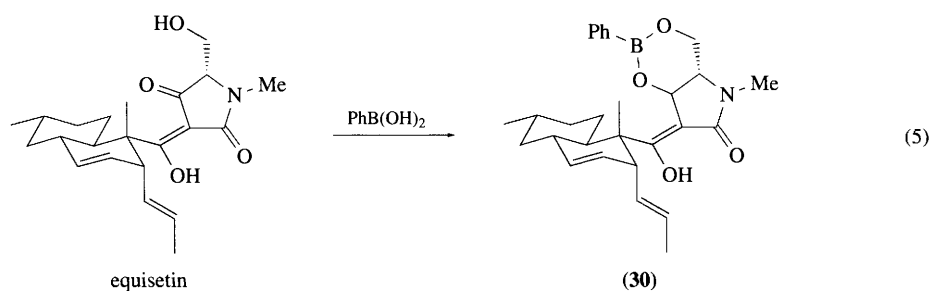
7.09.8.1.2 From [5 + 1] atom fragments

A series of 1,2,3-diazaborine derivatives have been prepared and their antibacterial properties examined. The diazaborine ring is formed by cyclocondensation of a substituted thiophene, pyrrole, or furan with boron tribromide (Equation (4)) <84JMC947>. Higher yields are obtained and shorter reaction times are necessary if Lewis acid catalysts are added, the most effective being FeCl_3 . A variety of substituents on the five-membered ring are tolerated by the cyclisation (for example, alkyl, halogen, amino, alkylamino, and acylamino), if the ring bears electron-withdrawing substituents. However, a reduction in yield is observed.

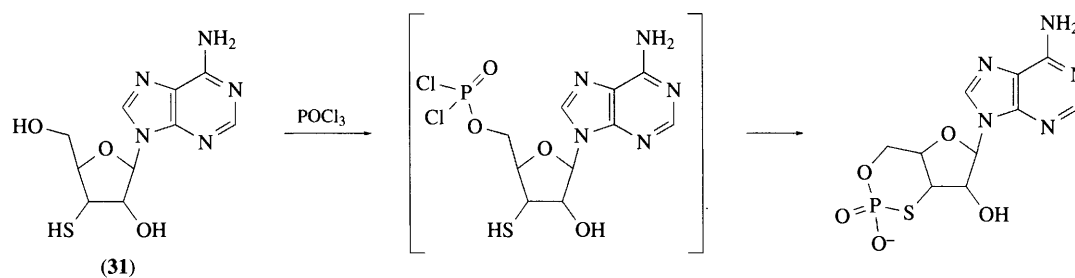


X	R ¹	R ²	R ³	Yield (%)
S	Br	H	4-MeC ₆ H ₄	90
S	H	Br	4-MeC ₆ H ₄	87
S	Br	H	C ₆ H ₅	66
S	Br	H	2-MeC ₆ H ₄	47
S	Me	H	2-MeC ₆ H ₄	78
O	Me	H	4-MeC ₆ H ₄	66
O	Br	H	4-MeC ₆ H ₄	25
O	Br	H	2,4,5-Cl ₃ C ₆ H ₂	84
NMe	H	H	C ₃ H ₇	37
NMe	H	H	4-MeC ₆ H ₄	45

Phenylboronic acid reacts with equisetin, a toxin from *Fusarium equiseti*, to give a 1:1 adduct (**30**) (Equation (5)) <89JA8223>. The reaction occurs under mild conditions and was used in the structural assignment of equisetin. The ¹H NMR of equisetin is poorly resolved, but that of the phenyl boronic ester (**30**) is well resolved and can be mapped out using two-dimensional techniques.

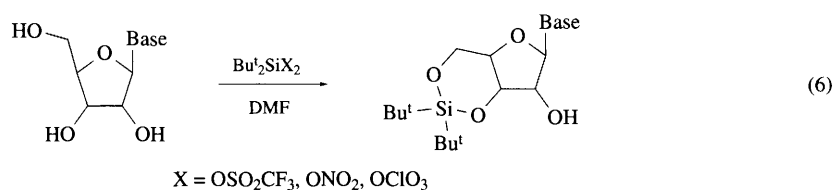


New cyclic AMP analogues have been prepared by phosphorylation of the sulfur analogue of adenosine (**31**) (Scheme 9) <82LA651>.



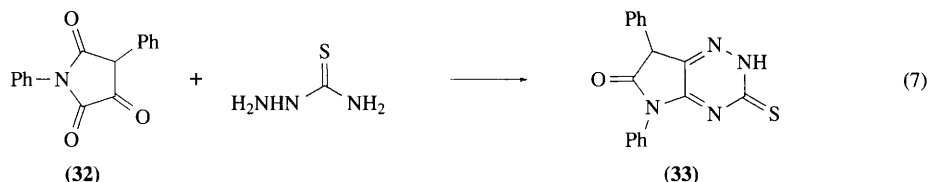
Scheme 9

Silicon containing analogues of nucleoside cyclic phosphates are also readily prepared by reaction of the nucleoside with di-*t*-butylsilicon diesters (Equation (6)) <90CL97>.

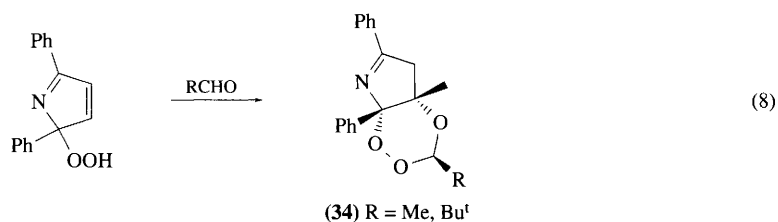


7.09.8.1.3 From [4 + 2] atom fragments

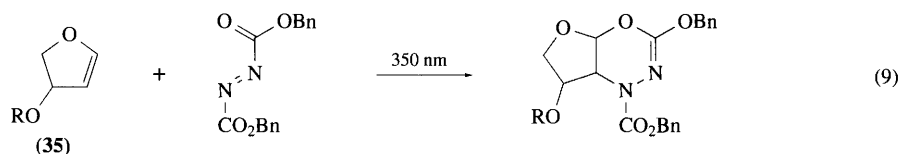
1,4-Diphenylpyrrolidine-2,3,5-trione (**32**) provides two ring atoms when it is condensed with thiosemicarbazide, which provides four ring atoms, to give 1,2,4-triazino[5,6-*b*]pyrrole-3-thione (**33**) in 72% yield (Equation (7)) <90ZN(B)382>. The condensation is carried out in alkaline medium.



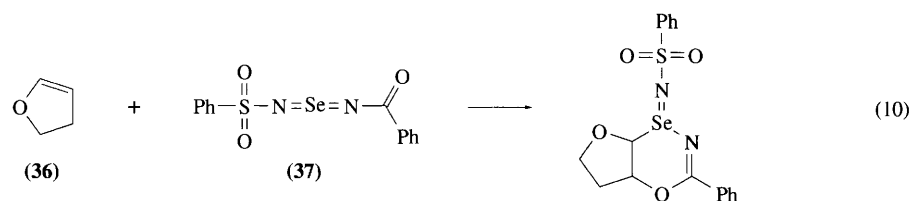
Aldehydes can act as a source of two ring atoms. For example, treating 2,5-diphenyl-2-hydroperoxypyrrole with acetaldehyde or pivalaldehyde affords the corresponding fused bicyclic system (**34**) in moderate yield (Equation (8)) <84HCA2254>. Cyclization occurs by incorporation of the carbonyl function of the aldehyde in the expected electronic sense to link the hydroperoxy group to the double bond of the pyrrole ring. The newly created six-membered ring is fused *cis*- to the pyrrole ring and it is postulated that the selectivity is due to the bulky phenyl substituent at the ring junction disfavoring the formation of the *trans*-isomer.



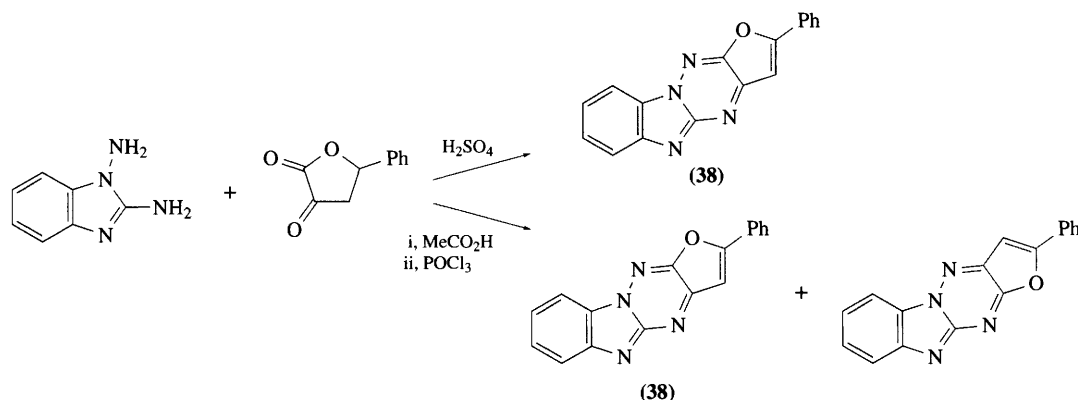
The double bond in glycals such as (**35**) contribute two atoms in a photochemical [4 + 2] cycloaddition reaction with dibenzyl azodicarboxylate (Equation (9)). The adducts so formed are useful intermediates in the preparation of carbohydrates with an amino function at the C-2 position <89JA2295>.



A similar cycloaddition reaction occurs between the glycal (**36**) and the substituted selenium diimide (**37**) (Equation (10)) <83ZOR1622>.



1,2-Diaminobenzimidazole reacts with 5-phenyl-2,3-dihydrofuran-2,3-dione in sulfuric acid conditions to give 2-phenylfuro[3,2-*e*]-1,2,4-triazino[2,3-*a*] benzimidazole (**38**) <87KGS444>. If the reaction is carried out in acetic acid, then both compound (**38**) and its isomer 2-phenylfuro[2,3-*e*]-1,2,4-triazino[2,3-*a*]benzimidazole are formed (Scheme 10).

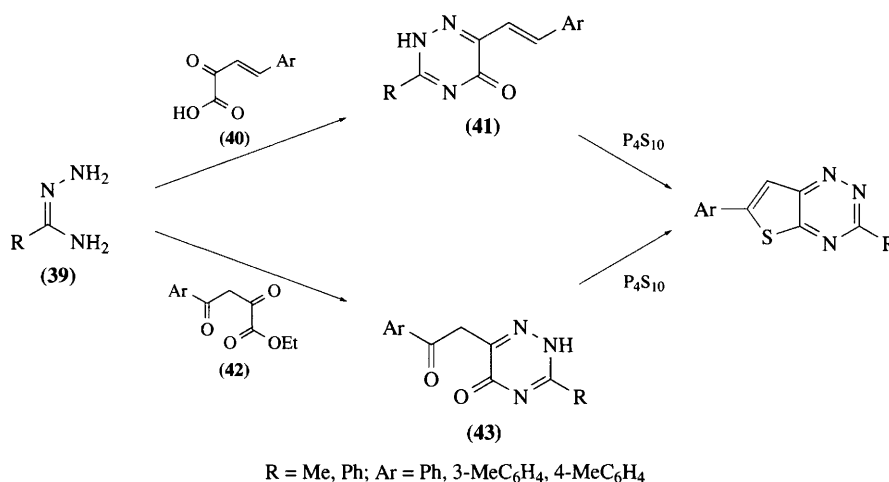


Scheme 10

7.09.8.2 Synthesis of the Five-Membered Ring

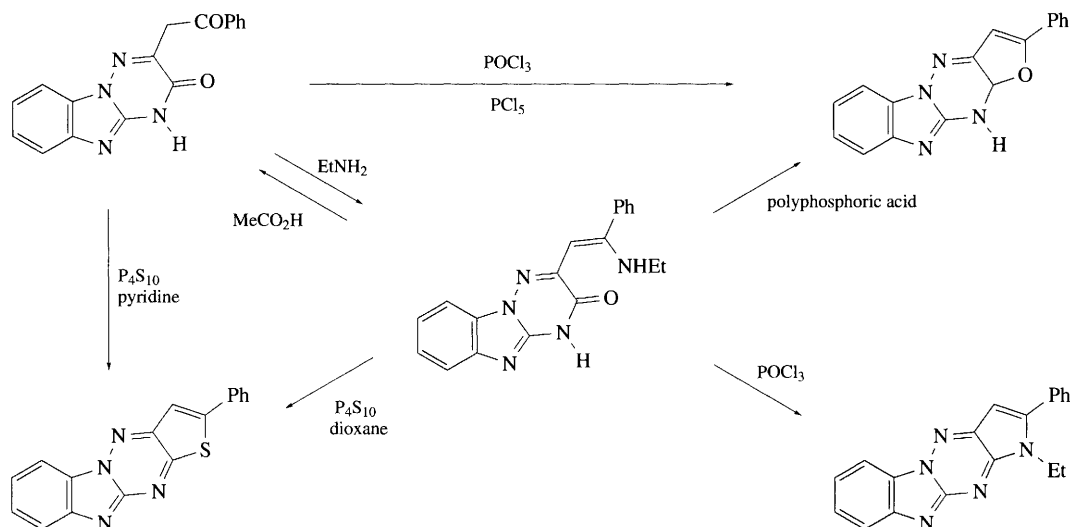
7.09.8.2.1 From [5 + 0] atom fragments

Thieno[2,3-*e*]-1,2,4-triazines are interesting fused heterocycles in that one ring, the thiophene, is π -electron rich but the other ring, the triazine, is π -electron deficient. Thus the thiophene ring is susceptible to electrophilic substitution whereas the triazine ring undergoes nucleophilic substitution at the six-position. These fused heterocycles are prepared by a two step synthesis (Scheme 11). The substituted hydrazones (39) condense with arylidenepyruvic acids (40) to give a substituted triazine (41). Cyclisation to give the thiophene ring is then achieved by heating (41) in pyridine under reflux in the presence of phosphorus pentasulfide (82HC913, 88SUL153). An alternative route is to synthesize the triazine by condensation of hydrazones (39) with ethyl aroylpyruvates (42) to give 3-phenyl-6-acylmethyl-5-oxo-2,5-dihydro-1,2,4-triazines (43) which, when treated with P_4S_{10} in refluxing pyridine, give the desired thieno[2,3-*e*]-1,2,4-triazines. 2-Arylfuro-, 2-arylpyrrolo-, and 2-arylthieno[2,3-*e*]-1,2,4-triazino[2,3-*a*]benzimidazoles are prepared by cyclisation of 2-aroyle-1,2,4-triazino[2,3-*a*]benzimidazol-4*H*-3-ones as shown in Scheme 12 (89KGS928). It should be noted that the product is dependent upon the nature of the dehydrating agent.



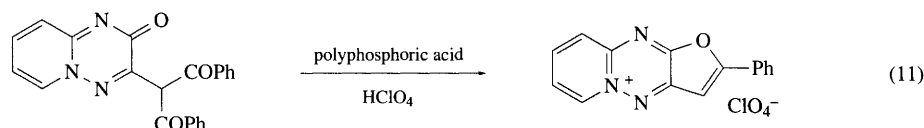
Scheme 11

Fused-*as*-triazinium salts are prepared by a similar route again using dehydrating agents to effect cyclization of a dibenzoyl substituted triazinone to give a furan ring (89CB1935). For example, heating 3-(dibenzoylmethyl)-2*H*-pyrido[1,2-*b*]-*as*-triazin-2-one in polyphosphoric acid at 160°C followed by



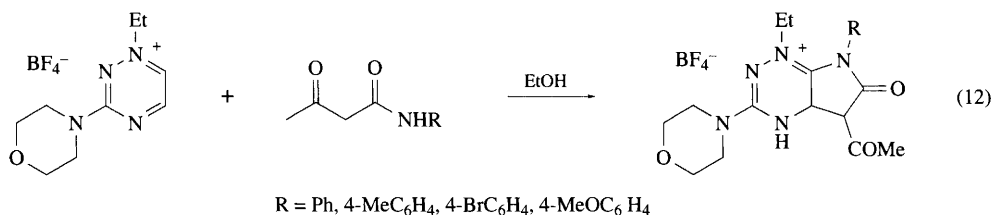
Scheme 12

addition of perchloric acid gives 2-phenyl furo[2,3-*e*]-1,2,4-triazino[2,3-*a*]pyridinium perchlorate in 70% yield (Equation (11)).



7.09.8.2.2 From [3 + 2] atom fragments

Azinium cations undergo cycloaddition reactions with acetoacetamide to give the pyrrolo[3,2-*e*]-1,2,4-triazine ring system (Equation (12)) <89IZV438, 89IZV1501>. The reaction takes place under very mild conditions; an ethanolic solution of the reactants is heated and then allowed to stand at room temperature for two days whereupon the desired fused heterocyclic product crystallizes.



7.09.9 APPLICATIONS

Little has been reported concerning applications of the fused heterocyclic systems discussed in this chapter. As with many other heterocyclic molecules, they have been prepared and their antibacterial activity examined <84JMC947, 87MI 709-01>, but this has not resulted in any molecules with significantly greater antibacterial effect than compounds already available. One interesting use of a phenylboronate system was in the structural determination of the toxin esquisetin from *Fusarium equiseti* (Equation (5)) <89JA8223>. The ^1H and ^{13}C NMR spectra of esquisetin show very broad resonances and are of little use in structural assignment. However, the phenylboronate derivative (**30**) has well resolved NMR spectra and so a structural assignment was possible. One class of compounds which is outside the scope of this review are the 3',5'-nucleoside cyclic phosphates (**1**) and their analogues. Many thousands of reports have been made regarding these important molecules dealing with their synthesis and application in medicine.

7.10

Bicyclic 5-6 Systems: Four Heteroatoms 3 : 1

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7.10.1 INTRODUCTION

While the chemistry of the bicyclic [5-6]heterocycles with 3 : 1-heteroatom orientation is diverse, there has been no compendium on these heterocycles. A review in the early 1980s discussed all the isomeric triazolopyridines <83AHC(34)79> and various aspects of the chemistry of these systems were discussed in parts of the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(6)400, 84CHEC-I(6)415, 84CHEC-I(6)524, 84CHEC-I(6)712, 84CHEC-I(6)731>. Most of the understanding of the chemistry of these systems has been gleaned from various studies of the syntheses of nucleoside mimics or comparative studies of the reactivity of these analogues and the corresponding benzoannulated systems. In spite of the topological similarity of many of these heterocycles, their reactivity varies.

Since many triazolopyridines were prepared as nucleoside mimics, they are often described in the literature using the nucleoside nomenclature format in lieu of the systematic IUPAC nomenclature. Some examples (1)–(3) are shown below in Table 1.

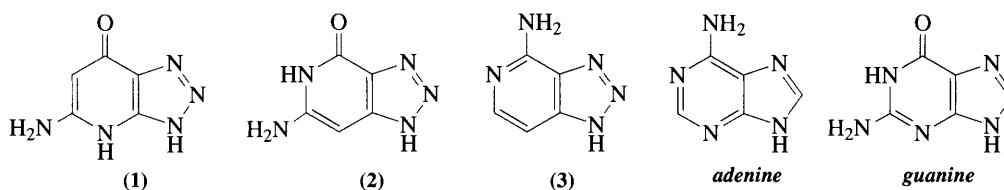


Table 1 Triazolopyridines: nucleoside and IUPAC nomenclature.

Structure	Nucleoside nomenclature	IUPAC nomenclature
(1)	8-aza-1-deazaguanine	5-amino[1,2,3]triazolo[4,5- <i>b</i>]pyridin-7-one
(2)	8-aza-3-deazaguanine (8-aza-3-carbaguanine)	6-amino[1,2,3]triazolo[4,5- <i>c</i>]pyridin-4(5H)-one
(3)	8-aza-3-deazaadenine	4-amino[1,2,3]triazolo[4,5- <i>c</i>]pyridine

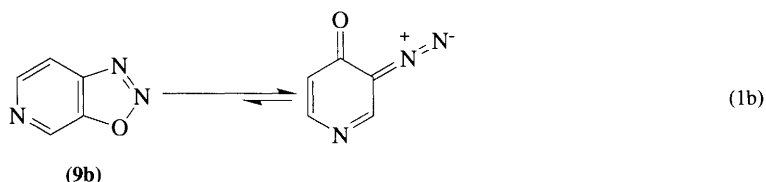
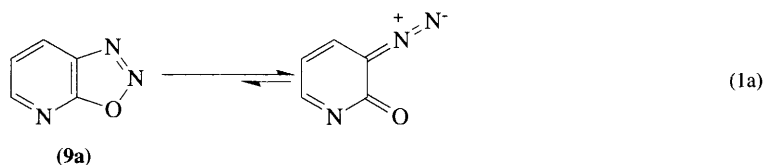
7.10.2 THEORETICAL METHODS

Since there are no extensive studies on the relative aromaticity of the heterocycles covered in this chapter, the relative order of aromaticity of these systems has been gleaned from disparate studies. *A priori*, the combined effects of the π -electron-deficient five-membered heterocycles annulated to a pyridine nucleus provides a series of bicyclic heterocycles with low reactivity towards electrophiles. In the presence of suitable leaving groups, they are prone to undergo nucleophilic substitution. Since these heterocycles are readily obtained from either appropriately substituted pyridines or five-membered heterocycles, methods for direct functionalization of the parent heterocycles are not frequently studied. Based on the diversity of reactions these heterocycles undergo, it can be inferred that the pyridofuroxans are the least aromatic.

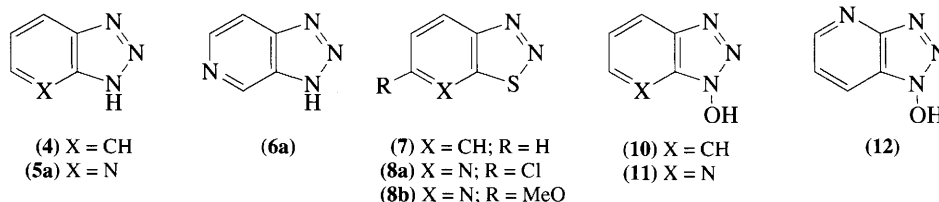
The comparative ionization potentials of various triazolopyridines and [1,2,3]-thiadiazolopyridines versus benzotriazole or benzothiadiazole were determined by electron-impact mass spectrometry (Table 2) <74CS222>. Since their ionization potentials are similar to the benzo-fused analogues, it infers that they have comparable aromaticity profiles. The same technique shows that the [1,2,3]oxadiazolopyridines (**9a,b**) occur exclusively as the *ortho*-quinoid-like pyridodiazoxide tautomers (Equation (1)).

Table 2 Mass spectrometer derived ionization potentials.

Heterocycle	Ionization potential (eV)
Benzotriazole (4)	9.20 $\pm$ 0.05
[1,2,3]Triazolo[4,5- <i>b</i>]pyridine (5a)	9.20 $\pm$ 0.05
[1,2,3]Triazolo[4,5- <i>c</i>]pyridine (6a)	9.10 $\pm$ 0.05
Benzo[1,2,3]thiadiazole (7)	9.50 $\pm$ 0.05
5-chloro[1,2,3]thiadiazolo[5,4- <i>b</i>]pyridine (8a)	9.57 $\pm$ 0.05
5-methoxy[1,2,3]thiadiazolo[5,4- <i>b</i>]pyridine (8b)	9.01 $\pm$ 0.05



The electron-withdrawing effect of the pyridine nucleus is very substantial, as evidenced by comparisons of the pK_a of the benzo-fused systems versus the pyridyl-fused systems. For example, the pK_a of benzotriazole (4) and triazolo[4,5-*b*]pyridine (5a) (in 80% aqueous 2-methoxyethanol) are 9.36 and 7.44, respectively $\langle 75HCA1521 \rangle$. Similarly, the pK_a for *N*-hydroxybenzotriazole (10), 3-hydroxytriazolo[4,5-*b*]pyridine (11), and 1-hydroxytriazolo[4,5-*b*]pyridine (12) are 4.60, 3.28, and 3.02, respectively $\langle 76KGS1418 \rangle$.



7.10.3 EXPERIMENTAL STRUCTURAL METHODS

Extensive nuclear magnetic resonance and ultraviolet spectroscopy methods were reported in the 1970s for establishing the site(s) of *N*-substitution in the triazolopyridines $\langle 72JOC3601, 73JOC1095, 76JOC1449, 78JOC4910 \rangle$. Notably the method of Townsend and co-workers $\langle 76JOC1449 \rangle$, which employs a combination of ^{13}C magnetic resonance chemical shifts and long range ^{13}C - ^1H coupling constant analysis, is a powerful tool for structural studies $\langle 80JCS(P2)1586 \rangle$.

The mass spectral fragmentation patterns of [1,2,3]triazolo[4,5-*b*]pyridines are discussed in Section 7.10.8.1.

7.10.4 THERMODYNAMIC ASPECTS

Nothing is known about the relationship between thermodynamic aspects of these heterocycles versus their physicochemical properties (boiling point, melting point, volatility, chromatographic behavior).

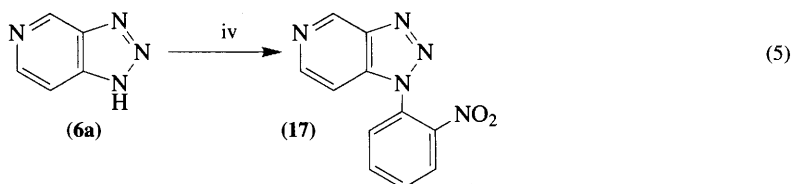
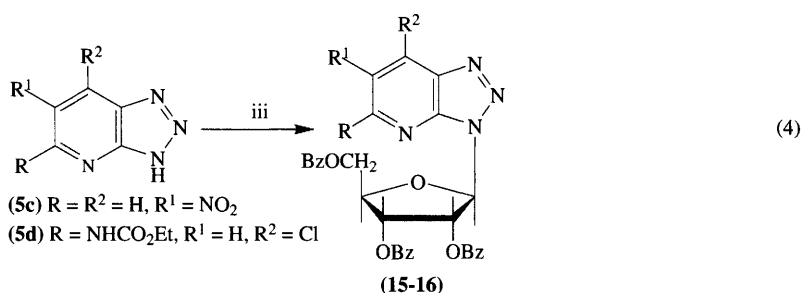
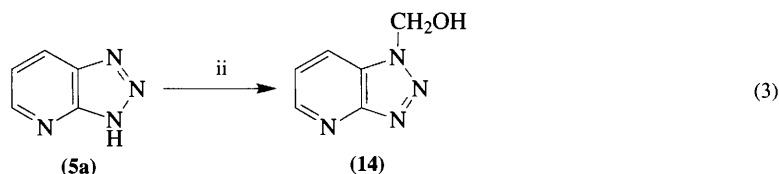
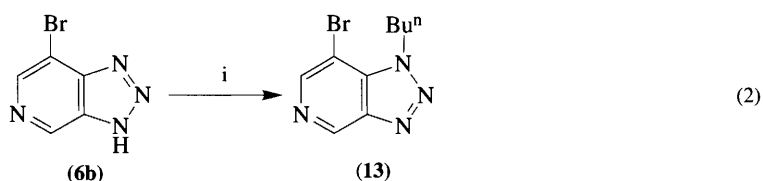
7.10.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.10.5.1 [1,2,3]Triazolo[4,5-*b*]pyridines and [1,2,3]Triazolo[4,5-*c*]pyridines

7.10.5.1.1 Ring substitution

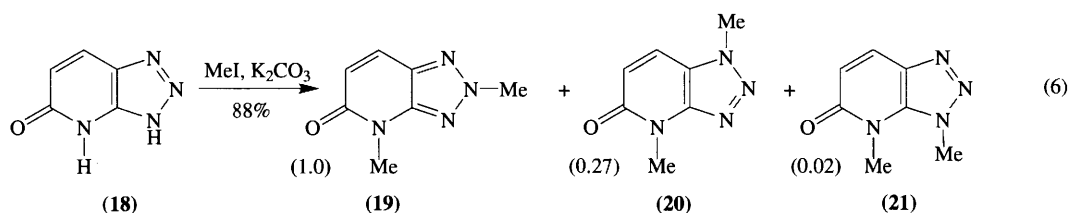
Direct functionalization of a triazolopyridine was first reported by Bremer who showed that alkylation of 7-bromotriazolo[4,5-*c*]pyridine (6b) afforded 1-(*n*-butyl)-7-bromotriazolo[4,5-*c*]pyridine (13) $\langle 34LA(514)279, 37LA(529)288, 39LA(539)276 \rangle$. Subsequently, much interest was focused on the synthesis of triazolopyridine *N*-ribosides. On the basis of empirical observations, there is no

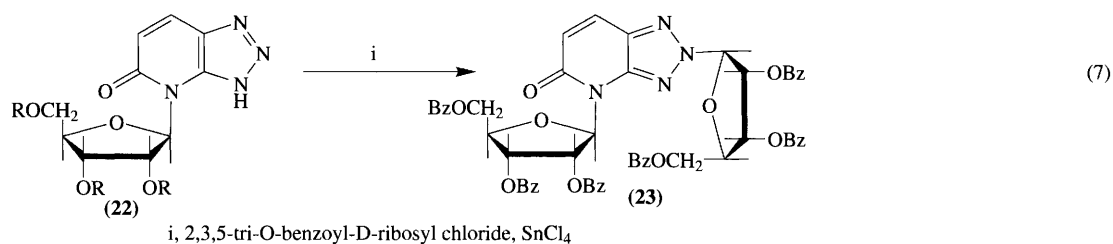
predominant factor that determines the site of *N*-functionalization. As shown in Equations (2) to (5), *N*-substitution regiochemistry is dependent collectively on the substituents on the triazolopyridines, the electrophiles and the reaction conditions employed. For example, triazolo[4,5-*b*]pyridine (**5a**) and formaldehyde gave 1-(hydroxymethyl)triazolo[4,5-*b*]pyridine (**14**) <75HCA1521> exclusively. Ribosylation of triazolo[4,5-*b*]pyridine (**5a**) under standard Knorr–Koenig conditions afforded all possible ribosides, with the *N*-2 product predominating <71RTC1181>, while 7-chlorotriazolo[4,5-*b*]pyridine (**5b**) gave *N*(2)- and *N*(3)-ribosides <71RTC1181>. In contrast, 6-nitrotriazolo[4,5-*b*]pyridine (**5c**) <68IJC123> and 5-(ethoxycarbonylamino)-7-chlorotriazolo[4,5-*b*]pyridine (**5d**) gave *N*(3)-ribosides (**15**) and (**16**) exclusively <76JHC1365, 78JOC4910>. Contrasting electronic effects are observed in the *N*-arylation of compounds (**5a**) and (**6a**); isomer (**6a**) with 2-chloro-nitrobenzene afforded 1-(2-nitrophenyl)triazolo[4,5-*c*]pyridine (**17**) exclusively <86BSB1107>. On the other hand, compound (**5a**) afforded mixtures of 1-(2-nitrophenyl)triazolo[4,5-*b*]pyridine, 3-(2-nitrophenyl)triazolo[4,5-*b*]pyridine and 2-(2-nitrophenyl)triazolo[4,5-*b*]pyridine.



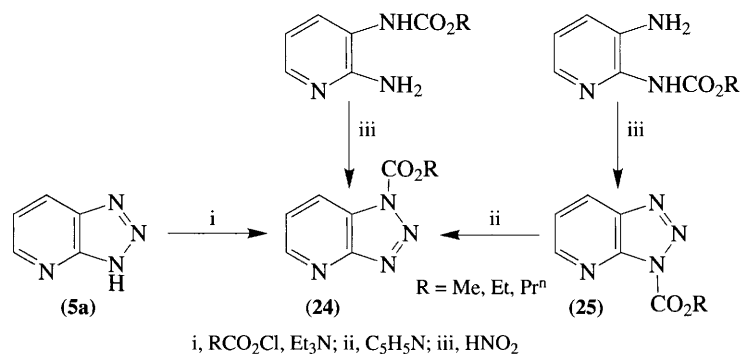
i, Bu^nBr, K_2CO_3 ; ii, 30% CH_2O ; iii, 2,3,5-tri-*O*-benzoyl-D-ribose chloride, $SnCl_4$; iv, 2-Cl(NO_2) C_6H_4

Further exemplification (Equations (6) and (7)) of the subtle stereoelectronic effects is found in the permethylation of 5-oxotriazolo[4,5-*b*]pyridine (**18**), which affords the 2,4-, 1,4-, and 3,4-dimethyl isomers (**19**)–(**21**) in a 1.00:0.27:0.02 ratio <76CJC1029>. In contrast, ribosylation of 4-(2,3,5-tri-*O*-acyl-D-ribsyl)-5-oxotriazolo[4,5-*b*]pyridine (**22**) afforded exclusively the 2,4-bis(riboside) (**23**).



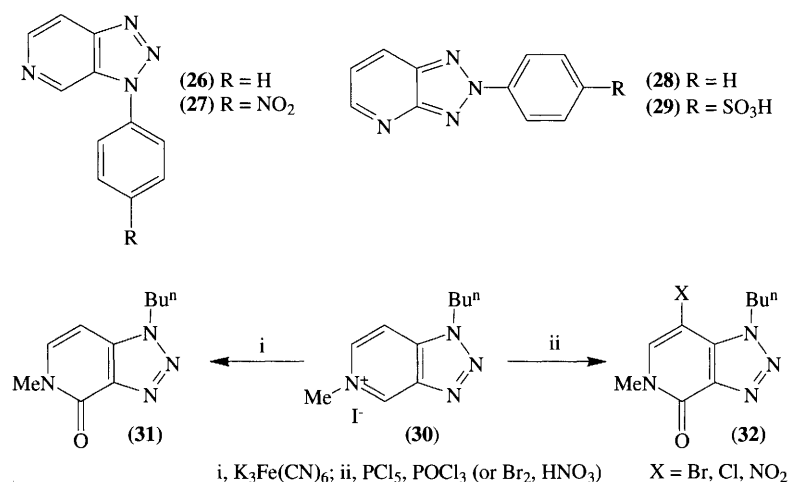


Paradisi and co-workers reported that acylation and alkoxycarbonylation of compound (**5a**) resulted predominantly in 1-substitution (cf. products (**24**) in Scheme 1). However, in pyridine the 3-isomers (**25**) convert to the 1-isomers (**24**) <85JHC313, 86JHC1459, 86TL5029>. Each isomer was prepared unambiguously by nitrosation of the appropriate (acylamino)aminopyridines (cf. Section 7.10.9.1.1). While *N*-acyltriazolo[4,5-*b*]pyridines are excellent and selective acylation reagents, they are also useful in biphasic media (CH₂Cl₂, 30% H₂O₂) for the selective oxidation of sulfides to sulfoxides. For example, *N*-acetyltriazolo[4,5-*b*]pyridine facilitates the oxidation of methyl benzylpenicillanate to the (*S*)-sulfoxide <87SC515>.



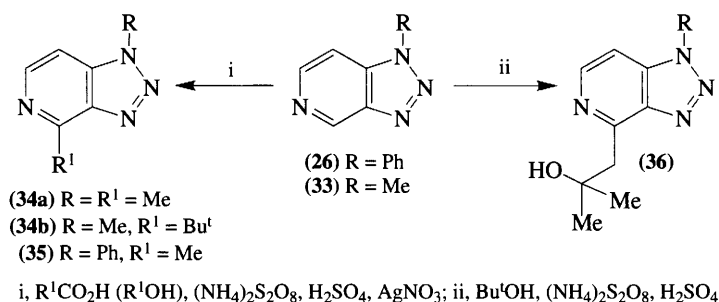
Scheme 1

In contrast to the ease of *N*-functionalization, shown in Scheme 1, the triazolopyridine nucleus is resistant to direct nuclear oxidation or electrophilic additions. Electrophilic additions will occur on aryl substituents; for example, nitration of 1-phenyltriazolo[4,5-*c*]pyridine (**26**) and sulfonation of 2-phenyl-2*H*-triazolo[4,5-*b*]pyridine (**28**) occur exclusively in the *para* position of the phenyl ring <34LA(514)279, 38MI 710-01>. Nuclear functionalization was observed when 1-(*n*-butyl)-5-methyl-triazolo[4,5-*c*]pyridinium iodide (**30**) was treated with potassium ferricyanide to afford triazolopyridin-4-one (**31**), as shown in Scheme 2. Similarly, the iodide (**30**) is converted by either phosphorus oxychloride–phosphorus pentachloride, or bromine or nitric acid to 7-substituted triazolopyridin-4-ones (**32**) <37LA(529)288>.



Scheme 2

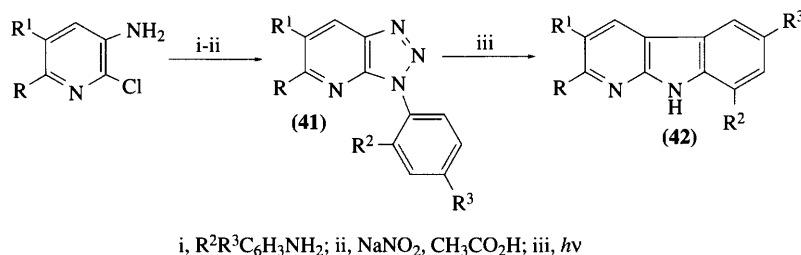
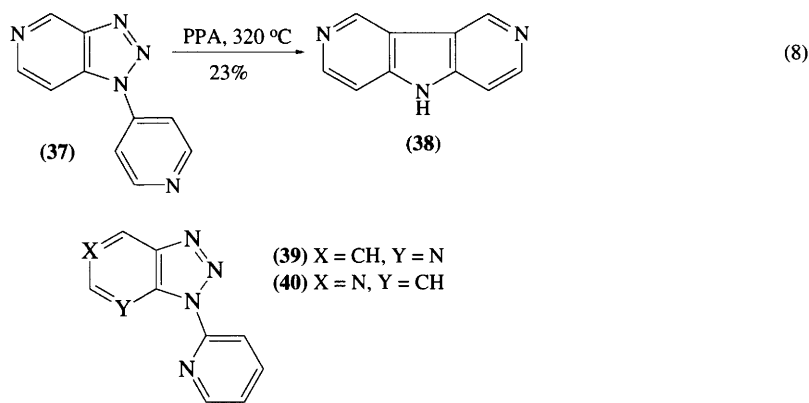
In an approach to direct C-functionalization of triazolo[4,5-*c*]pyridines, shown in Scheme 3, 1-methyl (or phenyl)[1,2,3]triazolo[4,5-*c*]pyridines (**26**, **33**) are alkylated exclusively at C-4 by radicals generated by decarboxylation of carboxylic acids (ammonium persulfate–sulfuric acid–silver nitrate) <90ZOB683>. However, with *t*-butanol various products are obtained depending on the catalyst employed. For example, with ammonium persulfate–sulfuric acid–silver nitrate, exclusive C(4)-methylation (**34**) was observed, while ammonium persulfate–sulfuric acid gave exclusively C(4)- β -hydroxy- β , β -dimethylethylation (cf. (**36**)). The *t*-butyl analogue (**35**) was obtained by decarboxylation of pivalic acid.



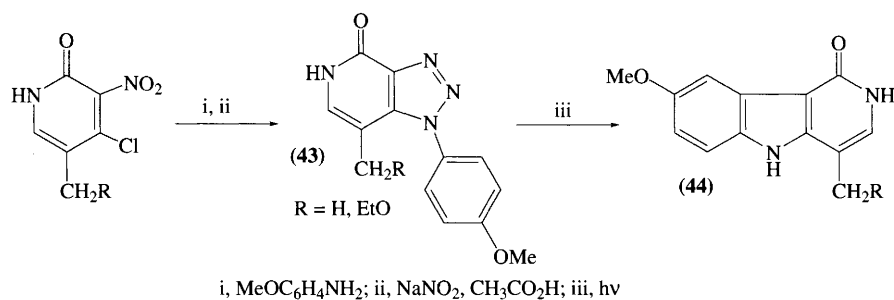
Scheme 3

7.10.5.1.2 Photochemistry and thermolysis

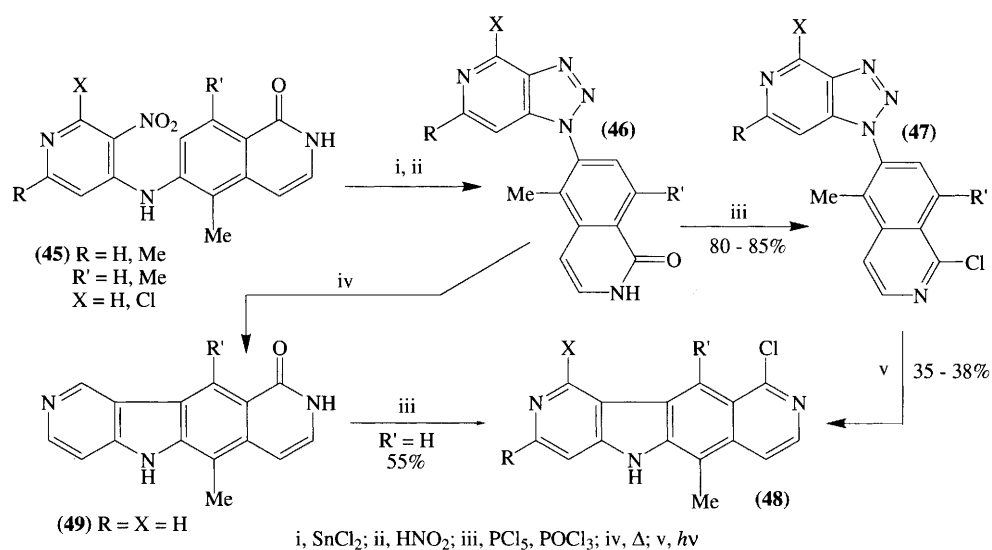
The thermolysis or photolysis of triazoles has shown great utility in carbon–carbon bond formation and heterocyclic syntheses; notable is the Graebe–Ullmann rearrangement of *N*-phenylbenzotriazole to carbazoles. The comparable transformation of 3-(4-pyridyl)-[1,2,3]triazolo[5,4-*c*]pyridine (**37**) to 3,6-diazacarbazole (**38**) was reported by Koenigs and Nantka <40CB(74)215>; however, the isomeric 3-(2-pyridyl)-[1,2,3]triazolo[5,4-*b*]pyridine (**39**) and 3-(2-pyridyl)-[1,2,3]triazolo[5,4-*c*]pyridine (**40**) were resistant to rearrangement <84PJC125>. It was subsequently found that the rearrangements are sensitive to electronic effects of the substituents and that complementary reaction conditions (photochemical or thermal) are required, depending on the substituents <80JOC2176>. The photolytic process is tolerant of many substituents, as shown in Equation (8), Schemes 4, 5, and 6, and Table 3 for the synthesis of numerous ellipticine analogues <84EJM525, 88AP(321)463, 92MI 710-01>.



Scheme 4



Scheme 5



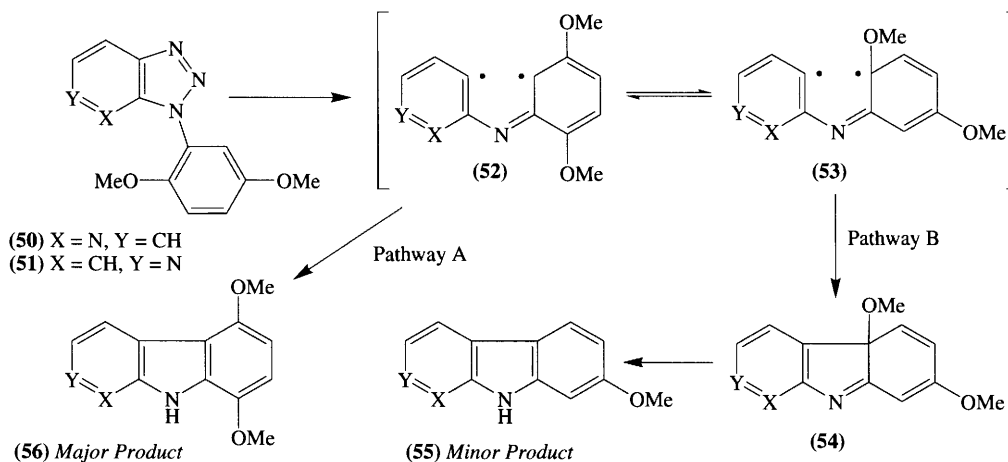
Scheme 6

Table 3 Photochemical rearrangement of 3-phenyltriazolo[4,5-*b*]pyridines (**41**) to 9H-pyridol [2,3-*b*]indoles (**42**)(α -carboline)s(Scheme 4).

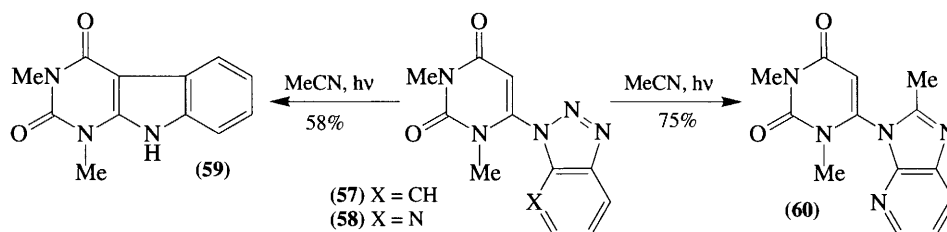
Compound	R	R ¹	R ²	R ³	mp (°C)	Ref.
42a	H	H	H	H	115–116	81H(15)483
42b	H	H	H	Bu ¹	191–192	81MI 710-01
42c	H	H	H	OMe	202–203	81MI 710-01
42d	H	H	H	Ph	236–238	81MI 710-01
42e	H	H	H	F	221–222	81MI 710-01
42f	H	H	H	Br	263–265	81MI 710-01
42g	H	H	Me	H	230–232	81MI 710-01
42h	H	H	Cl	H	247–248	81MI 710-01
42i	H	H	OMe	H	211–213	81MI 710-01
42j	H	H	H	Cl	^a	80JCR(S)43
42k	Ph	H	H	H	233–235	78MI 710-01
					245–246	81H(15)483
42m	3-pyridyl	H	H	H	265–267	78MI 710-01
42n	Me	EtO ₂ C	H	H	227–228	81H(15)483
42o	Me	MeCO	H	H	255–257	81H(15)483
42p	—(CH ₂) ₄ —		H	H	254–255	81H(15)483
42q	—(CH ₂) ₃ —		H	H	294–295	81H(15)483
42r	—CH=CH—CH=CH—		H	H	346	88AP(321)463

^aNot available.

Additional mechanistic insights (Scheme 7) on the rearrangements were revealed by the photolyses of 3-(2,4-dimethoxyphenyl)triazolo[4,5-*b*]pyridine (**50**) and 3-(2,4-dimethoxyphenyl)triazolo[4,5-*c*]pyridine (**51**). Both afforded, in addition to the desired dimethoxyazacarbazoles (**56**), sideproduct monomethoxyazacarbazoles (**55**) which reflects the equilibrium of the intermediate diradicals (**52**) and (**53**) <90JCR(S)1, 93JCS(P1)1261>. By analogy to the photolysis of 1-phenylbenzotriazole, the reactive intermediate is probably a triplet-state diradical <68JA1923, 73PAC339, 80JA1421>. However, its formation and reactivity is sensitive to electronic effects. As shown in Scheme 8, under identical conditions in acetonitrile, the 6-(1-benzotriazolyl)uracil (**57**) is transformed to the indolo[2,3-*d*]pyrimidines (**59**) while the 6-(3-triazolyl[4,5-*b*]pyridyl)uracil (**58**) undergoes insertion of solvent to give the 6-(3-imidazolyl[4,5-*b*]pyridyl)uracil (**60**) <91TL323>.

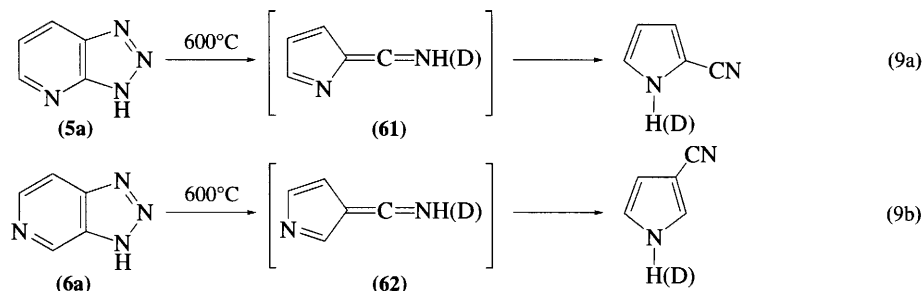


Scheme 7



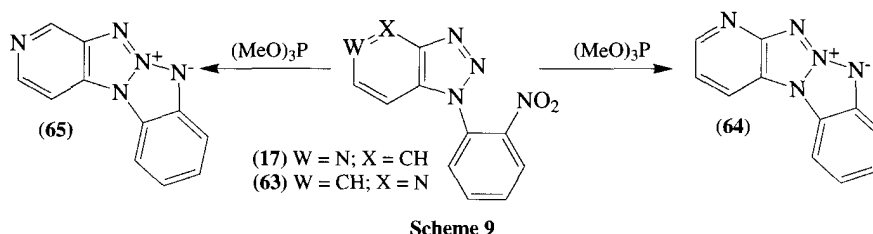
Scheme 8

In contrast to the *N*-aryltriazolopyridines, thermolysis (600°C) of compounds (**5a**) and (**6a**) affords pyrrole-2-carbonitrile and pyrrole-3-carbonitrile, respectively <70T3965, 91JSP(147)229>. Mechanistically, the intermediate pyroloketenimines (**61**), (**62**) undergo proton shift to the nitriles (Equation (9)).



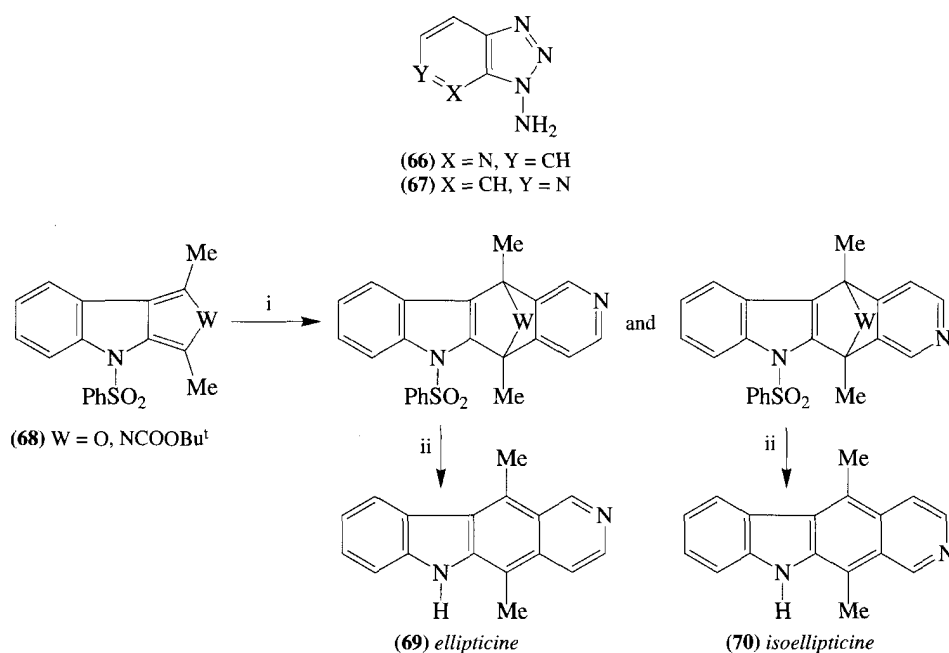
While there are substantial differences between the chemistry of benzotriazoles and triazolopyridines, the systems also have some similar reactivity profiles. As shown in Scheme 9, reductive

cyclization (triethyl phosphite) of 1-(*o*-nitrophenyl)triazolo[4,5-*b*]pyridine (**63**) and 1-(*o*-nitrophenyl)triazolo[4,5-*c*]pyridine (**17**) gives [2,3-*b*]pyridino[4,5]benzo-1,3a,6,6a-tetraazapentalene (**64**), and [2,3-*c*]pyridino[4,5]benzo-1,3a,6,6a-tetraazapentalene (**65**), respectively <86BSB1107>.

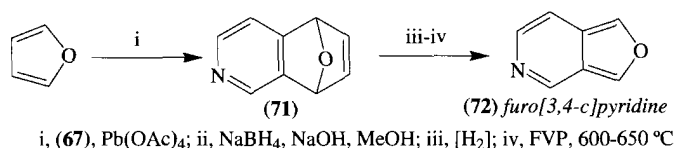


7.10.5.2 *N*-Amino[1,2,3]triazolopyridines

The intermediates (**66**), (**67**), upon *in situ* oxidation, afford 2(or 3)-pyridynes or 2(or 3)-quinolynes <71JCS(C)3948> which are highly reactive in Diels–Alder reactions, as shown in Schemes 10 and 11 for syntheses of ellipticine (**69**), isoellipticine (**70**) <84JOC4518, 92T10645>, and furo[3,4-*c*]pyridine (**72**) <77TL1741>. Nitrosation of the aminotriazolopyridines affords the parent triazolopyridines.



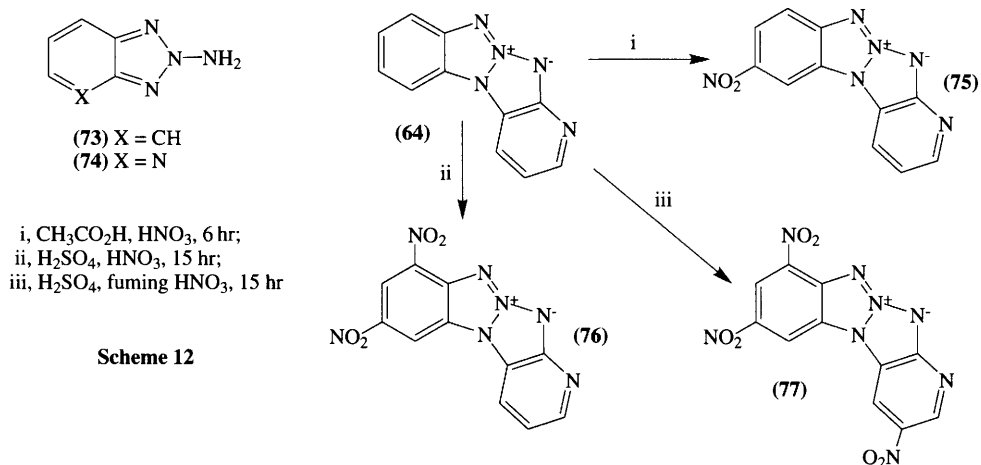
Scheme 10



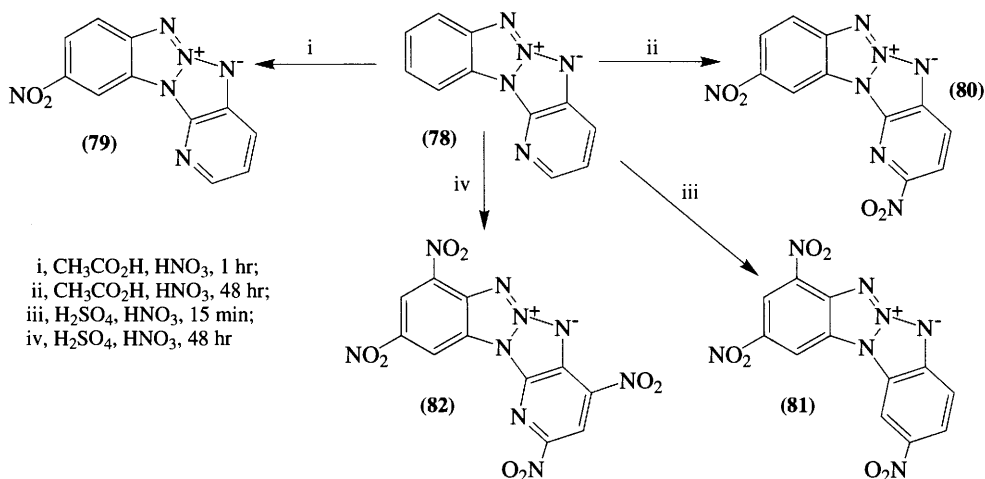
Scheme 11

While 2-amino-2*H*-triazolopyridines (**74**) have not been reported, the close structural features found in the pyridino[4,5]benzo-1,3a,6,6a-tetraazapentalenes (see Section 7.10.5.1) provide an excellent framework to study the differential electronic effects between the benzene system and the pyridine system. In general, all the isomeric pentalenes show greater ease for electrophilic addition

reactions on the benzene ring than on the pyridine ring. For example, the rate of nitration of compound (64) occurs at C-2 > C-4 >> C-7 (Scheme 12). In the isomer (78) (Scheme 13), the nitration rate is C-2 > C-7 > C-4 >> C-5, while the bromination rate is C-2 > C-4 > C-7 >> C-5 <86BSB1107>.



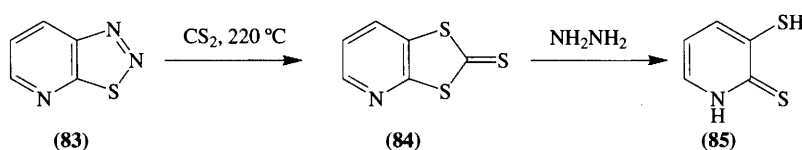
Scheme 12



Scheme 13

7.10.5.3 [1,2,3]Thiadiazolo[3,4-*b*]pyridines and [1,2,3]Thiadiazolo[3,4-*c*]pyridines

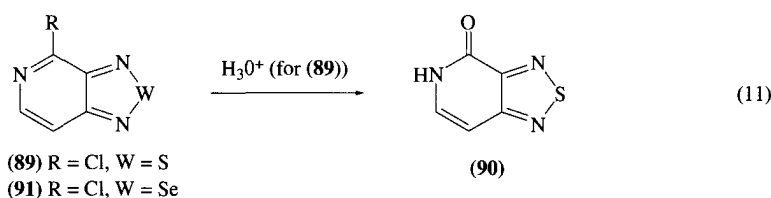
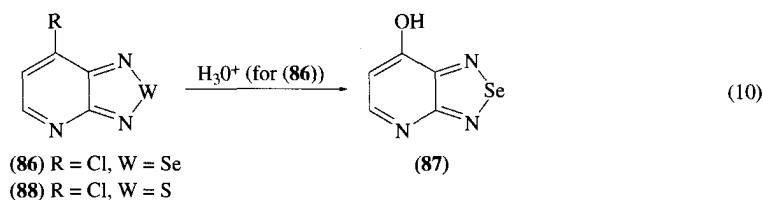
A notable aspect of the chemistry of the annelated [1,2,3]thiadiazoles is their characteristic thermolysis to [1,3]-diradicals (Scheme 14). Trapping of the diradical from thiadiazolo[4,5-*b*]pyridine (83) with carbon disulfide afforded pyridyl dithiolthione (84), which on hydrazinolysis afforded the air-unstable 2,3-pyridinedithiol (85) <78PJC2039>.



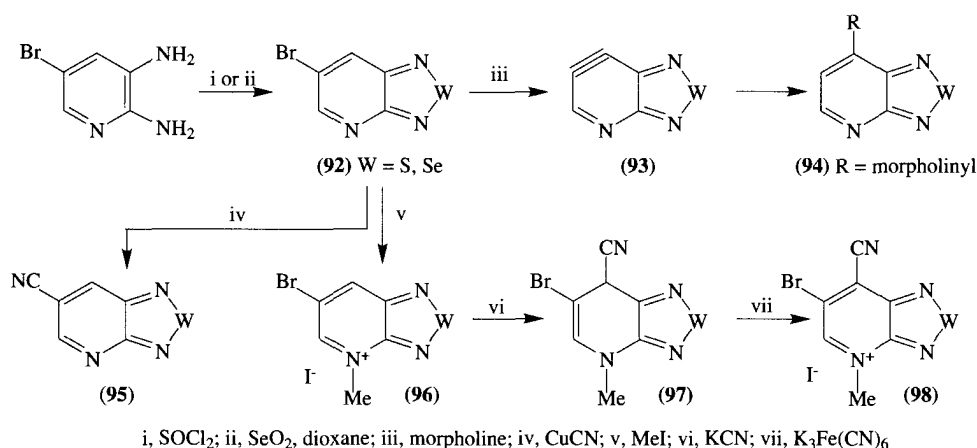
Scheme 14

7.10.5.4 [1,2,5]Thiadiazolo[3,4-*b*]pyridines, [1,2,5]Thiadiazolo[3,4-*c*]pyridines, [1,2,5]Selenadiazolo[3,4-*b*]pyridines, and [1,2,5]Selenadiazolo[3,4-*c*]pyridines

While the thiadiazolopyridine and selenadiazolopyridine ring systems are resistant to direct oxidation and electrophilic additions, the halogenated analogues show diverse reactivity patterns. For example, 7-chloroselenadiazolo[3,4-*b*]pyridine (**86**) is converted to 7-hydroxyselenadiazolo[3,4-*b*]pyridine (**87**) in aqueous acid, while 7-chlorothiadiazolo[3,4-*b*]pyridine (**88**) is stable (Equation (10)). In contrast, the isomeric 4-chlorothiadiazolo[3,4-*c*]pyridine (**89**) is converted to thiadiazolopyridone (**90**), while 4-chloroselenadiazolo[3,4-*c*]pyridine (**91**) is stable (Equation (11)) <70RTC5>.



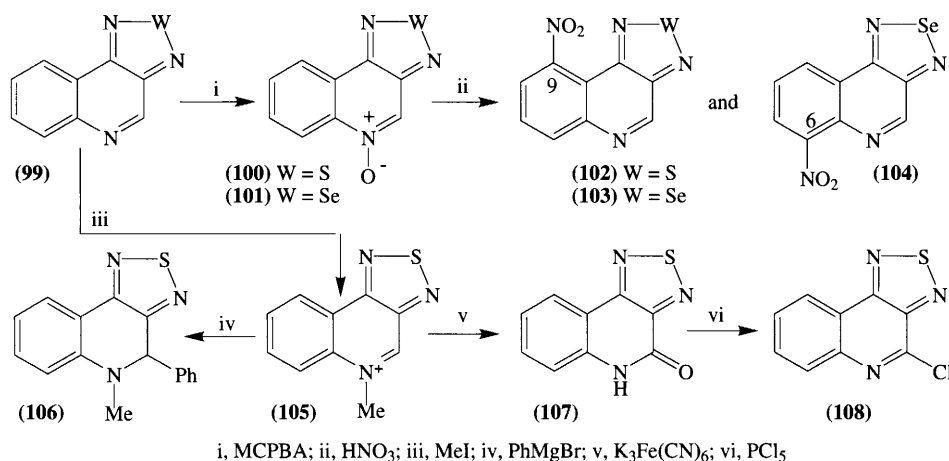
Subtle reactivity differences are also found in the reaction of 6-bromo[1,2,5]thia- (or seleno) diazolo[3,4-*b*]pyridines (**92**) with morpholine and cuprous cyanide which afford the C(7)-amine (**94**) and C(6)-nitrile (**95**), respectively (Scheme 15). Under identical reaction conditions, 6-bromobenzo[1,2,5]thiadiazole affords exclusive C(6)-amination and C(6)-cyanation. The anomalous regiochemistry in the formation of (**94**) is attributed to initial formation of a hetaryne intermediate (**93**), which adds morpholine at the more electron-deficient C-7 position <79IJC(B)13, 86IJC(B)500>.



Scheme 15

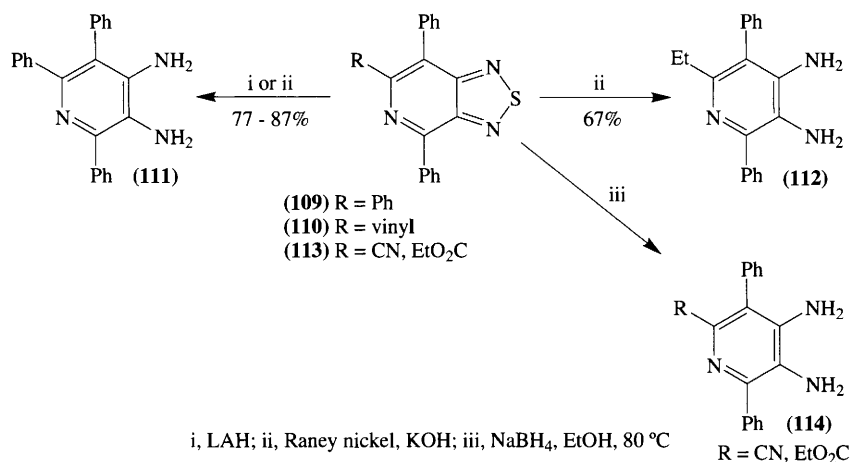
Subtle electronic effects have also been observed with the [1,2,5]thiadiazolo- and [1,2,5]selenadiazolo[3,4-*c*]quinolines (**99**) (Scheme 16). Nitration of thiadiazolo[3,4-*c*]quinoline *N*-oxide (**100**) affords 9-nitrothiadiazoloquinoline (**102**) exclusively, while the selenadiazoloquinoline *N*-oxide (**101**) affords both 6-nitro- (cf. (**104**)) and 9-nitroselenadiazolo[3,4-*c*]quinolines (**103**). By analogy with the previously discussed *N*-methylthiadiazolo[4,5-*c*]pyridinium salts (cf. Section 7.10.5.1.1), the *N*(5)-methylthiadiazoloquinolinium salts (**105**) are easily functionalized at C-4 with potassium ferricyanide or Grignard reagents. Cyanation of *N*(4)-methyl-6-bromothiadiazole (or selenadiazolo) pyridinium salts (**96**) occurred exclusively at C-7, instead of at C-5. The regiochemical preference may be attributed to electronic stabilization effects of the bromine substituent.

From the synthetic perspective, the 1,2,5-oxadiazole and 1,2,5-thiadiazole ring systems can also



Scheme 16

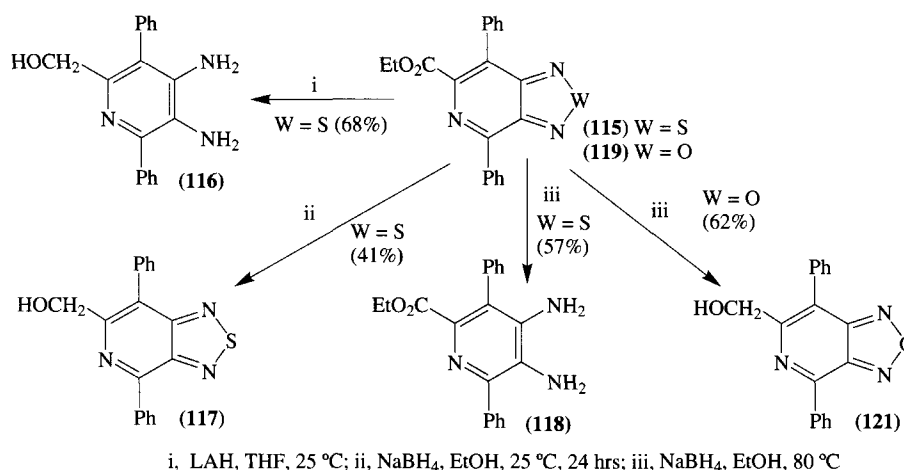
be considered as 1,2-diamine synthons <67G1614, 74BCJ1493>. Aside from empirical studies, general desulfurization (or deoxygenation) conditions are lacking because these reactions are sensitive to the substituents on the nucleus (Schemes 17 and 18). For example, the 6-substituted-4,7-diphenyl-[1,2,5]thiadiazolo[3,4-*c*]pyridines (**109**) and (**110**) are converted to the 3,4-diamino-2,6-diphenylpyridines (**111**) and (**112**) with either lithium aluminum hydride or Raney nickel base (Scheme 17) <82JHC1481>. Less harsh conditions (sodium borohydride) can also be employed for desulfurization, provided there are electron-withdrawing substituents on the pyridine nucleus (cf. (**113**) to (**114**)). In the presence of other reducible groups (e.g. EtO₂C) disparate chemoselectivity is found with sodium borohydride-ethanol; for example, at ambient temperature, the carboxylate function is preferentially reduced ((**115**) to (**117**)). However, with short reaction times at 80 °C, desulfurization occurs prior to ester reduction ((**115**) to (**118**)) (Scheme 18).



Scheme 17

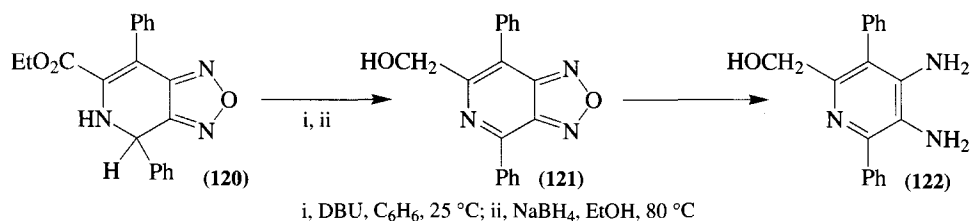
7.10.5.5 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]Oxadiazolo[3,4-*c*]pyridines, and their Oxides

Of the various heterocycles discussed in this chapter, the pyridofuroxans show the least aromatic character. In Section 7.10.5.4, subtle differences in aromaticity between the [1,2,5]thiadiazolo[3,4-*c*]pyridines and the [1,2,5]oxadiazolo[3,4-*c*]pyridines are apparent from their dissimilar reactivity towards various reducing agents. In contrast to the former where desulfurization of the thiadiazole ring or substituent reduction occur, the latter heterocycles undergo initial reduction of the C=N bond to form the 4,5-dihydro[1,2,5]oxadiazolo[3,4-*c*]pyridines (**120**) with sodium borohydride at ambient temperature (Scheme 19). However, at 80 °C, the oxadiazole moiety is preferentially reduced



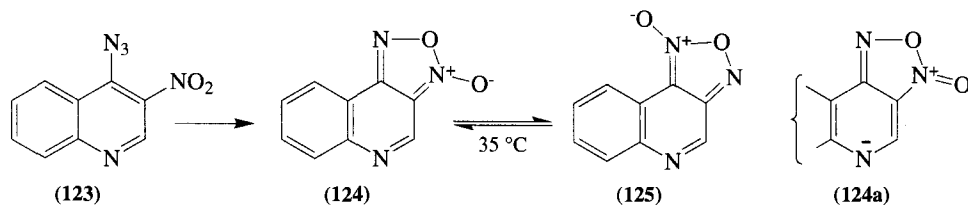
Scheme 18

(39%). Heterocycle (120) is sequentially converted to alcohol (121) and then to diamine (122). The rearomatization of the dihydro heterocycle (120), which is easily accomplished by either sodium hydroxide or DBU in ethanol, is insensitive to substituent effects.



Scheme 19

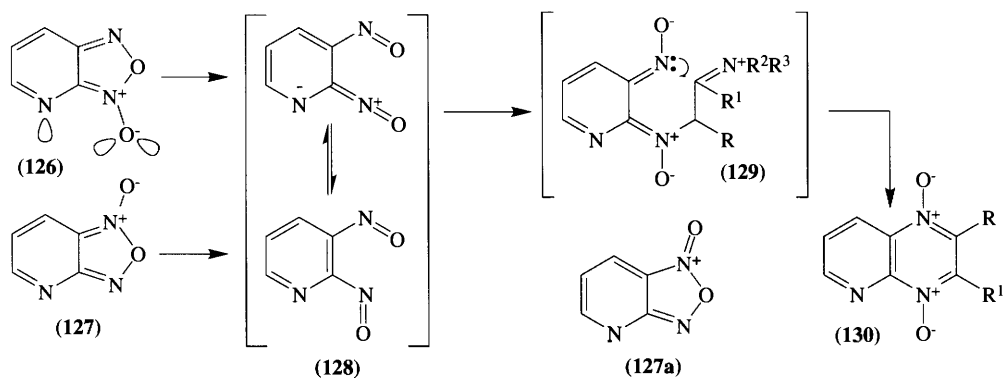
This is further observed in the reactivity profile of the furoxans and their structural characterization where there is concomitant *N*-oxide tautomerization <93T8441>. While tautomerization of simple alkyl- or aryl-substituted furoxans is a slow process (ΔG° ca. 33 kcal mol⁻¹), benzo-fusion and quinolino-fusion enhances the tautomerization rates (ca. 14 kcal mol⁻¹ and 20 kcal mol⁻¹, respectively) <68JCS(B)1516, 69AHC(10)1>. For example, thermolysis of 4-azido-3-nitroquinoline (123) affords initially [1,2,5]oxadiazolo[3,4-*c*]quinoline 3-oxide (124) which at 35 °C exists as a 40:60 mixture of [1,2,5]oxadiazolo[3,4-*c*]quinoline 1-oxide (125) and the 3-oxide (124) ($\Delta G^\circ = 250 \pm 100$ cal mol⁻¹ (Scheme (20)). Preference for the 3-oxide (124) is attributed to the greater resonance stabilization (124a) between the N—O moiety and the quinoline nitrogen <85AJC1045>. Similarly, the equilibrium between the [1,2,5]oxadiazolo[3,4-*b*]pyridine 3-oxide (126) and the 1-oxide (127) favors the 1-oxide because of the lone electron-pair repulsion between the pyridine nitrogen and the *N*-oxide unit (126) and also charge delocalization (127a) <70JCS(B)636>.



Scheme 20

Little is known about the chemistry of pyridylfuroxans, but reaction of the [1,2,5]oxadiazolo[3,4-*b*]pyridine oxides (126) and (127) with activated methylene synthons provides pyrido[2,3-*b*]pyrazine-1,4-dioxides (130) in moderate yields (Beirut reaction) (Table 4, Scheme 21) <80M407, 82AF10>. The actual reactive species is presumed to be the bis(nitroso)pyridine isomer (128). Direct oxidation

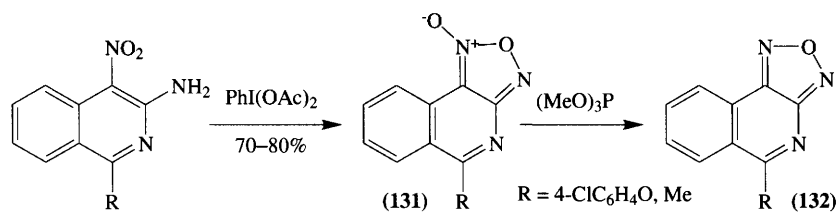
(90% hydrogen peroxide–30% oleum) of compound (127) afforded 2,3-dinitropyridine in 60% yield <90JOC3755>. The deoxygenation ((131) to (132)) was readily accomplished using trimethyl phosphite (Scheme 22) <93AJC411>.



Scheme 21

Table 4 Synthesis of pyridine[5,6-*b*]pyrazines dioxides (130) (Scheme 21).

Compound	<i>R</i>	<i>R</i> ¹	<i>mp</i> (°C)	Yield (%)	Ref.
130a	H	Me	202	20	82AF110
130b	Me	H	221	31	82AF110
130c	Pr ⁱ	H	185	7.5	80M407
130d	Me	Me	202	52	82AF110
130e	Me	CO ₂ Et	190	27	82AF110
130f	Me	CONMe ₂	208	32	82AF110
130g	Me	CH ₂ CO ₂ Me	186	35	82AF110
130h	Me	CH ₂ CONMe ₂	180	13	82AF110
130i	H	CH(OMe) ₂	164	2.4	82AF110
130j	CO ₂ Me	Me	163	6	82AF110
130k	CH(OMe) ₂	H	151	13.5	82AF110
130m	Ph	H	215	38	82AF110



Scheme 22

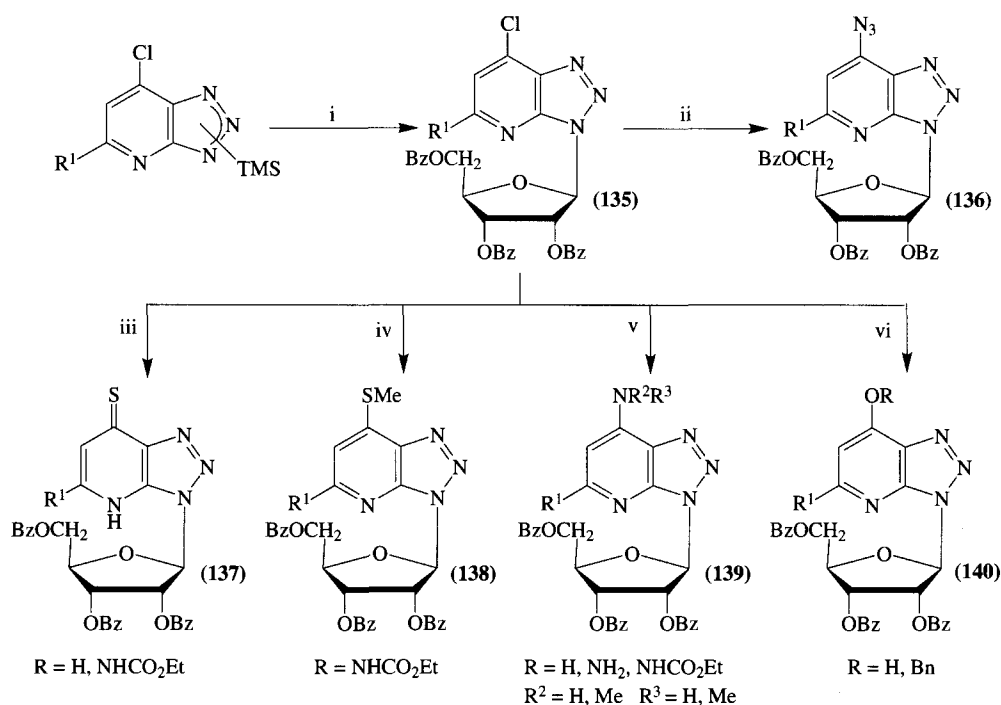
7.10.6 REACTIVITY OF NONCONJUGATED SYSTEMS

Examples of either the dihydro or tetrahydro analogues of the heterocycles in this chapter are rare. A synthesis of 3-aryl-4-methyl-4,5,6,7-tetrahydro-3*H*-1,2,3-triazolo[4,5-*b*]pyridines was reported (see Section 7.10.9.1.1), but its chemistry was not discussed <86CB3591>.

7.10.7 REACTIVITY OF SUBSTITUENTS ON RING CARBONS

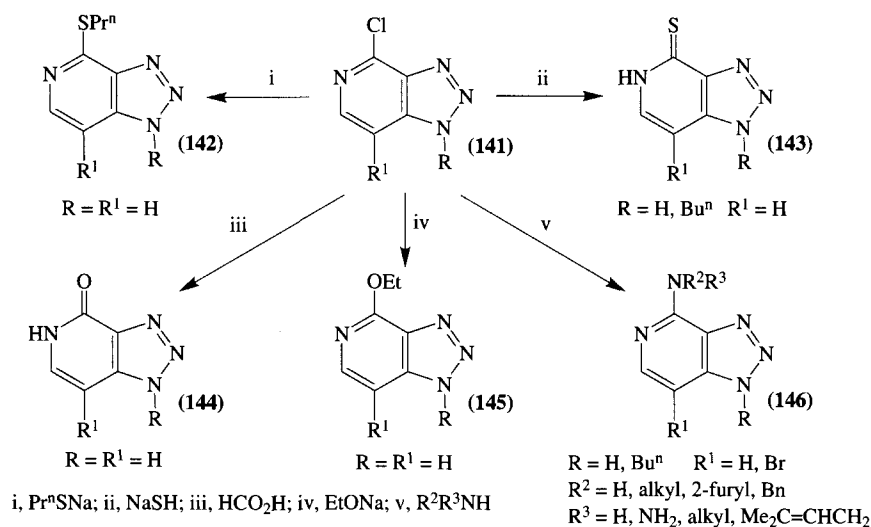
7.10.7.1 Triazolopyridines

Numerous triazolopyridine nucleoside analogues have been synthesized by nucleophilic displacement (S_NAr) on halotriazolopyridines. As partially illustrated in Schemes 23 and 24, 7-chlorotriazolo[4,5-*b*]pyridines (**5b**), (**135**) and 4-chlorotriazolo[4,5-*c*]pyridines (**141**) <39LA(539)276> react with amines <72JOC3601, 73P2087, 76JHC1365>, alkoxides <71RTC1166, 76JHC1365, 78JOC4910>, sodium azide <72JOC1095>, hydrazine <64RZC887, 71RTC1181>, or thiolates <71RTC1166, 72JOC3601, 76JOC3784, 78JOC4910>, irrespective of the nitrogen substituents (Tables 5 and 6). For reference purposes, compound (**5b**) is intermediate in reactivity between 6-chloropurine (most reactive) and 7-chloroimidazolo[4,5-*b*]pyridine.

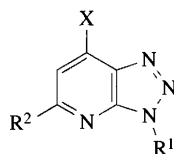


i, 2,3,5-tri-O-benzoyl-D-ribose; ii, NaN₃; iii, NaSH; iv, MeSNa; v, R²R³NH; vi, ROH

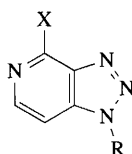
Scheme 23



Scheme 24

Table 5 7-Substituted-[1,2,3]triazolo[4,5-*b*]pyridines from 7-chloro[1,2,3]triazolo[4,5-*b*]pyridines (Scheme 23).

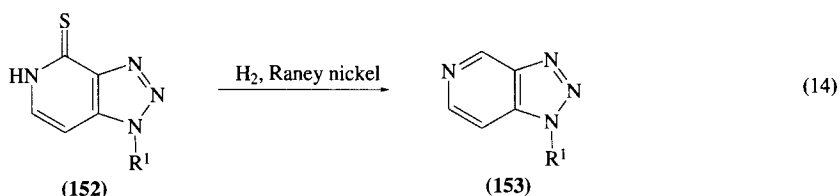
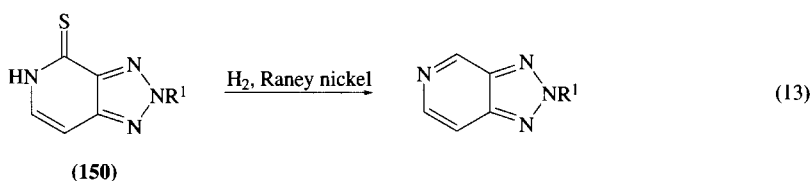
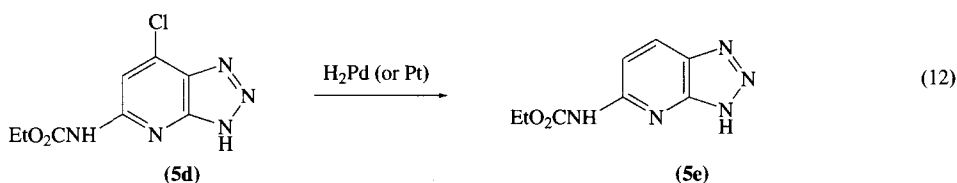
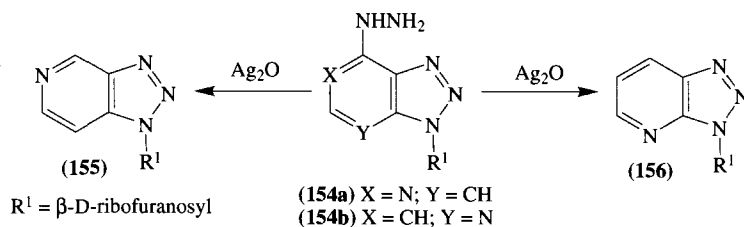
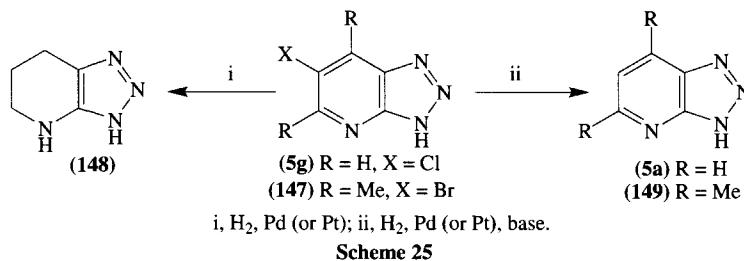
No	R ¹	R ²	X	mp (°C)	Yield (%)	Ref.
1	H	H	SH	176–177	75	72JOC3601
2	H	H	SMe	208–209	51	72JOC3601
3	H	H	NH ₂	185–187	72	72JOC3601
4	H	H	OH	> 290	30	72JOC3601
5	H	H	NHNH ₂	> 260	76	71RTC1166
6	H	H	N ₃	explodes	96	71RTC1166
7	H	H	NHCH ₂ CH=CM ₂	215	75	73P2087
8	H	H	NHMe	^a	^a	71RTC1166
9	H	H	NMe ₂	224	72	71RTC1166
10	H	H	NHCH ₂ (2-furyl)	272–273	^a	71RTC1166
11	H	NH ₂	SH	235–236	40	78JOC4910
12	H	NHCO ₂ Et	H	183–185	93	78JOC4910
13	H	NHCO ₂ Et	N ₃	160 (dec)	60	73JOC1095
14	H	NHCO ₂ Et	NH ₂	> 300	75	73JOC1095
15	D-ribosyl	NH ₂	OEt	141–143	77	78JOC4910
16	D-ribosyl	NH ₂	SMe	149–151	95	78JOC4910
17	D-ribosyl	NH ₂	OBn	154–156	72	78JOC4910
18	D-ribosyl	NH ₂	SH	113–116	65	78JOC4910
19	D-ribosyl	NHCO ₂ Et	H	182–184	75	78JOC4910
20	D-ribosyl	H	NH ₂	205–207	45	92MI 710-02
21	D-2-deoxyribosyl	H	NH ₂	219–222	91	92MI 710-02
22	D-ribosyl	H	NHMe	205	51	76JOC1449
23	D-ribosyl	H	NMe ₂	152	65	76JOC1449
24	D-ribosyl	H	NHCH ₂ (2-furyl)	ca. 100	^a	76JOC1449

^aNot available.**Table 6** 4-Substituted-[1,2,3]triazolo[4,5-*c*]pyridines from 4-chloro[1,2,3]triazolo[4,5-*c*]pyridines (Scheme 24).

No.	R	X	mp (°C)	Yield (%)	Ref.
1	H	SH	234	84	72JOC3601
2	H	SMe	170	75	72JOC3601
3	H	SP ⁿ	190–191	30	72JOC3601
4	H	NH ₂	< 325	^a	72JOC3601
5	H	OH	< 360	91	72JOC3601
6	H	NHCH ₂ (2-furyl)	260	52	73P2087
7	H	NHCH ₂ CH=CM ₂	210–211	75	73P2087
8	N(1)-D-ribosyl	NH ₂	212–215	51	76JOC1449
9	N(1)-D-ribosyl	SMe	174–175	68	76JOC1449
10	N(1)-D-ribosyl	NHNH ₂	^a	^a	76JOC1449
11	N(1)-D-ribosyl	H	161–163	38	76JOC1449
12	N(3)-D-ribosyl	SH	177–178	58	76JOC1449
13	N(3)-D-ribosyl	H	166–168	67	76JOC1449

^aNot available.

Catalytic dehalogenation or desulfurization of 6-halotriazolo[4,5-*b*]pyridines (**5g**) and (**147**) <49JA1885>, 2*H*-[1,2,3]triazolo[4,5-*c*]pyridine-4-thiones (**150**) <76JOC1449>, 7-chlorotriazolo[4,5-*b*]pyridine (**5d**) <57JA6421, 78JOC4910>, and the triazolo[4,5-*c*]pyridine-4-thione (**152**) <76JOC1449> occur in high yields (Schemes 25 and 26, Equations (12)–(14)). However for dehalogenation, the presence of a base is necessary to minimize nuclear reduction. For example, reduction of compound (**147**) with either palladium or platinum catalyst gave tetrahydrotriazolo[4,5-*b*]pyridine (**148**), while (**5a**) was obtained exclusively when the reduction was done in the presence of a base (Scheme 25) <49JA1885>. Alternatively, oxidative deamination (silver oxide) of the hydrazinotriazolopyridines (**154**) afforded the parent triazolopyridines (**155**) and (**156**) <71RTC1181, 76JOC1449>.

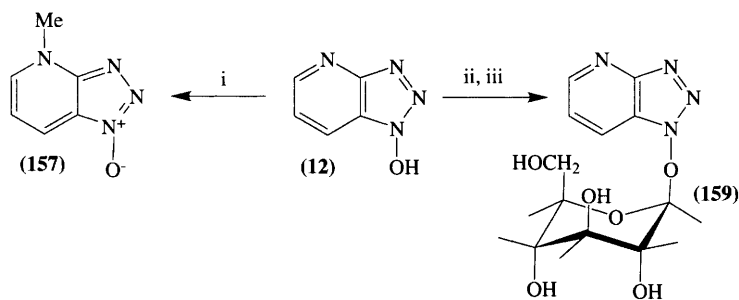


7.10.8 REACTIVITY OF SUBSTITUENTS ON RING HETEROATOMS

7.10.8.1 *N*-Hydroxy[1,2,3]triazolo[4,5-*b*]pyridines

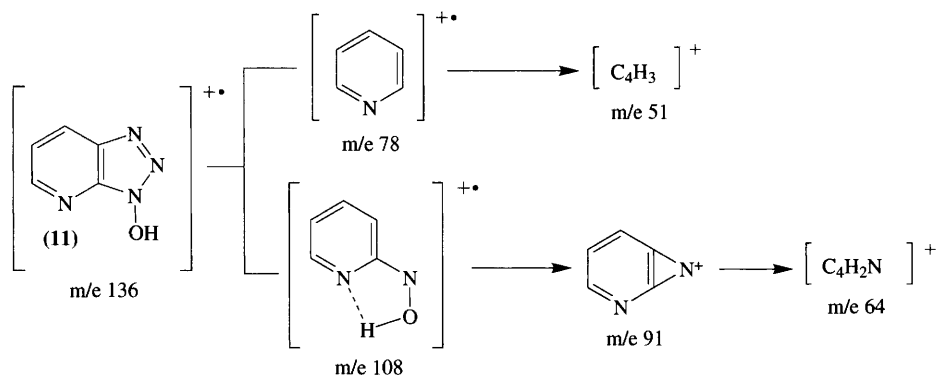
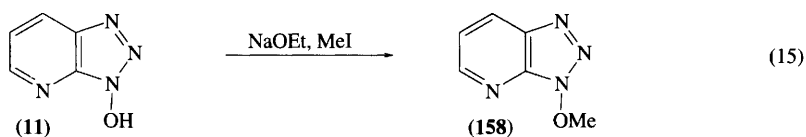
In contrast to the well-established chemistry of *N*-hydroxybenzotriazoles, very little is known about the analogous *N*-hydroxytriazolopyridines. Azev *et al.* described the syntheses of 1-hydroxy-

[1,2,3]triazolo[4,5-*b*]pyridine (**12**) and 3-hydroxy[1,2,3]triazolo[4,5-*b*]pyridine (**11**) from 2-hydrazino-3-nitropyridine and 3-hydrazino-2-nitropyridine, respectively <76KGS1418>. However, methylation of the two isomers (**12**) and (**11**) affords 4-methyl[1,2,3]triazolo[4,5-*b*]pyridine 1-oxide (**157**) and 3-methoxy[1,2,3]triazolo[4,5-*b*]pyridine (**158**), respectively. In contrast, glycosidation of (**12**) with tetra-*O*-acetyl-glucopyranosyl chloride and sodium ethoxide-acetonitrile afforded exclusively *O*-glycosyl nucleoside (**159**) (Scheme 27 and Equation (15)) <80PJC2229>. The mass spectra of the two methylation products also differ (Schemes 28 to 30); notably, under electron-impact ionization conditions, (**11**) and (**158**) show a predominant ion due to initial losses of nitrogen. In contrast, (**157**) shows initial cleavage of the pyridine nucleus.

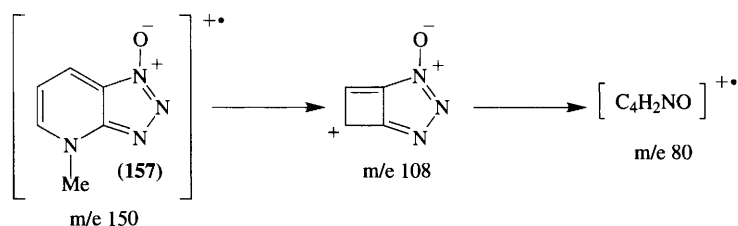


Scheme 27

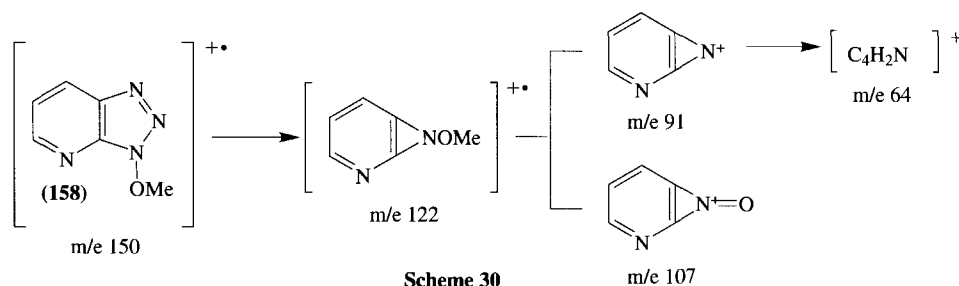
i, NaOEt, MeI; ii, NaOEt, tetra-*O*-acetylglucopyranosyl bromide; iii, Dowex H⁺ resin



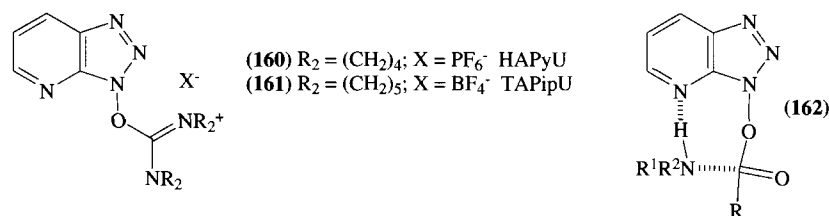
Scheme 28



Scheme 29



In the early 1990s, compound **(11)** (also known as 1-hydroxy-7-azabenzotriazole, HOAt) and its uronium salts **(160)** and **(161)** have shown superiority to 1-hydroxybenzotriazole (HOBt) in peptide coupling reactions, especially with sterically encumbered amines. Although exact mechanistic details have not been established, the faster reaction rates and reduced racemization $\langle 93JA4397, 93TL4781 \rangle$ is attributed to base catalysis by the adjacent pyridine nitrogen during the coupling reactions (cf. **(162)**). Reagent **(160)** has shown utility in problematic macrolactamizations of the linear gonadotropin releasing hormone (GnRH)-derived decapeptides.



7.10.9 RING SYNTHESIS FROM MONOCYCLIC HETEROCYCLES

7.10.9.1 Synthesis by Formation of the Five-Membered Ring

7.10.9.1.1 Triazolopyridines

Triazolo[4,5-*b*]pyridine (**5a**; $R = R^1 = R^2 = R^3 = H$) and triazolo[4,5-*c*]pyridine (**6a**; $R = R^1 = R^2 = R^3 = H$) were first reported by Chichibabin and Kirsanov $\langle 27CB766 \rangle$ and by Bremer $\langle 35LA(518)274 \rangle$, respectively. Traditionally, these heterocycles are prepared by nitrosative electrocyclization of diaminopyridines (the $[N + N-C=C-N]$ protocol). This procedure continues to be widely employed and is permissive of numerous substituents on the diaminopyridines (Tables 7 and 8), even the cyclization of the pentasubstituted precursor **(163)** occurred with minimal difficulty (Equations (16) and (17) and Scheme 31).

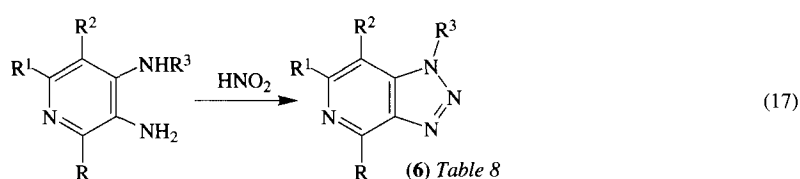
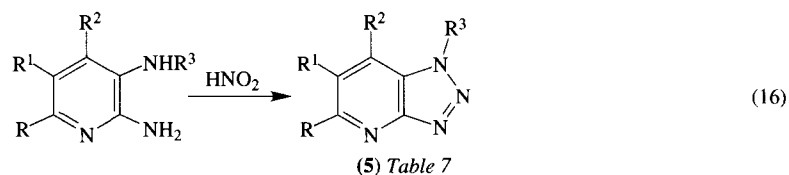
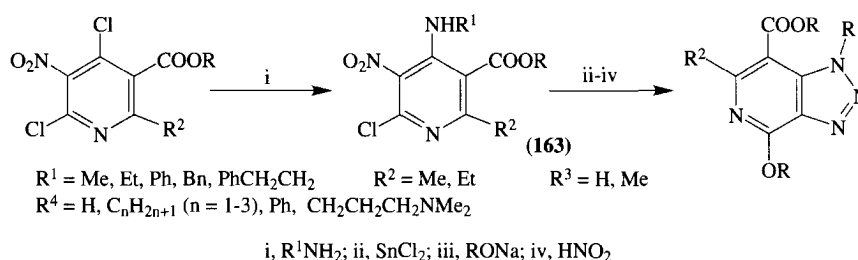


Table 7 3-Substituted-triazolo[4,5-*b*]pyridines (**5**) via 2,3-diaminopyridines.

Compound	R	R ¹	R ²	R ³	mp (°C)	Ref.
5a	H	H	H	H	196	67CB(100)1646
5b	H	H	Cl	H	> 300	72JOC3601
5c	H	NO ₂	H	H	206–207	68IJC123
5d	NHCO ₂ Et	H	Cl	H	211 (dec)	73JOC1095
5e	NHCO ₂ Et	H	H	H	182–184	78JOC4910
5f	H	H	NH ₂	H	270	71RTC1166
5g	H	Cl	H	H	166–167	49JA1885
5h	Me	H	H	H	254	70RZC69
5i	Cl	H	H	H	208–210	79CZ387
5j	NH ₂	H	OBn	H	184–195	78JOC4910
5k	H	H	Me	H	227	70RZC69
5m	H	Me	H	H	173	70RZC69
5n	Cl	H	H	H	208–210	88USP4720496
5o	NH ₂	H	SMe	H	279–280	76JOC3784
5p	NH ₂	H	H	H	233–245	78HCA108
5q	H	H	H	N(1)-Me	120–122	71RTC1181
5r	H	H	H	N(1)-CO ₂ Me	112–114	85JHC313
5s	H	H	H	N(1)-CO ₂ Et	104–105	85JHC313
5t	H	H	H	N(1)-CO ₂ Bu ^t	113–114	86JHC1459
5u	H	H	H	N(1)-CO ₂ Bn	105–105.5	86JHC1459
5v	H	H	H	N(3)-CO ₂ Me	127–128	85JHC313
5w	H	H	H	N(3)-CO ₂ Et	120–121	85JHC313
5x	H	H	H	N(3)-CO ₂ Pr ⁿ	57–58	85JHC313
5y	H	H	H	N(3)-CO ₂ Bu ^t	96–97.5	86JHC1459
5z	H	H	H	N(3)-CO ₂ Bn	98–100	86JHC1459
5aa	H	H	H	N(1)-Me		85JHC313
5ab	H	H	H	N(3)-2,5-C ₆ H ₃ F ₂	144–145	78JMC965
5ac	H	H	H	N(3)-2,4-C ₆ H ₃ Cl ₂	150–151	78JMC965
5ad	H	H	H	N(3)-3,4-C ₆ H ₃ Cl ₂	175–176	78JMC965
5ae	H	H	H	N(3)-2,6-C ₆ H ₃ F ₂	173–174	78JMC965
5af	H	H	H	N(3)-4-EtC ₆ H ₄	61–62	78JMC965
5ag	H	H	H	N(3)-2-ClC ₆ H ₄	100–101	78JMC965
5ah	H	H	H	N(3)-2,6-Me ₂ C ₆ H ₃	155–156	78JMC965
5ai	H	H	H	N(3)-2-(Pr ^t)C ₆ H ₄	oil	78JMC965
5aj	H	H	H	N(3)-(CH ₂) ₂ Ph	69–70	78JMC965
5ak	H	H	H	N(3)-2-FC ₆ H ₄ CH ₂	84–85	78JMC965
5am	H	H	H	N(3)-3-MeOC ₆ H ₄	78–80	78JMC965
5an	H	H	H	N(3)-4-PhOC ₆ H ₄	60–61	78JMC965
5ao	H	H	H	N(3)-4-MeCOC ₆ H ₄	184–185	78JMC965

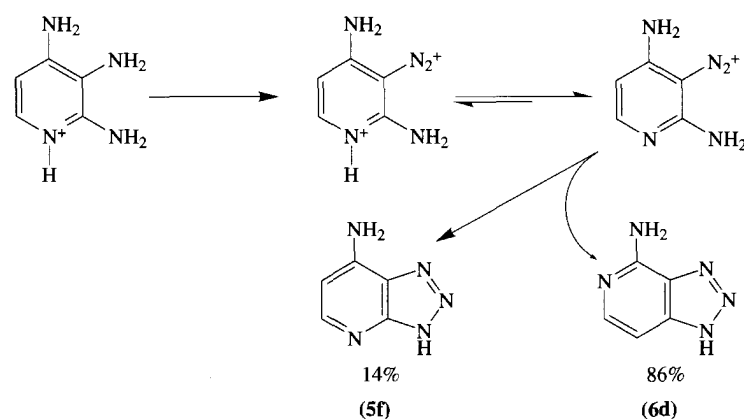
**Scheme 31**

By modification of reaction conditions or reactants, even polyamine-substituted pyridines can be selectively cyclized to various isomers. For example, diazotization of 2,3,4-triaminopyridine affords 4-aminotriazolo[4,5-*c*]pyridine (**6d**), as the major isomer. This is attributed to diazotization of the 3-amino group <27CB766, 28LA(467)1> in preference to either the 2- or 4-amino groups. The intermediate 2,4-diamino-3-diazoniumpyridinium ion, by the virtue of the electron-withdrawing diazonium functionality, becomes less basic and is present mainly as the unprotonated species. Preferential cyclization with the 4-amino group occurs because it is attached to a less electropositive carbon (Scheme 32) <71RTC1166>.

Alternatively, the reaction of diaminopyridines with *N*-nitrosodiphenylamine <67CB1646> or amyl nitrite–acetic acid <93KGS398> is especially useful for those diamines that are sparingly soluble in aqueous media.

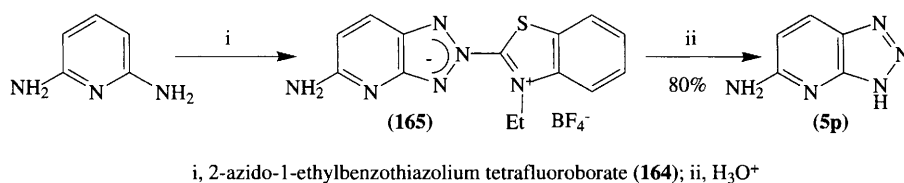
Table 8 1-Substituted-triazolo[4,5-*c*]pyridines (**6**) via 3,4-diaminopyridines.

Compound	<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>mp</i> (°C)	Ref.
6a	H	H	H	H	243–245	76JOC1449
6b	H	H	Br	H	>280	35LA(518)274
6c	H	NH ₂	H	H	265	69RTC1263
6d	NH ₂	H	H	H	>300	71RTC1166
6e	Cl	H	H	H	>325	72JOC3601
6f	Cl	H	Me	H	320	67RZC1887
6g	Me	Me	H	H	267	67RZC1887
6h	NHNH ₂	H	Me	H	265	67RZC1887
6i	H	H	Me	H	260	67RZC1887
6j	Me	H	H	H	258	70RZC69
6k	H	Cl	H	H		88USP4720496
6m	Ph	Ph	Ph	H	199–201	82JHC1481
6n	Ph	CO ₂ Et	Ph	H	153–155	82JHC1481
6o	Ph	CH ₂ OH	Ph	H	235–238	82JHC1481
6p	Ph	CN	Ph	H	232–234	82JHC1481
6q	NHMe	H	H	2-FB	280–282 ^a	93USP5240937
6r	NHPr ^c	H	H	2-FB	245–247 ^a	93USP5240937
6s	NHEt	H	H	2-FB	258–260 ^a	93USP5240937
6t	NMe ₂	H	H	2-FB	248–252 ^a	93USP5240937
6u	NHMe	H	H	Bn	269–273 ^a	93USP5240937
6v	NHMe	H	H	2,5-DFB	273–278 ^a	93USP5240937
6w	NHPr ^c	H	H	2,6-DFB	>260 ^a	93USP5240937
6x	NHMe	H	H	2,6-DFB	297–298 ^a	92USP5166209
6y	NHEt	H	H	2,6-DFB	285–289 ^a	92USP5166209
6z	NHPr ^a	H	H	2,6-DFB	268–273 ^a	92USP5166209
6aa	NMe ₂	H	H	2,6-DFB	240–249 ^a	92USP5166209
6ab	NH ₂	H	H	2,6-DFB	283–285 ^a	92USP5166209
6ac	H	H	H	(CH ₃) ₃ Ph	180–181 ^a	68JMC87
6ad	H	—CH=CH—CH=CH—	H	(CH ₂) ₂ Ph	97	68JMC87
6ae	H	—CH=CH—CH=CH—	H	Et		74BBA(342)155
6af	H	—CH=CH—CH=CH—	H	(CH ₂) ₂ CO ₂ H	239–244	74BBA(342)155
6ag	H	—CH=CH—CH=CH—	H	(CH ₂) ₃ CO ₂ H		74BBA(342)155

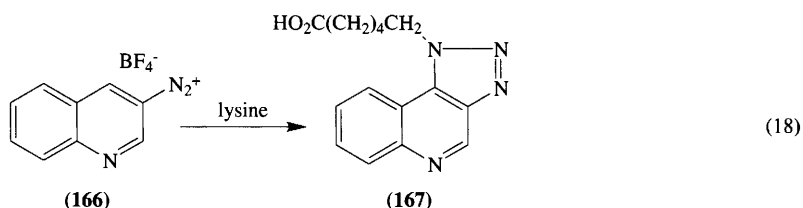
^a HCl salt; 2-FB = 2-fluorobenzyl; 2,6-DFB = 2,6-difluorobenzyl.**Scheme 32**

Specialized diazo transfer reactions have also been reported (Scheme 33 and Equation (18)), but their preparative value is limited. For example, *N*-ethylbenzothiazolium azide (**164**) and 2,6-diaminopyridine affords 5-aminotriazolo[4,5-*b*]pyridine (**5p**) <78HCA108>. Since the reaction is sensitive to the *pK_a* of the aminoheterocycles employed, the process has limited applicability. The highly specific colorimetric assay for ω -amino acids, which is based on a reaction with quinoline-3-diazonium tetrafluoroborate (**166**), affords 1-substituted-[1,2,3]triazolo[4,5-*c*]quinolines (**167**)

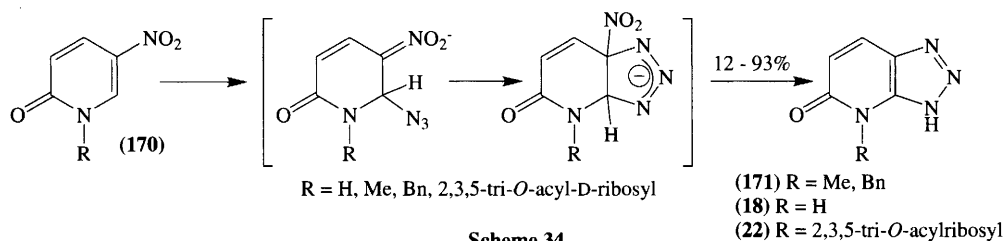
<74BBA(342)155>. While this is not a general synthesis of annelated triazoles, it appears to be specific for quinoline-3-diazonium salts.



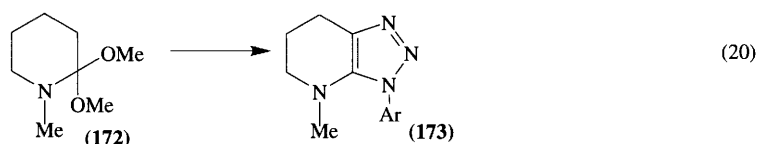
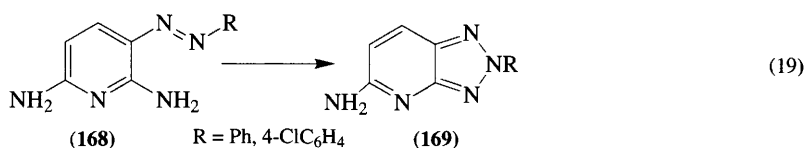
Scheme 33



Alternative electrocyclization protocols (Scheme 34 and Equations (19) and (20)) have also been employed for the synthesis of other triazolopyridines. The copper-catalyzed electrocyclization of *ortho*-aminoazopyridines (**168**) provides an entry to 2-substituted-2*H*[1,2,3]triazolo[4,5-*b*]pyridines (**169**) <62USP3058989, 66USP3227717, 91EUP446604>. The addition of azide to nitropyridone (**170**) provides various 5-oxotriazolo[4,5-*b*]pyridines (**18**, **22**, **171**) <68JA7175, 70JOC1131, 76CJC1029>. The reaction proceeds by initial conjugate addition of azide, followed by electrocyclization and elimination. A similar strategy was reported by Möhrle and Dwuletzi for the synthesis of 3-aryl-4-methyl-4,5,6,7-tetrahydro-3*H*-1,2,3-triazolo[4,5-*b*]pyridines (**173**) from lactam acetals (**172**) <86CB3591>.



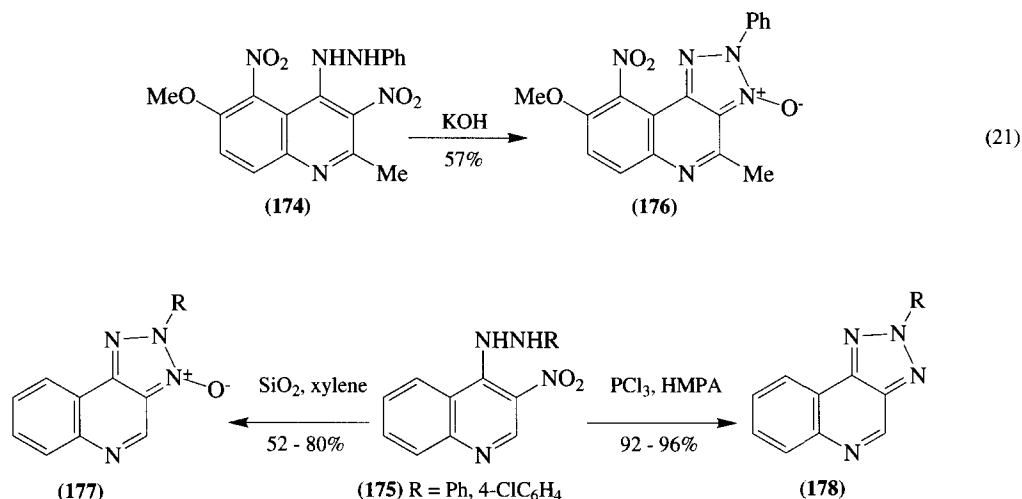
Scheme 34



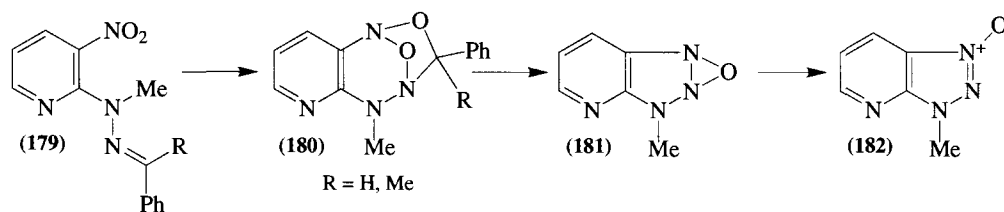
7.10.9.1.2 Triazolopyridine N-oxides and N-hydroxytriazolopyridines

The *N*-hydroxytriazolopyridines are generally obtained by intramolecular cyclization of hydrazinonitropyridines. Treatment of 2-chloro-3-nitropyridine and 2-nitro-3-fluoropyridine with excess

hydrazine affords compounds (12) and (11), respectively <75KGS1004>. Further substitution on the hydrazine moiety provides an entry to triazolopyridine *N*-oxides. For example, exposure of the 4-hydrazino-3-nitroquinolines (174) and (175) to either base or silica gel gave the [1,2,3]triazolo[4,5-*c*]quinoline 3-oxides (176) and (177), while phosphorus trichloride-hexamethylphosphoramide afforded 2-phenyl[1,2,3]triazolo[4,5-*c*]quinoline (178) <80M963, 89H(29)899> (Equation (21) and Scheme 35). Alternatively, as shown in Scheme 36, photolysis (338 nm) of 3-nitropyridylhydrazone (179) gave 3-methyl[1,2,3]triazolo[4,5-*b*]pyridine 1-oxide (182). Mechanistically, a sequential [3 + 2]-diradical cycloaddition ((179) to (180)) and *retro*-[3 + 2]-cycloaddition to the oxadiaziridine (181) is proposed. The rearrangement ((181) to (182)) is premised on N-1 being more electron-rich <74CPB1269>.



Scheme 35

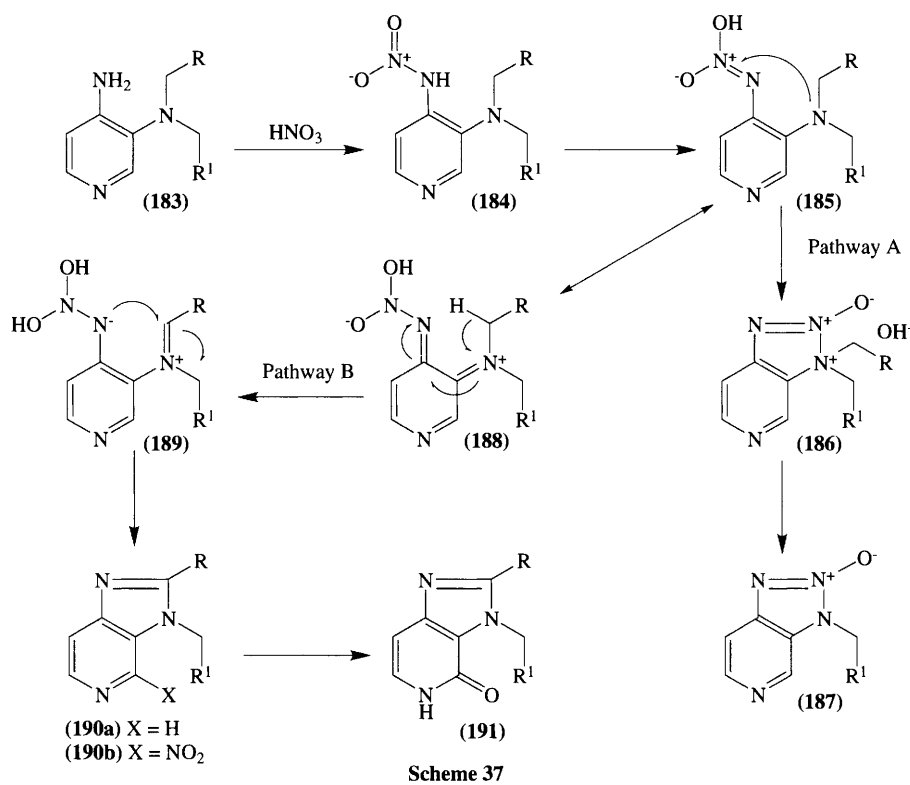


Scheme 36

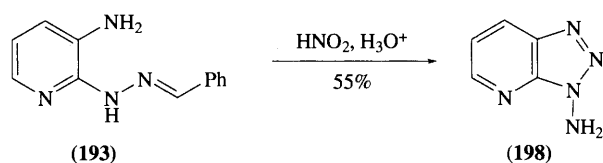
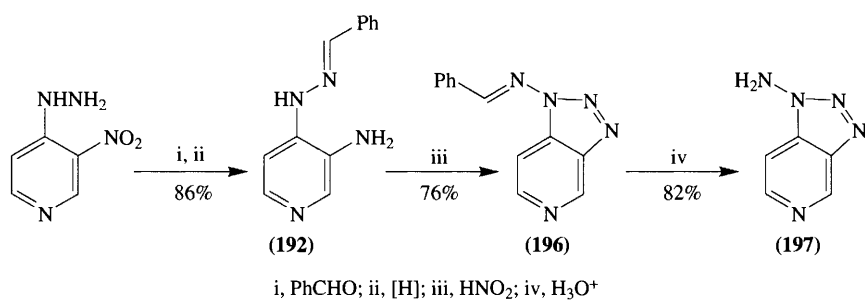
Few examples of triazole 2-oxides have been reported. However the anomalous nitration of 4-amino-3-(dialkylamino)pyridines (183), while not preparatively useful, provides triazolo[4,5-*c*]pyridine 2-oxides (187) <92H(34)1491>. As shown in Scheme 37 and Table 9 an intermediate 4-nitraminopyridine (184) undergoes two possible modes of cyclization. The first mode (pathway A) affords the *N*-oxides (187), while the second mode (pathway B) affords imidazolo[4,5-*c*]pyridines (190) and imidazolo[4,5-*c*]pyridin-4-ones (191).

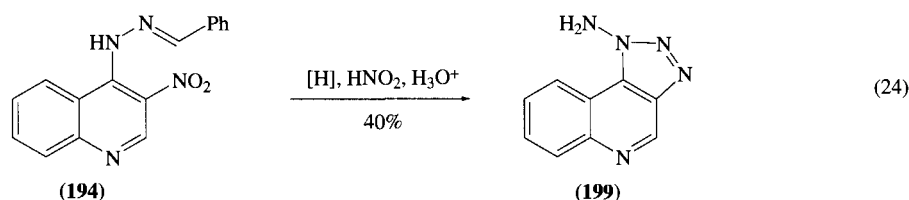
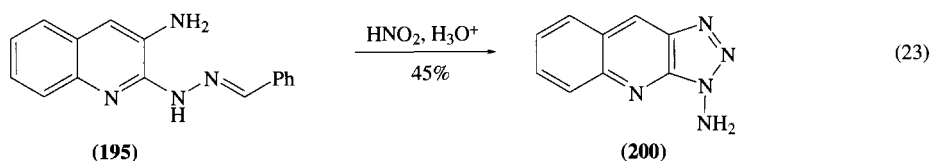
7.10.9.1.3 *N*-Amino[1,2,3]triazolopyridines

The cyclization of *ortho*-diazonium hydrazones provides a regioselective synthesis of *N*-amino-triazolopyridines (Scheme 38 and Equations (22)–(24)). Thus, 3-amino-4-(benzylidenehydrazino)pyridine (192), 3-amino-2-(benzylidenehydrazino)pyridine (193), 3-nitro-4-(benzylidenehydrazino)quinoline (194), and 3-amino-2-(benzylidenehydrazino)quinoline (195) afforded 1-amino-triazolo[4,5-*c*]pyridine (197), 3-aminotriazolo[4,5-*b*]pyridine (198), 1-aminotriazolo[4,5-*c*]quinoline (199), and 3-aminotriazolo[4,5-*b*]quinoline (200), respectively <69JCS(C)1758>.

**Table 9** Nitration of 4-amino-3-(dialkylamino)pyridines (Scheme 37).

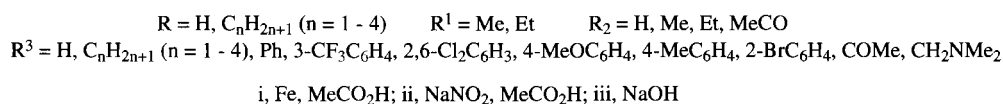
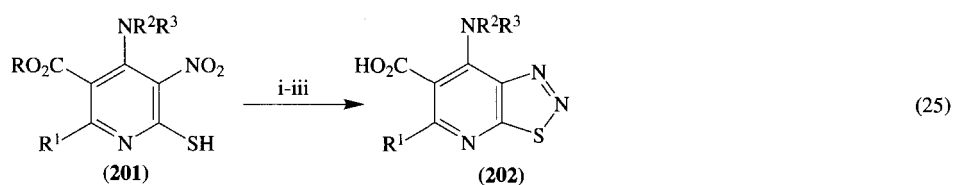
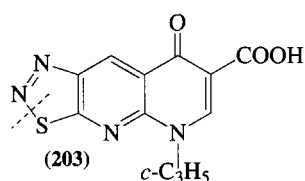
<i>R, R'</i>	(190a)	(190b)	(191)	(187)
—(CH ₂) ₃ —		12%		
—(CH ₂) ₂ —	10%	9%		
—CH ₂ OCH ₂ —	15%			
H, H	10%			
Me, Me			8%	76%
Et, Et			13%	43%
H, Pr ⁿ	8%			18%





7.10.9.1.4 [1,2,3]Thiadiazolopyridines

These heterocycles are prepared exclusively by the electrocyclization of *in situ* generated *ortho*-diazonium thiolates <78PJC2039>. This is illustrated by the syntheses of (i) antiinflammatory 7-amino[1,2,3]thiadiazolo[5,4-*b*]pyridine-6-carboxylic acids (**202**) <76USP3965108> from penta-substituted pyridines (**201**) and (ii) antibacterial thiadiazolo[5,4-*b*][1,8]naphthyridine carboxylic acids (**203**) (Equation (25)) <80CPB761>.



7.10.9.1.5 [1,2,5]Thiadiazolopyridines and [1,2,5]selenadiazolopyridines

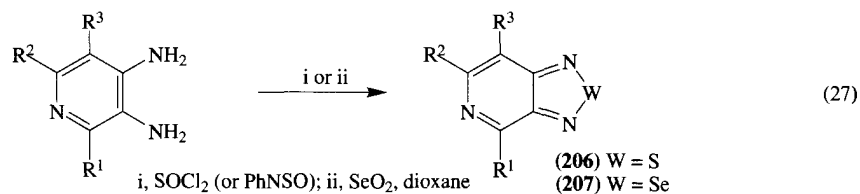
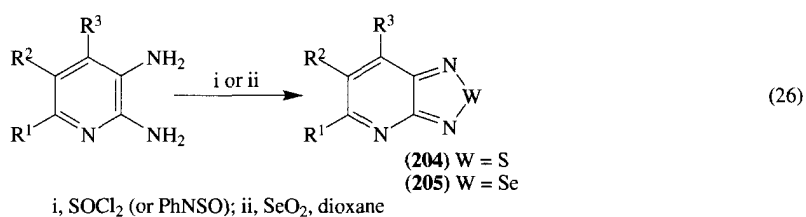
These heterocycles are typically synthesized by the formal insertion of either selenium or sulfur into appropriate 1,2-diaminopyridines (Tables 10 and 11). For example, 2,3-diaminopyridine reacts with either thionyl chloride (or *N*-sulfanylaniline) or selenium dioxide to afford 1,2,5-thiadiazolo[3,4-*b*]pyridine (**204**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$) and 1,2,5-selenadiazolo[3,4-*b*]pyridine (**205a**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$), respectively (Equations (26) and (27)) <70RTC5, 81S316, 83H(20)1043, 83S581, 91CB1237>. In general, the thiadiazolo analogues are more stable than the corresponding selenadiazolo analogues.

Table 10 [1,2,5]Thiadiazolo[4,5-*b*]pyridines (**204**) and [1,2,5]selenadiazolo[4,5-*b*]pyridines (**205**) from 2,3-diaminopyridines.

Compound	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>X</i>	Yield (%)	<i>mp</i> (°C)	Ref.
204a	H	H	H	S	65	48.7–49.0	70RTC5
204b	H	H	Cl	S	54	134	70RTC5
204c	H	Br	H	S	54	139.5–140	83H(20)1043
204d	—CH=CH—CH=CH—		H	S	24	144–145	81S316
205a	H	H	H	Se	29	118	70RTC5
205b	H	H	Cl	Se	45	190 (dec.)	70RTC5
205c	H	H	OH	Se	24	> 260	70RTC5
205d	H	Br	H	Se	68	180.5–181	83H(20)1043
205e	—CH=CH—CH=CH—		H	Se	20	240–241	81S316

Table 11 [1,2,5]Thiadiazolo[4,5-*c*]pyridines (**206**) and [1,2,5]selenadiazolo[4,5-*c*]pyridines (**207**) from 3,4-diaminopyridines.

Compound	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>X</i>	Yield (%)	<i>mp</i> (°C)	Ref.
206a	Cl	Cl	NH ₂	S	86	175–176	83H(20)1043
206b	H	Br	H	S	54	139.5–140	83H(20)1043
206c	Cl	H	H	S	27	116	70RTC5
206d	OH	H	H	S	28	216	70RTC5
206e	H	—CH=CH—CH=CH—		S	26	118–119	83S581
206f	OH	—CH=CH—CH=CH—		S	59	295–298	91CB1237
207a	H	H	H	Se	9	181	83H(20)1043
207b	H	Br	H	Se	68	180.5	83H(20)1043
207c	H	H	Br	Se	61	205.5	83H(20)1043
207d	Cl	Cl	NH ₂	Se	87	188	83H(20)1043
207e	Cl	H	H	Se	49	> 200 (sub.)	70RTC5
207f	OH	H	H	Se	52	348–349	91CB1237
207g	H	—CH=CH—CH=CH—		Se	19	214–215	83S581
207h	OH	—CH=CH—CH=CH—		Se	52	348–350	91CB1237
207i	Ph	Ph	Ph	Se	93	247.5–249.5	82JHC1481
207j	Ph	CO ₂ Et	Ph	Se	36	176.0–179.0	82JHC1481
207k	Ph	CH ₂ OH	Ph	Se	66	247.0–249.0	82JHC1481
207m	Ph	CN	Ph	Se	90	282.0–284.5	82JHC1481



7.10.9.1.6 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]oxadiazolo[3,4-*c*]pyridines and N-oxides

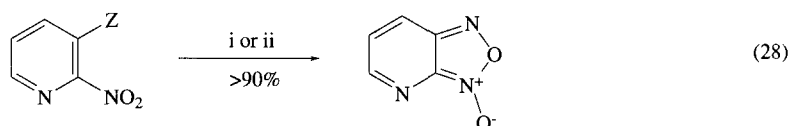
The pyridofuroxans are typically prepared by either (i) thermolysis of *ortho*-azidonitropyridines or (ii) oxidative cyclization of *ortho*-nitroamines (Scheme 39 and Equations (28) and (29)). Dyll and Wong have characterized the thermolysis of *ortho*-azidonitropyridines and *ortho*-azido-

The reaction scheme shows the conversion of 2-nitro-4-R-1H-1,2,3-triazole (209) to 2-nitro-4-R-1H-1,2,3-triazole (210) via intermediate (208).

 (209) $\rightleftharpoons$ (208) $\rightarrow$ (210)

 R = H (96%) R = NO₂ (92%)

Scheme 39



(211a) W = NO₂
 (211b) W = H

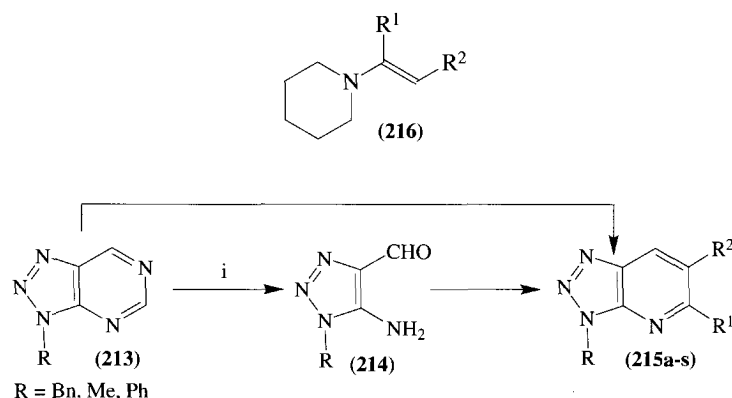
(212a) W = NO₂
 (212b) W = H

(29)

The reaction of 3-substituted triazolo[4,5-*d*]pyrimidines (8-azapurines) (**213**) with activated methylene synthons in the presence of sulfuric acid is reported to afford 5,6-disubstituted triazolo[4,5-*b*]pyridines (**215**). Since these reactions occur via 5-amino-4-formyltriazoles (**214**) $\langle 79\text{CPB}2861, 88\text{SCB}85 \rangle$, similar cyclizations of other derivatives of 5-amino-4-formyltriazole have afforded additional analogues (Table 12) $\langle 73\text{JCS(P1)}1620 \rangle$. Higashino and co-workers have also shown that 3*H*-triazolo[4,5-*d*]pyrimidines (**213**) participate in an inverse-electron Diels–Alder reaction with enamines (**216**) to afford the derivatives (**215**), albeit in low yields (Schemes 40 and 41) $\langle 91\text{CPB}282 \rangle$.

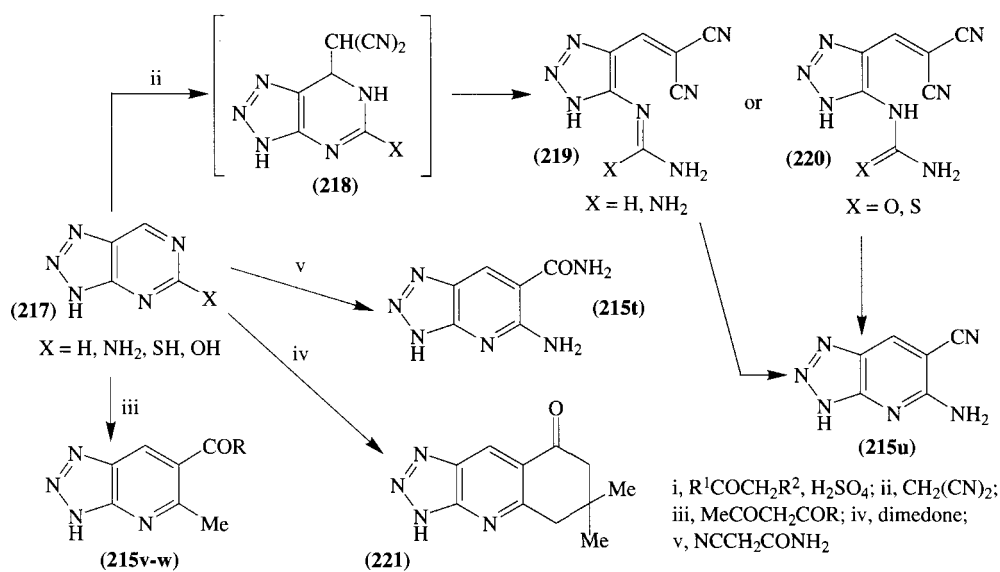
Table 12 Conversion of 3*H*-triazolo[4,5-*d*]pyrimidines (**213** and **217**) and 5-amino-4-formyltriazoles (**214**) to triazolo[4,5-*b*]pyridines (**215**).

Compound	R	R ¹	R ²	Yield (%)	mp (°C)	Ref.
215a	Me	Me	COMe	75	151–152	79CPB2861
215b	Me	Me	CO ₂ Et	72	102–103	79CPB2861
215c	Me	—(CH ₂) ₃ —		78	139–140	79CPB2861
215d	Me	—(CH ₂) ₄ —		82	124–125	79CPB2861
215e	Ph	Me	COMe	50	150–151	79CPB2861
215f	Ph	Me	CO ₂ Et	48	102–103	79CPB2861
215g	Ph	Me	H	30	112–113	79CPB2861
215h	Ph	Ph	H	21	124–125	79CPB2861
215i	Ph	—(CH ₂) ₃ —		47	117–118	79CPB2861
215j	Ph	—(CH ₂) ₄ —		68	111–112	79CPB2861
215k	Ph	Me	H	68	113	88BSB85
215m	Bn	Me	H	76	100	88BSB85
215n	Ph	Me	CO ₂ Et	16	100	88BSB85
215o	Ph	NH ₂	CN	78	260	88BSB85
215p	Bn	NH ₂	CN	77	276	88BSB85
215q	Ph	HO	CO ₂ Et	85	185	88BSB85
215r	Ph	HO	CN	42	236	88BSB85
215s	Bn	HO	CN	44	220	88BSB85
215t	H	NH ₂	CONH ₂	58	> 320	73JCS(P1)1620
215u	H	NH ₂	CN	41	> 300	73JCS(P1)1620
215v	H	Me	COMe	39	172	73JCS(P1)1620
215w	H	Me	CO ₂ Et	39	189	73JCS(P1)1620

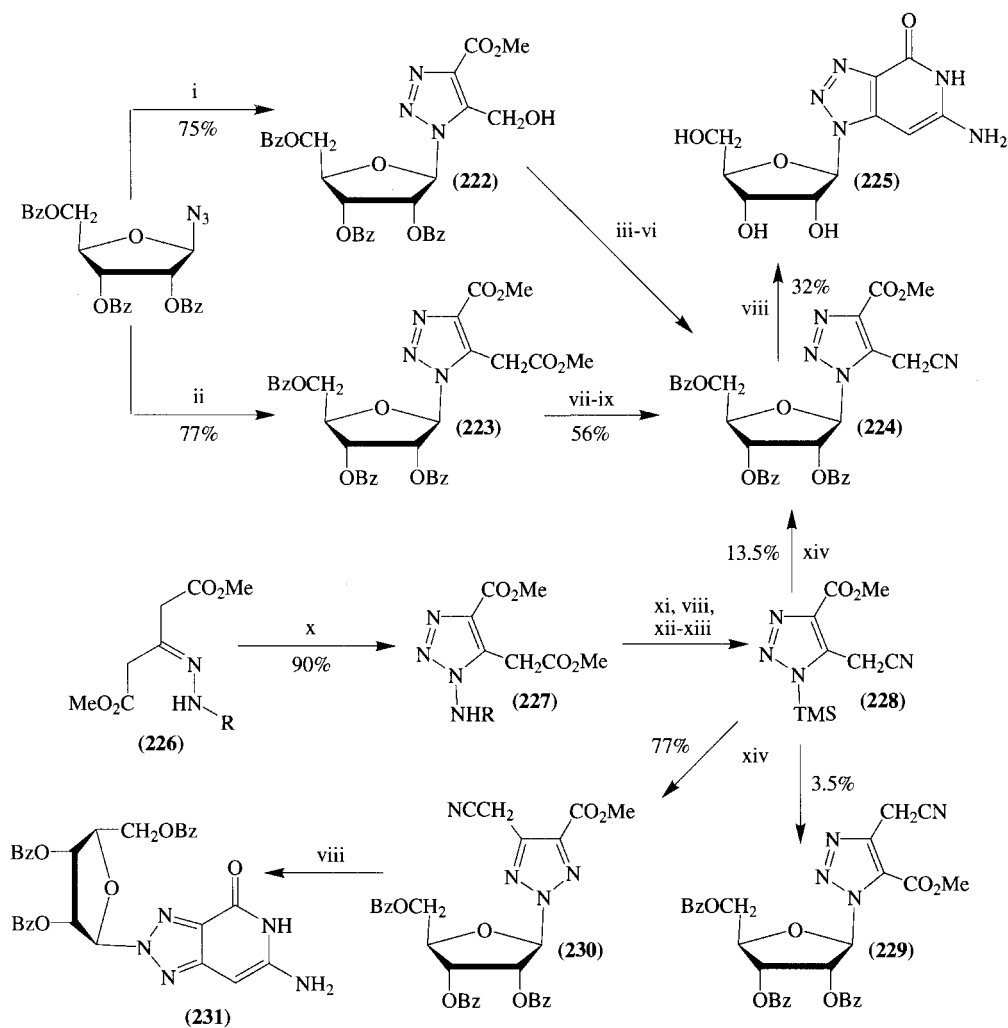
**Scheme 40**

Alternatively, (**217**) react with activated methylene synthons in the presence of potassium bicarbonate to afford transient C=N adducts (**218**) which revert to the 4-amino-5-(β,β -disubstituted vinyl)triazoles (**219**) or (**220**). Recyclization of these products (**219**) or (**220**) affords (**215**). Similar transformations of 1-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidines <77CPB535>, pyrido[2,3-*d*]pyrimidines <75CPB2939, 78CPB3242>, and quinazolines <79CPB2861> have also been reported.

Similar approaches (Scheme 42) were employed for the synthesis of 8-aza-3-deazaguanine (**2**) and 8-aza-3-deazaguanosine (**225**), but the synthetic challenges lie in the synthesis of the appropriate trisubstituted triazoles. The first synthesis is based on a [3 + 2] cycloaddition of 2,3,5-tri-*O*-benzoyl-D-ribose azide to various alkynes which afford two triazole regioisomers. The major cycloadducts (**222**) and (**223**) are converted sequentially to the nitrile (**224**) and then to 8-aza-3-deazaguanosine (**225**) <80CJC2550, 91MI 710-01>. The second synthesis, based on diazo transfer to the β -hydrazonoglutamate (**226**), afforded the *N*-(2,4-dinitrophenylamino)triazole (**227**) <80JHC159>. Sequential deprotection and cyclization with ammonia then affords 8-aza-3-deazaguanine (**2**) which is a poor substrate for ribosylation. Ribosylation of the *N*-(trimethylsilyl)triazolenitrile (**228**) with tri-*O*-benzoyl-D-ribose chloride affords the 1-, 2-, and 3-isomers ((**224**), (**230**) and (**229**)) in a ratio of 13.5:77.0:3.5, respectively. The desired isomer (**224**) is converted to 8-aza-3-deazaguanosine (**225**), while the 2-isomer (**230**) was converted to 6-amino-2-(β -D-ribofuranosyl)[1,2,3]triazolo[4,5-*c*]pyridin-4(5*H*)-one (**231**) <80JHC159>.



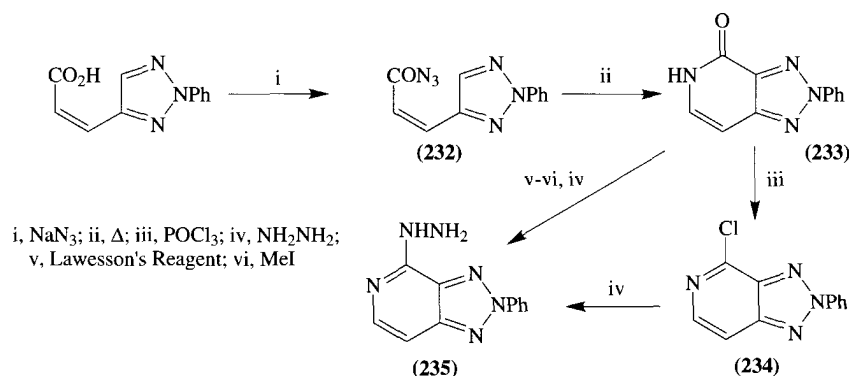
Scheme 41



i, $HOCH_2C=CCO_2Me$; ii, $CH_2=C=CHCO_2Me$; iii, act. MnO_2 ; iv, HCN ; v, $DMF, SOCl_2$; vi, $H_2, 5\% Pd-C, Et_3N$; vii, $NaOMe, MeOH$; viii, NH_3 ; ix, $Ac_2O, DMAP$; x, $TosN_3, DBU$; xi, H_2, PtO_2 ; xii, $POCl_3$; xiii, $HMDS$; xiv, 2,3,5-tri-O-benzoyl-D-ribose chloride, $SnCl_4$

Scheme 42

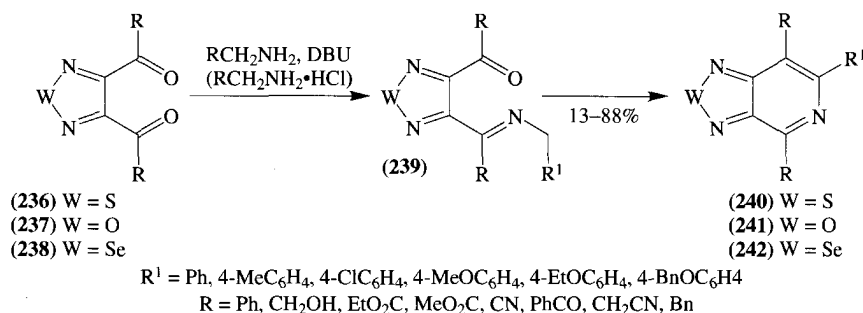
Triazole-based annulations have also been used to prepare 2-phenyl-2*H*-[1,2,3]triazolo[4,5-*c*]pyridin-4-one (**233**) from 2-(2-phenyl-1,2,3-triazole)acrylic acid via a thermal Curtius reaction of the α,β -unsaturated acyl azide (**232**) (Scheme 43). Further functionalization of the nucleus was accomplished using the intermediate 2*H*-4-chlorotriazolo[4,5-*c*]pyridine (**234**) (85LA1922).



Scheme 43

7.10.9.2.2 [1,2,5]Thiadiazolo[4,5-*c*]pyridines, [1,2,5]selenadiazolo[4,5-*c*]pyridines, and [1,2,5]oxadiazolo[4,5-*c*]pyridines

Annulation of a pyridine nucleus onto a preformed 1,2,5-thia(selena or oxa)diazole unit has been accomplished (Scheme 44). Specifically, 3,4-diaroyl[1,2,5]heterodiazoles (**236**)–(**238**) react with alkylamines under either basic or acidic conditions to afford [1,2,5]heterodiazolo[3,4-*c*]pyridines (**240**)–(**242**) in moderate to good yields (Table 13) (79S687, 80S842, 83H(20)1285, 89JHC215). These cyclizations occur via an intermediate *ortho*-iminoketone (**239**).



Scheme 44

7.10.10 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROBICYCLIC SYSTEMS

7.10.10.1 Triazolopyridines

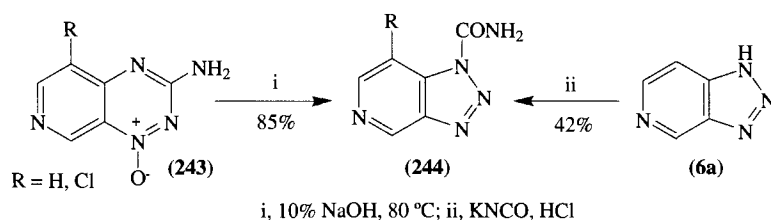
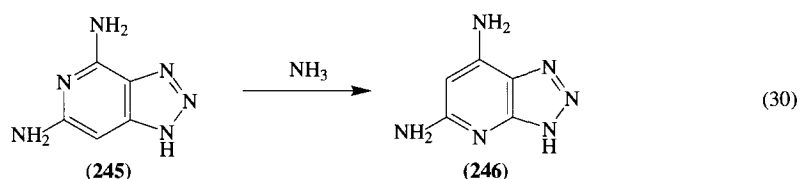
Few examples of synthesis of triazolopyridines by rearrangements of other heterobicyclic systems have been reported. The structure of the product, *N*-triazolopyridine carboxamides (**244**), obtained from the rearrangement of 3-aminopyrido[4,3-*e*]triazine 1-oxides (**243**) (62JOC2504, 71JHC47, 76MI 710-02) was unambiguously determined by synthesis from [1,2,3]triazolo[4,5-*c*]pyridine (**6a**) (Scheme 45). The Dimroth rearrangement is a well-established sequence for the interconversion of bicyclic triazoles to other bicyclic triazoles. A notable example, shown in Equation (30), is the conversion of 4,6-diaminotriazolo[4,5-*c*]pyridine (**245**) to 5,7-diaminotriazolo[4,5-*b*]pyridine (**246**) in the pres-

Table 13 Synthesis of [1,2,5]thia(oxa or seleno)diazolo[3,4-*c*]pyridines (**240**)–(**242**) from 3,4-aroaryl-[1,2,5]thia(oxa or seleno)diazoles (**236**)–(**238**) (Scheme 44).

Compound	<i>R</i>	<i>R'</i>	<i>W</i>	Yield (%)	<i>mp</i> (°C)	Ref.
240a	Ph	Ph	S	88	187–189	79S687
240b	4-MeC ₆ H ₄	Ph	S	77	238–239	79S687
240c	4-ClC ₆ H ₄	Ph	S	86	248–249	79S687
240d	Ph	CH ₂ OH	S	42	152–154	79S687
240e	Ph	CO ₂ Et	S	83	149–150	80S842
240f	4-MeC ₆ H ₄	CO ₂ Et	S	88	157–159	80S842
240g	4-ClC ₆ H ₄	CO ₂ Et	S	75	147–148.5	80S842
240h	Ph	CO ₂ Me	S	70	156–158	80S842
240i	4-MeC ₆ H ₄	CO ₂ Me	S	70	163–165	80S842
240j	4-ClC ₆ H ₄	CO ₂ Me	S	70	162–163.5	80S842
240k	Ph	CN	S	95	200–202	80S842
240m	Ph	COPh	S	42	181–182	80S842
240n	Ph	CH ₂ Ph	S	44	173–174	83H(20)1285
240o	Ph	CH ₂ CN	S	17	178–180	83H(20)1285
240p	Ph	vinyl	S	75	139–141	82JHC1481
240q	4-MeOC ₆ H ₄	2-MeOC ₆ H ₄	S	71	230–232	89JHC215
240r	4-MeOC ₆ H ₄	3-MeOC ₆ H ₄	S	66	170–172	89JHC215
240s	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	S	68	161–162	89JHC215
240t	4-MeOC ₆ H ₄	3,4-(MeO) ₂ C ₆ H ₃	S	71	144–145	89JHC215
240u	4-MeOC ₆ H ₄	Ph	S	68	198–199	89JHC215
240v	4-EtOC ₆ H ₄	2-MeOC ₆ H ₄	S	67	218–219	89JHC215
240w	4-EtOC ₆ H ₄	3-MeOC ₆ H ₄	S	12	154–156	89JHC215
240x	4-EtOC ₆ H ₄	4-MeOC ₆ H ₄	S	81	174–176	89JHC215
240y	4-EtOC ₆ H ₄	3,4-(MeO) ₂ C ₆ H ₃	S	64	168–171	89JHC215
240z	4-EtOC ₆ H ₄	Ph	S	70	205–207	89JHC215
240aa	4-Bu ⁿ OC ₆ H ₄	2-MeOC ₆ H ₄	S	9 ^a	153–155	89JHC215
240ab	4-Bu ⁿ OC ₆ H ₄	2-MeOC ₆ H ₄	S	65 ^a	148–150	89JHC215
240ac	4-Bu ⁿ OC ₆ H ₄	3,4-(MeO) ₂ C ₆ H ₃	S	80	162–164	89JHC215
241a	Ph	Ph	O	13	161.0	79S687
241b	Ph	CO ₂ Et	O	41	122–124	80S842
241c	Ph	CO ₂ Me	O	45	157–158	80S842
241d	Ph	CN	O	73	178–182	80S842
241e	Ph	COPh	O	44	177–178	80S842
242a	Ph	Ph	Se	93	247–249	82JHC1481
242b	Ph	CO ₂ Et	Se	36	176–179	82JHC1481
242c	Ph	CN	Se	90	282–284.5	82JHC1481
242d	Ph	CH ₂ OH	Se	66	247–249	82JHC1481

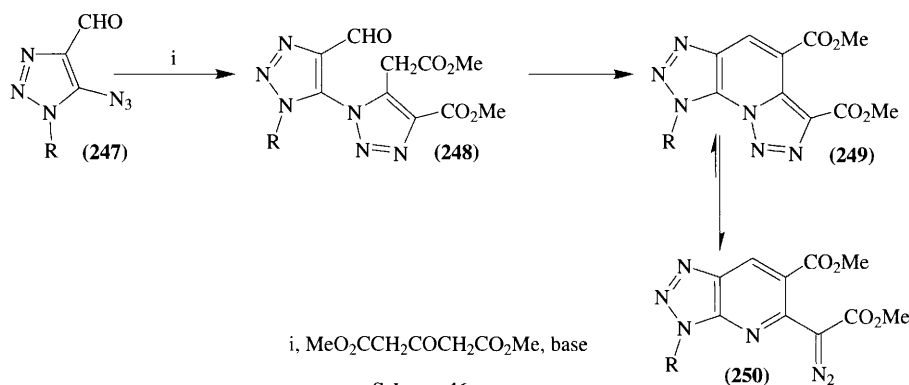
^aThese two are distinct thermochromic isomers.

ence of excess ammonia at 150 °C (72JOC3601, 73JOC1095). These rearrangements are sensitive to substituent effects and are discussed in Section 7.10.10.2.

**Scheme 45**

In a different strategy (Scheme 46), albeit specialized, the tandem cycloaddition–aldol synthesis of triazolo[1,5-*a*]pyridines (**249**) from the azidotriazoles (**247**) proceeds with the intermediacy of the

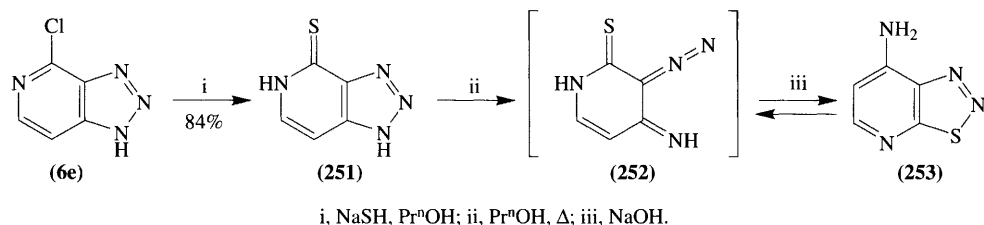
bis-triazoles (**248**). The tricyclic bis-triazoles (**249**) undergo isomerization to the 5-(α -diazocarbonyl)triazolo[4,5-*b*]pyridines (**250**) <93ACS323>.



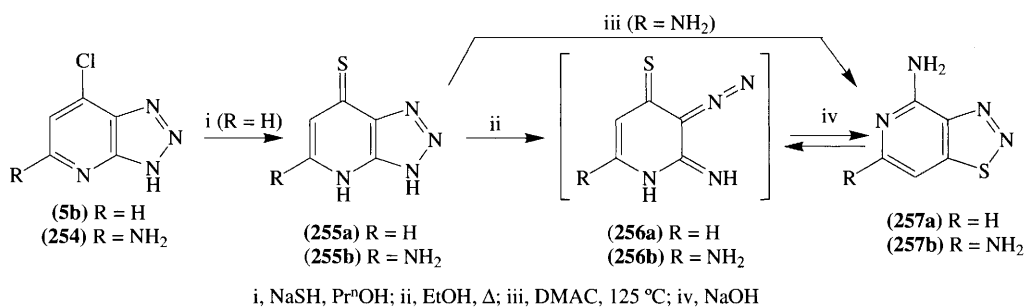
Scheme 46

7.10.10.2 Thiadiazolopyridines

During the early studies of nucleoside analogues by various research groups, rearrangements of thiolpyridyltriazoles to aminopyridylthiadiazoles were observed. These rearrangements, which are base catalyzed and proceed via α -diazothione intermediates (**252**) and (**256**), have been used effectively to generate thiadiazolopyridines. As shown in Schemes 47 and 48, 4-chloro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (**6e**) is converted to 7-amino[1,2,3]thiadiazolo[5,4-*b*]pyridine (**253**) via 1,5-dihydro-4*H*-[1,2,3]triazolo[4,5-*c*]pyridine-4-thione (**251**). Similarly, 7-chloro-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine (**5b**) affords 4-amino[1,2,3]thiadiazolo[4,5-*c*]pyridines (**257a**) <72JOC3601, 76JOC3784>.



Scheme 47

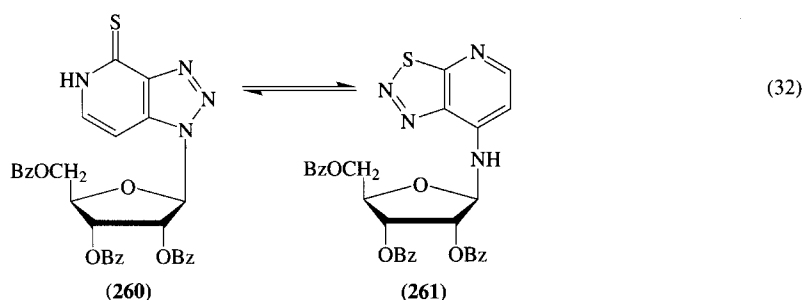
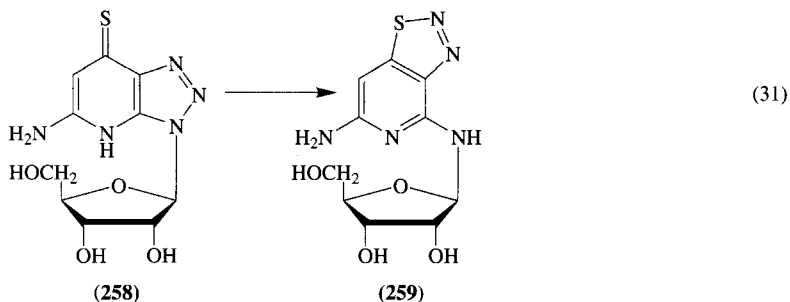


Scheme 48

Similarly, treatment of 5-amino-7-chloro-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine (**254**) with sodium hydrosulfide–butanol affords 5-amino-1,4-dihydro-7*H*-[1,2,3]triazolo[4,5-*b*]pyridine-7-thione (1-deaza-8-aza-6-thioguanine) (**255b**) which isomerizes to 4,6-diamino[1,2,3]thiadiazolo[4,5-*c*]pyridine (**257b**) in *N,N*-dimethylacetamide (125 °C) <76JOC3784>.

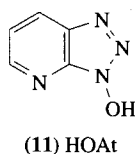
The Dimroth-type rearrangements are sensitive to both solvent and electronic effects. Electron-withdrawing substituents on the pyridine nucleus (—HNC=S or $\text{—NC=SH} \gg \text{—NCNH}_2$) facilitate the rearrangement, while the solvent effect is based on empirical observations. For example, 5-amino-1,4-dihydro-7*H*-[1,2,3]triazolo[4,5-*b*]pyridine-7-thione 3-riboside (**258**) is converted in DMF

(25 °C) to 4-(ribosylamino)-6-amino-[1,2,3]thiadiazolo[4,5-*c*]pyridine (**259**), but not in water (Equation (31)). In contrast, 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)triazolo[4,5-*c*]pyridine-4-thione (**260**) and 4-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)amino-[1,2,3]thiadiazolo[5,4-*b*]-pyridine (**261**) exist as an equilibrium mixture (Equation (32)) <78JOC4910>.



7.10.11 IMPORTANT COMPOUNDS AND APPLICATIONS

In addition to fundamental chemical interest, representative heterocycles have been evaluated as (i) antiallergy agents <88USP4720496>, (ii) antiinflammatory agents <76USP3971800, 78JMC965>, (iii) antibacterials <80CPB761>, (iv) anticonvulsants <93USP5240937>, (v) antivirals <75ANY(255)342>, (vi) gastric (H^+/K^+)-ATPase inhibitors <90JMC527>, (vii) CNS agents <68JMC87>, (viii) plant-growth regulants <73P2087, 76MI 710-01, 91EUP453065>, (ix) thromboxane synthetase inhibitors <91EUP446604>, (x) *Lactobacillus trans*-ribosylase substrates <75MI 710-01> and (xi) substrates for rabbit liver aldehyde oxidases and adenosine kinases <79JBC(254)2346, 86MI 710-01>. 1-Hydroxy-7-azabenzotriazole (HOAt) (**11**) has been found to be an excellent peptide-coupling reagent (see Section 7.10.8.1) with minimal racemization.



7.11

Bicyclic 5-6 Systems: Purines

GORDON SHAW

University of Bradford, UK

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7.11.1 INTRODUCTION

Since the preceding account of purines was written in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) [84CHEC-I(5)499] there has been a continuation of the explosive interest in purines and pyrimidines which arose in the 1950s following the Watson–Crick statement. However, by far the main thrust of research in the 1980s and 1990s has been towards the chemistry and especially biochemistry of purine and pyrimidine nucleosides and nucleotides but especially polynucleotides and the nucleic acids. Most of this work is clearly beyond the scope of this chapter but reviews covering some of the chemical, biochemical, and biological aspects are recorded in Table 1. In addition, whereas much of the basic chemistry of purines was largely completed by the 1980s, there has nevertheless been a steady and continuing interest in purine base chemistry including improvements in methods used for calculating and measuring interaction energies, new studies of tautomeric forms, refined x-ray diffraction data, new mass spectral studies, especially collision-induced dissociation data, and new examples of free-radical reactions. Also, several new naturally occurring purine bases have been isolated and studied, including the agelasines and agelasimines derived from marine sponges, and the cytokinins derived from plants and corals. A new intermediate in *de novo* purine nucleotide biosynthesis has been proposed together with two new pathway enzymes.

Table 1 Purine reviews.

Subject	Author(s)	Ref.
Tautomerism	Person <i>et al.</i>	89JST(194)239
<i>Ab initio</i> MO calculations	Nagata and Aida	88JST(48)451
Electronic states	Callis	83MI 711-03
Photochemistry	Duker and Gallagher	88MI 711-01
Redox chemistry	Steenken	89CRV503, 92MI 711-04
Radiochemistry	Neta and Dizdaroglu	B-89MI 711-06
Purine receptors	Jacobson and Daly	91MI 711-12
Purine analogues	Hitchings	91MI 711-05
Photooxidation	Cadet <i>et al.</i>	89MI 711-08, 91MI 711-09
Chemotherapy	Elion	89AG870, 93MI 711-05
	Abbrachio <i>et al.</i>	93MI 711-06
Cytokinins	Shaw	B-94MI 711-03
Nucleoside analogues in chemotherapy	Perigand <i>et al.</i>	92MI 711-08
Imidazole nucleosides	Shaw	B-94MI 711-04
9-Substituted guanines	Clausen and Christensen	93OPP373
Carbocyclic nucleosides	Marquez and Lim	86MI 711-04
Antiviral nucleoside analogues	De Clercq	94MI 711-05

7.11.2 THEORETICAL METHODS

Much work has been concerned with the analysis of pairing and stacking interaction energies between purines and other compounds, especially nucleic acid bases. Thus using only *ab initio* MO calculations the fact that *O*(6)-methyl guanosine is more protomutagenic than *N*(7)-methyl guanine is explained by differences in pairing interaction energies [88JST(43)487, 88JST(48)451]. Similar cal-

culations indicated that the interaction energy between nucleic acid bases is highly sequence dependent, especially when the sequence includes guanine (G) and cytosine (C) <86IJQ1253>. A theoretical attempt has been presented <92JA3675> to explain why adenine (A) and thymine (T) or G and C pair, following a note <90NAT33> which reported the design, synthesis, and incorporation into DNA and RNA of new base pairs with H-bonding patterns different from those in A–T or G–C using PM3, AM1, and AMBER (Ex 1/2) methods. Monte Carlo statistical mechanics simulation and analysis has also been used to elucidate <90JA7269> the strong binding of adenine with Zimmerman's molecular tweezer (a polyaromatic amino acid) and improved *ab initio* pair potentials for the interaction of purines and pyrimidines with water were used to investigate the hydration patterns of the bases; also, by means of Monte Carlo simulations, preferential hydration sites were analyzed and discussed <91JST(81)355>.

The molecular geometries of purines have also been examined. Thus semiempirical (AM1) and *ab initio* (3-21G and 4-31G) calculations for adenine, 2-fluoro-, and 2-chloroadenine indicate that the molecules are flat. For the halo (especially chloro) adenines, the results from the semiempirical method differ from the *ab initio* findings more widely than for adenine <93JST(99)211>. Molecular geometries of adenine and guanine have also been studied using *ab initio* LCAO–MO methods <90JA5324> at the Hartree–Fock level with 6-3G* basis set. They point to flat molecules with associated pyramidal amino groups <92IJQ43>. The optimal geometry, dipole moment and ionization potentials have been computed for 6-thioguanine using MINDO/3 and MNDO procedures. The calculated geometry is in good agreement with x-ray data and a dipole moment of less than 1 D was observed <91JST(77)103>. *Ab initio* studies also indicate that the major gas-phase tautomer of adenine is essentially planar <91CPL(177)447>.

AM1 calculations have been used to study the effects of methylation <92IJQ605> and protonation <92IJQ587> of guanine on the structures, energies, and proton-transfer reactions between G–C pairs. Thus methylation of guanine at N-3 and O-6 is predicted to lead to significant concentrations of base pairs arising from H⁺ transfer from G-1 to C-3 positions and the biological implications of this to potential miscoding in DNA is discussed <92IJQ605>. Also protonation at G-6 or at various ring sites leads to a stable complementary base pair following proton transfer from the C-3 position.

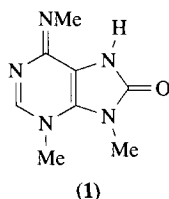
Calculated SCF deformation densities for five purines and pyrimidines were partitioned into atomic fragments which were integrated to give atomic multipole moments. The atomic fragments were transferable between related molecules, for example uracil and guanine from appropriate fragments of cytosine and adenine. Simple rules are provided for estimating the effects of polarization functions on the atomic multipole moments of most atom types in the purines <88IJQ127>. Cumulative atomic multipole moments (Camm) were also calculated for normal, rare, and protonated forms of adenine and 2-aminopurine from *ab initio* LCAO–MO–SCF wave functions obtained from an all-valence MODPOT (model potential) basis set with *ab initio* core potentials. Camm may also be used to calculate electrostatic molecular potentials, field gradients, etc. in addition to intermolecular interaction energies <87IJQ111>.

7.11.3 EXPERIMENTAL STRUCTURAL METHODS

7.11.3.1 X-ray Diffraction

A survey of the 832 hydrogen bonds in 214 crystal structures of purines and pyrimidines and 45 barbiturates has appeared <86JST(147)127>. X-ray structures of several purines have appeared during the period under review; they include caissaron (1), a new quaternary purine derivative isolated from the sea anemone *Bunodosoma caissarum* <86JCS(P1)2051>, 9-benzyl-*N*(6)-methoxyadenine <90CPB912>, some dimethoxydihydrouic acids <87AX(C)539, 87AX(C)542>, an adenine–hydrogen peroxide adduct in which each H₂O₂ molecule bonds with three adjacent adenine molecules <92AX(C)1957>, 3-isobutylxanthine <88AX(C)2138>, and 9-(2'-phosphonomethoxyethyl)adenine <91JCS(P1)1348>. The charge-density distribution in adenine hydrochloride hemihydrate was also determined from x-ray diffraction data. Some significant differences in molecular geometry were observed when compared with earlier work; lone-pair electronic density is clearly revealed and the acidic nature of the C-8 hydrogen is confirmed <93AX(B)524>.

Nucleosides examined include 1-allylisoguanosine, 1-allylxanthosine <92MI 711-01>, and 3-methyladenosine *p*-toluene sulfonate <89CPB1208>.

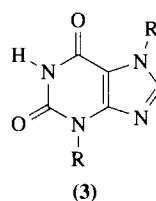
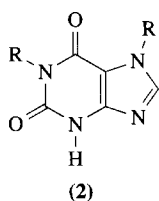


7.11.3.2 Electron Scanning Tunnelling Microscopy

The relatively new technique of scanning tunnelling microscopy has been used to obtain images of adenine and thymine attached to the basal plane of highly oriented pyrolytic graphite. The aromatic regions of both bases are strongly detected but the side chain groups were not well resolved. However the technique is claimed to discriminate between pyrimidines and purines (91MI 711-01). Similar studies of a plasmid DNA and various synthetic oligonucleotides have also been carried out (90MI 711-01, 91MI 711-02).

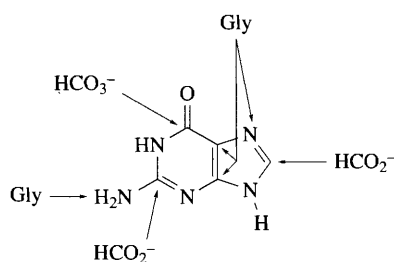
7.11.3.3 Proton NMR Spectra

Proton NMR spectral data for 1,7- and 3,7-dialkylxanthines, (2) and (3) respectively, have been used to distinguish signals due to *N*-alkyl substituents at various positions in the xanthines (91CPB2855, 92TL4867). The effect of methylation on the association ability of purines with pyrimidines has also been examined. The self-association constants for 6-methylpurine and 4-methylpyrimidine were 2.24 ± 0.07 and 2.00 ± 0.07 respectively and the heteroassociation constants could be ordered in the decreasing series: caffeine–6-methylpurine > theophylline–6-methylpurine > caffeine–4-methylpyrimidine > theophylline–4-methylpyrimidine. The equilibrium constants imply that methylation enhances the association ability (89MRC592). The same authors (89MRC249) have also studied the interaction of caffeine and theophylline in D₂O at 35°C by measuring the concentration-dependent selective changes in the chemical shifts of the *N*-methyl protons of the xanthine derivatives. Using a competitive dimer model the equilibrium constants show a decreasing tendency for heteroassociation in the series caffeine–purine ($2.97 \pm 0.15 \text{ L mol}^{-1}$) > theophylline–purine ($2.44 \pm 0.10 \text{ L mol}^{-1}$) > caffeine–pyrimidine ($1.18 \pm 0.21 \text{ L mol}^{-1}$) > theophylline–pyrimidine ($0.70 \pm 0.08 \text{ L mol}^{-1}$) and the upfield dimer shifts suggest a plane-to-plane arrangement. Pyrimidine–purine and pyrimidine–6-methylpurine cross-interactions were also compared by measuring the mutually induced concentration-dependent changes in proton chemical shifts in D₂O at 35°C. The equilibrium constants (0.41 and 0.74 M^{-1}) for the pyrimidine–purine and pyrimidine–6-methylpurine heteroassociations respectively and the dimer shifts implied that methylation of purine significantly influences the stacking interaction between the parent molecules of nucleic acid bases (92MI 711-02). The location of alkyl groups following phase-transfer catalyzed alkylation of purines without organic solvents has been determined by analysis of coupling interaction through 2-dimensional $\delta\delta$ -heteronuclear ^1H , ^{13}C -correlated NMR spectroscopy (87T2101). Deuterium quadrupole coupling constants and asymmetry parameters have been determined for 8-deuterated, 9-ethyladenine, 9-ethylguanine, adenosine, guanosine, inosine, AMP, and GMP using solid-state ^2H quadrupole echo NMR spectroscopy and lineshape fitting techniques (87JMR(71)276). Similar methods lead to the measurement of ^{14}N - and ^2H -nuclear quadrupole coupling constants and asymmetry parameters in adenine, xanthine, hypoxanthine, their nucleosides, and other heterocyclic bases. Zeeman studies and the detection of simultaneous transitions of neighbouring nuclei allowed in many cases a complete assignment of the observed spectral lines to particular ^{14}N and two deuterium sites (87JMR(72)422).



7.11.3.4 Carbon-13 NMR Spectra

Correlation of nucleic acid base conformations to 43 purine nucleosides with high-field ^{13}C NMR data has been recorded <87MRC937>, the key to the correlation being the chemical shift difference between C-2' and C-3'. It has also been shown by ^{13}C NMR spectroscopy (Scheme 1) that the skeleton of adenine and guanine arises from bicarbonate which enters C-6, from formate which enters C-2 and C-8, and from an intact glycine unit which gives rise to the C-2—N, C-4, C-5, and N-7. These findings substantiate earlier work concerning the biochemical origin of purines in yeast <87JA4698>. ^{13}C NMR spectra were also recorded for CHCl_3 solutions of 2',3'-*O*-isopropylidene-5'-*O*-*t*-butyldimethylsilylguanosine and 2',3'-*O*-isopropylidene-5'-*O*-acetylguanosine, and various pyrimidine nucleoside derivatives in which the imino groups are partially exchanged by ^2H . Upfield two-bond ^2H isotope effects on ^{13}C -chemical shifts were detected and ranged from 40 ppb for the amino interaction with C-2 in guanosine to 217 ppb for the imino interaction with C-4 in a uridine self association dimer <88JA7460>.



Scheme 1

7.11.3.5 Nitrogen-15 NMR Spectra

The ^{15}N NMR spectra of purine, 7-methylpurine, and 9-methylpurine have been measured in aqueous NaOH , H_2O , aqueous D_2SO_4 , $(\text{CD}_3)_2\text{SO}$, TFA, and FSO_3H . Protonation sites and tautomer ratios were obtained; for example in $(\text{CD}_3)_2\text{SO}$ and in $(\text{CD}_3)_2\text{SO}$ -TFA (1:2) the N-7(H):N-9(H) ratio of purine was 1:1. The effects of *N*-protonation on the ^{15}N - ^1H geminal coupling constants were also discussed <83MI 711-01>. ^{15}N NMR spectra have also been used to assign structures of isomeric N-7 and N-9 substituted purines. Comparison of ^{15}N -chemical shifts among seven pairs of N-7 and N-9 isomers revealed that the N-3 resonances are shielded by 18–20 ppm in all N-9 isomers and the amino nitrogens at C-2 or C-6 are always shielded by 3–4 ppm in the N-7 isomers. Also the N-7 chemical shifts in the N-7 isomers are always more shielded by 6–7 ppm than the N-9 resonances in the N-9 isomers. Additionally, it was found by protonation studies that N-9 of the N-7 isomer is more basic than N-7 of the N-9 isomer <86T5073>. Similarly, ^{15}N NMR shifts of the different atoms of adenine and uridine have been correlated to their π -charge densities <88BSB23>. The ^1H and ^{15}N spin lattice and spin-spin relaxation rates of purine have been measured at the natural abundance level as a function of added cupric ions. In the anionic form of the purine ligand N-7 and N-9 resonances are selectively broadened by Cu^{2+} while N-1 and N-3 are not significantly affected. The metal ions bind exclusively to the imidazole ring of the negatively charged purine ligand. The neutral ligand binds at N-7, N-9, and N-1. Electronic properties of some purine nucleosides have been examined by ^{15}N -spectroscopy <88MI 711-09>.

7.11.3.6 UV and UV Photoelectron Spectra

Zero-order first and second derivative UV absorption spectra of 18 purines and pyrimidines were determined in aqueous solution at 298 K. The procedure, based on the direct comparison of the derived maximum and minimum wavelengths and of the sequences of relative amplitudes, can be used for concentrations of purines as low as $5 \times 10^{-6} \text{ M}$ <85MI 711-01>. A similar study has shown that second derivative spectra can be used for the identification of eight mixtures of purines and pyrimidines <88TAL513>. The structure and equilibrium of purine in ethanol has been studied by UV spectroscopy which indicates the existence of annular automery in purine and the presence of associated species of only one of its tautomers <88JST(174)83>. Both polarized UV and Raman

spectra of adeninium sulfate single crystals were measured at 10 K on the same modular UV-VIS spectrometer. Slight changes of the adenine geometry around the amino group were found <90JST(219)299>. Polarized reflection spectra have also been used to study 6-methylaminopurine and 9-methyladenine from 370 to 135 nm. Corresponding absorption curves were obtained by Kramers-Kronig analysis and the transitions assigned <90JPC2873>. The electronic absorption and fluorescence spectra of adenine were also studied in aqueous solution at two different pH values and in the presence, and absence, of oxygen, as a function of time. A strong absorption found at 305 nm is interpreted as an $n-\pi^*$ transition in adenine. The rare (protonated) tautomer of adenine fluoresces near 370 nm while the normal species under interaction with O_2 fluoresces near 345 nm from the singlet $n-\pi^*$ excited state <90JST(220)25>.

UV resonance Raman spectra have been widely used to study nucleic acid bases. Thus published harmonic force fields for guanine and cytosine were tested by calculation of the relative intensities of the in-plane modes in the UV resonance Raman effect from the two lowest lying absorption bands using a theoretical approach. The study has developed a new force field that is claimed to give better agreement with the observed UV resonance Raman intensities than previously published ones <91MI 711-03>. The same authors <91JST(77)103> obtained the harmonic general force constants for 9-methylguanine and 1-methyluracil by fitting the experimental UV resonance Raman spectra recorded at 266 and 213 nm for 5'-CMP and 5'-GMP, and 266 nm for 5'-UMP. A set of general valence force constants for the in-plane modes of each compound were obtained. The same technique has been used to study adenine and thymine in several solvents at low concentrations (0.5–10 mM) where H-bonding between solute molecules is negligible. The Raman spectral patterns depend on the proton accepting and donating properties of the solvents <91JST(242)87>. UV resonance Raman spectra of protonated adenine, guanine, cytosine, and 5-methylcytosine and their nucleoside monophosphates were taken with a UV spectrometer based on an excimer laser system. Four wavelengths (220, 230, 260 and 270 nm) were used for resonant excitation of the Raman spectra and most were measured in water and D_2O . For adenine, the excitation is most easily seen at 220 nm whereas it is at 260 nm for cytosine <91MI 711-04>. Similar methods have been used to examine various purine nucleotides with laser excitation at 299, 266, 253, 240, 229, 218, 209 and 200 nm <85PNA(82)2369>.

7.11.3.7 IR and Raman Spectra

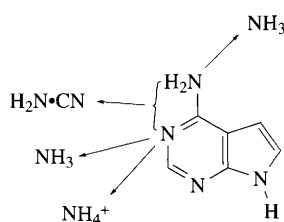
Amino-oxo and amino-hydroxy forms of 9-methylguanine have been identified in approximately equal amounts by IR studies in an argon matrix at 12 K. The amino-hydroxy tautomer occurs as two rotamers. The tautomer ratio is sensitive to UV <91MI 711-05>. The same authors have similarly studied matrix-isolated guanine, 2-dimethylamino-6-hydroxypurine and some related compounds. The estimated molecular equilibrium constants in nickel matrixes were ca. 3.6 for guanine and 5.9 for 9-methylguanine <91JST(156)29>.

Surface-enhanced Raman spectra (SERS) of purines and pyrimidines absorbed on silver electrodes were recorded in the $100\text{--}1700\text{ cm}^{-1}$ range, by using the 514.5 nm excitation wavelength from an argon laser and protonated (pH 0.5) or neutral bases. Prominent bands for the bases are 648 cm^{-1} (guanine) and 728 cm^{-1} (adenine) <82JST(79)185>. In 1991 adenine and 2-dAMP at positive surface potentials of a silver working electrode were examined using surface-enhanced Raman scattering. It is suggested that complexes of the purines with silver generate the absorption spectra. The spectrum of the adenine-silver complex shows broad bands between 1200 and 1500 cm^{-1} whereas 2-dAMP shows clearly resolved bands. The spectra are completely different from the classical SERS spectra of adenine and 2-dAMP. Thus the spectrum is characterized by an intense band at 729 cm^{-1} . At open loop potential the spectra of the Ag-dAMP complex changes slowly to the classical SERS spectrum of dAMP <91MI 711-06>. Surface-enhanced Raman scattering on active polyvinyl alcohol films doped with silver have been used to detect guanine, adenine, and various pyrimidines at a level of $10^{-8}\text{--}10^{-9}\text{ M}$ <93MI 711-01>.

7.11.3.8 Mass Spectra

The use of tandem mass spectrometry <88MI 711-08> to study the collision-induced dissociation of protonated heterocycles has invited further attention in the 1990s. Thus following collisional acti-

vation at 30 eV translational energy under multiple-collision conditions, protonated adenine decomposes along three independent major pathways which are of only minor occurrence in electron ionization mass spectra. The three pathways involve expulsion of ammonia, in approximately equal proportions from N-1 and N-6, loss of NH_2CN derived almost exclusively from N-1—C-6—N-6 and formation of NH_4^+ principally from N-1 (Scheme 2). A fourth major pathway also prevalent in EI mass spectra involves sequential expulsion of three molecules of HCN in the first step involving N-1 and C-2. Protonated methyladenine isomers and their ^{15}N and ^2H analogues show analogous reaction pathways <92JA3661>. A similar study used several commercially available purine derivatives. The protonated molecules were mass selected and their collision-induced dissociation spectra monitored using 100 eV collision energy. The ion fragments observed appeared to reflect stereochemical differences between the isomeric precursors investigated <92RCM596>.



Scheme 2

Fragmentation patterns of *O*(6,7)- and *N*(9)-ethylguanines have been investigated by laser desorption Fourier transform mass spectrometry. The ethylguanines lose ethylene giving protonated guanine, *O*(6)-ethylguanine loses MeCHO but this was not observed in the spectra of the 7- and 9-ethyl derivatives. Ionized 7- and 9-ethylguanines both lose Me radicals whereas *O*-ethylguanine does not. Collision-induced dissociation was used to identify some of the fragment ions <91MI 711-07>.

Tandem mass spectrometry has been used to identify trace amounts of naturally occurring compounds including alkylpurines in urine, which can arise from human exposure to carcinogens <92OMS(27)1225, 93OMS(28)552> and cytokinins produced from a phytopathogenic *Pseudomonas* bacteria <92OMS(27)750>. The protonated molecular ions of the cytokinins can be fingerprinted from the breakdown pattern of their gaseous unimolecular dissociations. Similar studies have been used to study intermediates and products formed in the oxidation of uric acid and thioxanthine <88ANC720>.

7.11.3.9 ESR Spectra

Much of the research work in this area has been concerned with an examination of radicals produced from DNA or nucleosides by radiation, especially UV or x-irradiation, and the implications for providing gene changes especially from interaction with carcinogens. Aqueous solution redox chemistry and transformation reactions of purine radical cations and electron and hydroxyl adducts have been reviewed <89CRV503>. Modification of DNA purines by UV irradiation has also been reviewed <88MI 711-01>. Reactions identified include photochemical addition of amino acids, alkylation by alcohols, amines, etc., activation of procarcinogens to mutagenic electrophiles, and formation of covalent bonds between DNA purines and adjacent bases. ESR and ENDOR spectroscopy has identified at 65 K four products produced by x-radiation of xanthosine dihydrate single crystals <83JCP(79)3240>. Similarly x-irradiation of 6-methylthiopurine riboside gave three ESR resonances at 20 K <82JCP(77)4879> and the radicals were identified.

In 1993 free-radical formation in adenosine and some pyrimidines was investigated by ESR spectroscopy after bombardment with heavy ions at 100 K <93MI 711-02>. Spectra were observed at 77 K, after irradiation at 100 K, upon annealing to 300 K and storage at 300 K. Individual radical patterns were isolated from the spectra by computer manipulation and assigned to structures by powder simulation based on literature data. Adenosine exhibits two H-addition radicals at C-2 and C-8. Reactions of C-6 and N-9 substituted purines with OH radicals have been studied by pulse radiolysis <87JPC4138>.

7.11.4 THERMODYNAMIC ASPECTS

7.11.4.1 Tautomerism

A review of prototropic tautomerism of heteroaromatic compounds has been published <91H(32)329> (Table 1). The major gas phase tautomer of adenine is confirmed, in an *ab initio* study, as being essentially planar <91CPL(177)447>. The stabilities of several isolated tautomers of purine, adenine, and guanine have been calculated by *ab initio* quantum mechanical methods which included relative electronic energies at the SCF level and zero point vibrational energies. The calculations predict that the following tautomers are the most stable, namely: purine *N*(9)H, adenine *N*(9)H, and guanine-3 tautomers of similar energy, i.e. amino-oxo *N*(9)H and *N*(7)H and amino-hydroxy *N*(9)H, with the latter slightly predominating. The predictions agree with experimental findings based on IR spectra in inert gas low-temperature matrixes <90JST(67)35, 91SA(A)339>. Similarly, the *N*(9)H, *N*(7)H tautomerisms of purine, adenine and 2-chloroadenine have been studied using combined experimental IR matrix isolation and *ab initio* mechanistic methods <89CPL(157)14, 94JPC2813>. Changes in tautomeric equilibria of purines which may occur as a result of changes from an inert to a polar environment have been reviewed <89JST(194)239> and an analysis of tautomeric equilibria in the gas phase and aqueous solution has been carried out for guanine, inosine, adenine, and some pyrimidines <86JST(33)45>.

Tautomerism of 9-substituted purines in solution, in the gas phase and in low-temperature inert matrixes has shown that the amino-imino equilibrium of protomutagenic *N*(6)-OH and *N*(6)-OMe adenosine is highly dependent on solvent, the proportion of imino form varying from 10% in CCl₄ to 90% in water <85MI 711-02>. The influence of solvents on the tautomerism of adenine, however, was not found to favor rare tautomeric forms <84JPR407>. An investigation of tautomerism in adenine and guanine using the semiempirical AM1 and *ab initio* methods with the 3-21G basis set showed that the most stable forms of the purines at the AM1, STO-3G, and 3-21G levels are the normal forms. At the RMP2/6-31G* (5D)//RHF/6-31G* (5D) level there is an enol tautomer of guanine less than 2 kcal mol⁻¹ higher in energy than the normal form <90JPC1366>. NMR studies on 9-alkyl-*N*(6)-OMe adenines suggest that they exist as a 1 : 3 : 5 equilibrium mixture of amino and imino forms. Similar results were found for 6-thioguanine <93JPC3520> and other 9-alkyl-*N*(6)-alkoxyadenines. However, in contrast, *N*(6,9)-dimethyladenine was found to exist solely in the amino form in CDCl₃ or DMSO solution <87CPB4482>.

7.11.4.2 Thermochemistry

Heats of dilution data for 2-methylamino-9-methylpurine, 6-dimethylamino-9-methylpurine and caffeine are reported <84MI 711-01> and the same authors <92MI 711-03> report the determination of densities and apparent molar heat capacities of 2,9-dimethyladenine, 2-ethyl-9-methyladenine, 2-propyl-9-methyladenine, 8-ethyl-6,9-dimethyladenine, 6,8,9-trimethyladenine, and 8-ethyl-6,9-dimethyladenine using flow calorimetry and flow densimetry at 25°C. The partial molar volumes correlated linearly with the number of substituted methylene groups and the number of skeletal hydrogen atoms. Partial molar heat capacities and volumes of some nucleic acid bases in 1, 3, and 6 mol kg⁻¹ aqueous urea solutions were measured using dynamic-flow microcalorimetry and a vibrating tube digital densimeter. The corresponding heat capacity and volume transfer parameters from water to urea solution enabled understanding of the nature of base interaction with urea. Only weak interaction occurred at low urea concentrations, but at high concentrations the significantly positive values of heat capacities and volumes of transfer suggested stronger interaction, which may explain denaturation of the nucleic acid helix in high urea concentrated solutions <90JCS(F1)905>.

Enthalpies of solution in water have been determined for various 2-alkyl-9-methyladenines <87MI 711-03> and *N*-methyladenines <84MI 711-02, 84MI 711-05>. Alkyl groups at C-2 of adenine contribute additively to the Van der Waals part of the enthalpy of interaction. Heats of solution of some purines and related compounds have been combined with the heats of vaporization or sublimation to yield the energies of transfer from the gas phase to DMSO and to water. The calculated group enthalpies of transfer from water to DMSO indicates marked stabilization in DMSO so that hydrogen-bonding interactions between these groups and water are less important <88MI 711-02>. Related thermodynamic data in DMSO and water for 9-methyladenine, guanine, hypoxanthine, and adenosine has been reported and the enthalpies of transfer of B and BH⁺ emphasizes contrasting hydrogen-bonding properties of the solvents used <83MI 711-01>.

Heats of sublimation of adenine and alkyl derivatives were calculated from the temperature

dependence of their evaporation rates as determined by the low-temperature quartz-resonator method. Substitution of methyl groups at hydrogen-bonding sites results in small decreased ΔH values for adenine derivatives compared to those for pyrimidine derivatives, and this is ascribed to the high contributions of stacking interaction to the ΔH values of purines as compared to pyrimidine bases <84MI 711-02>.

7.11.4.3 Chromatographic Behavior

Many purines and similar compounds have been separated by reverse-phase HPLC. Good results were achieved using Spherisorb ODS-2 as the stationary phase and 0.05 M monobasic ammonium phosphate (pH 3.5) as the mobile phase <82JC165>. A sensitive electrochemical method for the simultaneous detection of nucleic acid bases used HPLC and a vinyl alcohol co-polymer gel column. The order of susceptibility to electrochemical oxidation was guanine > adenine > thymine > cytosine and the detection limit for each base was at the picomole level <92JLC1785>. A cation-exchange HPLC method has also been described for the separation of seven bases derived by oxidation of a nucleic acid with nitrous acid including xanthine, hypoxanthine, guanine, and adenine; the stationary phase was Nucleosil 10SA (10 μm) and the mobile phase was a mixture of water and 0.2 M ammonium formate (pH 5.0) and good resolution of all peaks was achieved <91MI 711-08>. Similar methods have been used to separate a wide range of compounds including purines in human urine and plasma <85JC101>. Methylated DNA purines have been analyzed on a Waters Bondapak C18 column using fluorimetric detection with excitation and emission wavelengths 286 and 366 nm, respectively. Elution was with 10 mM ammonium formate (pH 3.8) containing 10% MeOH at 1 ml min^{-1} <88JC364>.

Purines and pyrimidines in marine environmental particles have been investigated by HPLC. Purine and pyrimidine concentrations were 0.3–9.3 $\mu\text{g L}^{-1}$ ($n = 20$) for suspended matter and 0.3–0.6 mg g^{-1} ($n = 10$) for sinking particles and evidence for phytoplankton sources of the bases was presented <88MI 711-03>. A novel naturally occurring support, namely *Lycopodium clavatum* spore membranes, has been functionalized with bases and metals and used to separate nucleic acid bases and nucleosides <88MI 711-04, 89MI 711-01, 93MI 711-03>. The use of HPLC precoated plates NH₂F2545 to separate purines and pyrimidines has also been described. The plate is coated with silica gel modified chemically with alkylamino groups. The compounds are separated according to charge differences in aqueous eluants but the plate may also be used to separate polar compounds in organic solvents <83MI 711-02>.

7.11.5 REACTIVITY OF FULLY CONJUGATED RINGS

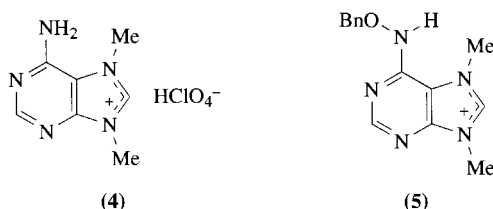
7.11.5.1 Thermal and Photochemical Reactions

Photo- and radioinduced oxidation of purines and pyrimidines has been reviewed <91MI 711-09>. The photochemistry and photophysics of purine and 6-methylpurine has been studied. The purine triplet state was determined using the energy-transfer technique for sensitizing the crocetin triplet. The purine triplet quenching rate coefficients were 7.1×10^9 , 3.4×10^9 , and $2.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for crocetin, O₂, and Mn²⁺, respectively. The decay time of the triplet under deoxygenated conditions and the triplet molar absorption coefficient at 390 nm are 1.7 μs and $2(\pm 0.5) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, respectively. Photoionization of the purines was observed at an excitation energy of 4.7 eV and the purine radical cation was produced by oxidation of the purine by radiolytically generated N₃ radicals. Its absorption maximum appeared at 290 nm. The purine anion radical, generated from radiolytically produced CO₂ radical anion, had absorption maximum and decay time of 275 nm and 16 μs , respectively <89JA8218>. Ionization of purines and their nucleosides has been studied by 193 nm laser photolysis <90MI 711-02>. The photoinduced reaction of metal enolates with 6-halogenopurine derivatives gives high yields of novel functionalized 6-alkylpurines which exist preferentially in the H-bonded enolic form in nonpolar solvents. High field ¹H and ¹³C NMR data gave unambiguous support for the proposed structures. An SRN1 mechanism is proposed for the transformations <85JA2183, 85JOC5069>.

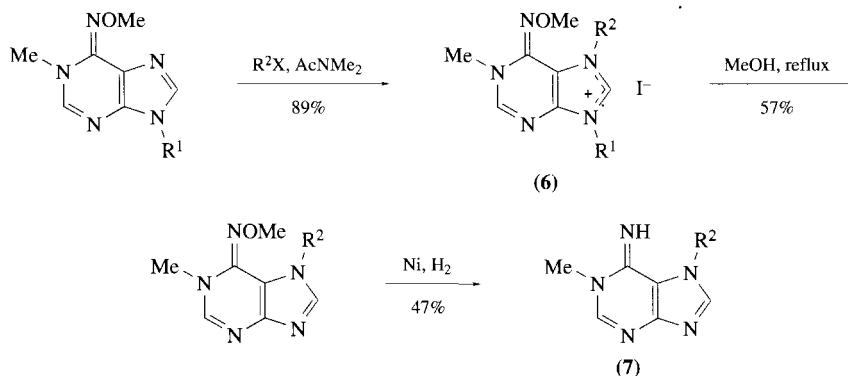
7.11.5.2 Reactions with Electrophiles

7.11.5.2.1 N-Alkylation

Phase-transfer catalysis has been increasingly used as the method of choice to alkylate various purines. Methylation of adenine under phase-transfer catalysis gave 98% 9-methyladenine whilst benzylation gave 9-benzyladenine as the major product accompanied by small amounts of the 3-benzyl isomer. Alkylation of xanthine, theobromine, and theophylline gave corresponding *N*-alkyl derivatives in high yields <82JHC249>. Regioselective *N*-alkylation of adenine was also observed under solid-liquid-phase transfer catalysis by 18-crown-6 or tetraglyme in the presence of KOCMe_3 at 0°C using $\text{AcOCH}_2\text{CH}_2\text{OCH}_2\text{Br}$ as the alkylating agent <91MI 711-13>. However, alkylation of 6-chloro-, 6-methylthio- and 6-benzylaminopurines in the presence of $\text{Bu}_4\text{N}^+\text{Br}^-$, tetraoctylammonium bromide and hexyltributylphosphonium bromide in methylene chloride or benzene with aqueous sodium hydroxide gave mixtures of the *N*(3)-, *N*(7)-, and *N*(9)-substituted derivatives <86KGS419, 87KGS113>. Similar phase-transfer catalyzed alkylation of theophylline and adenine gave regioselective 9-monoalkyl derivatives <89JHC1093, 89TL6165>. In contrast, methylation of *N*(6)-, *N*(1)-, *N*(3)-, *N*(7)-, and *N*(9)-methyl-*N*(6)-methoxyadenines with MeI in AcNMe_2 gave mixtures of the *N*(3), *N*(9)-methyl derivatives and the *N*(6,9)-dimethyl-*N*(6)-methoxyadenines. Further methylation produced *N*(6)-methoxy-1,7,9-trimethyladeninium iodide. Hydrogenolysis of the corresponding perchlorate over Pd-C gave a useful route to 7,9-dimethyladeninium perchlorate (**4**) <83CPB3149>. Similar alkylation of *N*(6)-methoxy and *N*(6)-benzyloxyadenosine led to 7-alkylation <90CPB652, 90CPB1886>. In a later exhaustive study of the methylation of *N*(6)-methoxyadenine under the same conditions the same authors reported formation of the 3-methyl derivative (17%), 9-Me (2%), *N*(6,9)-diMe (9%), 7,9-diMe (27%), 3,7-diMe (10%), and *N*(3,6)-diMe (11%). *N*(6)-Benzyloxyadenine gave similar mixtures after methylation including the 7,9-diMe derivative (**5**) (30%). In contrast, methylation of *N*(6)-methyladenine gave 3,6-diMe (82%), 6,9-diMe (1.3%), 3,7,9-triMe (1.8%), and 1,6,9-triMe (0.3%) derivatives <83CPB4270>. The same authors reported the preferential alkylation at N-7 of 3-alkyladenines (Me, Et, CH_2Ph) using MeI, EtI, and PhCH_2Br in AcNMe_2 or acetone. However, benzylation of 3-methyladenine and 3-ethyladenine and methylation of 3-benzyladenine resulted in formation of some 9-alkylated adenines <86CPB1821>.

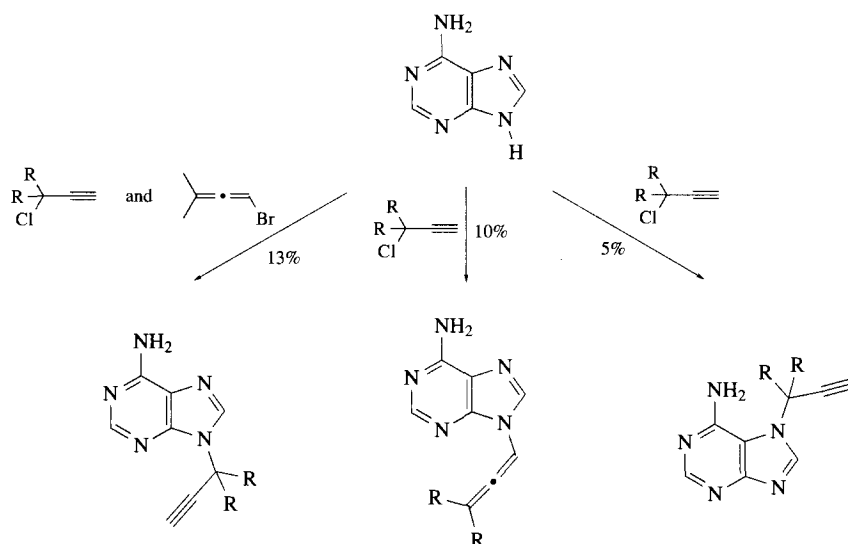


A general synthetic route to 7-alkyl-1-methyladenines (**7**) commenced with *N*(6)-methoxy-1-methyladenosine <93CPB2047> which after alkylation gave a quaternary derivative (**6**) which lost the sugar in hot methanol. The adenine was finally obtained by reduction (Scheme 3).



Scheme 3

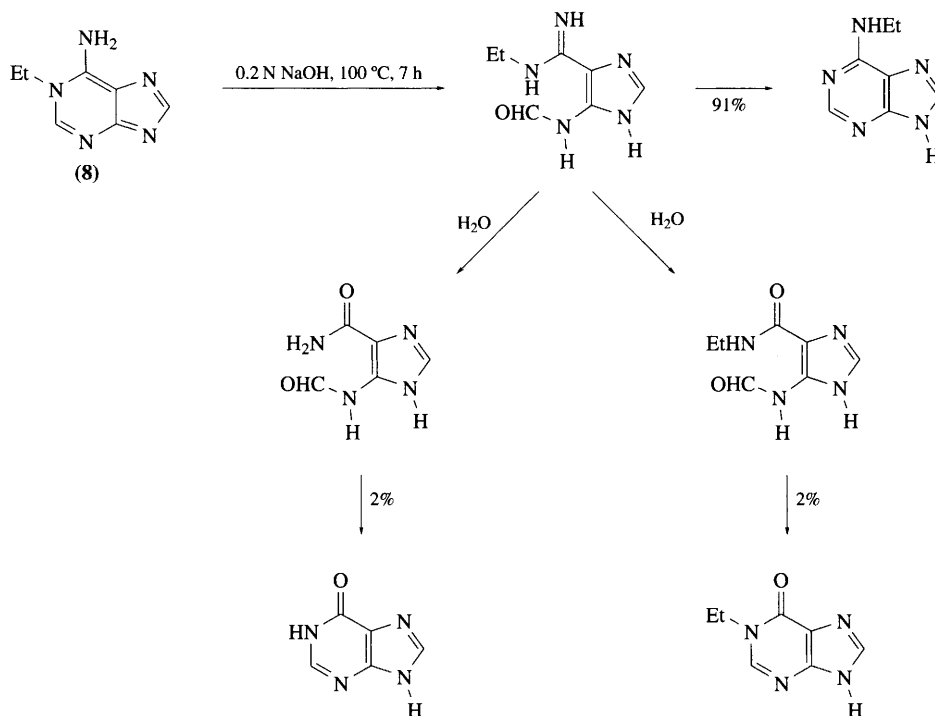
Various acyclonucleosides have been prepared by *N*-alkylation of substituted purines using alkyl halides or acetates in the presence of CsI in MeCN <88CL1045> or LiBr <88MI 711-05> and by more conventional methods <85JPS1302, 87JMC1636, 87MI 711-01, 87MI 711-02, 88AAC1025, 89CC1769, 89MI 711-02, 90JHC1801, 90JMC187, 90TL2185, 91MI 711-10, 92JCS(P1)1843, 93MI 711-07>. Alkylation of adenine with dialkylpropargyl chlorides gave *N*(9)- and *N*(7)-alkyne derivatives accompanied by *N*(9)-allenes. 1-Bromo-3,3-dimethylallene, however, gave only *N*(9)-alkynes but no allene derivative and reaction of propargyl chloride led to *N*(9)-propargyladenine whereas 4-chloroallene afforded both *N*(9)-alkyne and allene derivatives <93T2353> (Scheme 4). *N*-Alkylation of purines has also been achieved by addition of alkenes ($\text{ROCH}=\text{CH}_2$) to produce 9-(1-alkoxyethyl) derivatives <86KGS403>. Reaction of adenine with fluoromethyloxiranes in the presence of potassium carbonate produced *N*(9)-(3-fluoro-2-hydroxypropyl)adenine. 2-Amino-6-chloropurine gave similar results <92CCC1466>. *N*-Alkylation of 2-amino-6-chloropurine with *trans*- (and *cis*-) 2-alkyl-5-iodoethyl-1,3-dioxanes in basic conditions produced *N*-9 and *N*-7 substituted derivatives: the product ratio depends on the size of the alkyl group. In the *trans* series, increasing the size of the alkyl group encouraged *N*(9)-alkylation but no such tendency was observed in the *cis* series <94MI 711-01>.



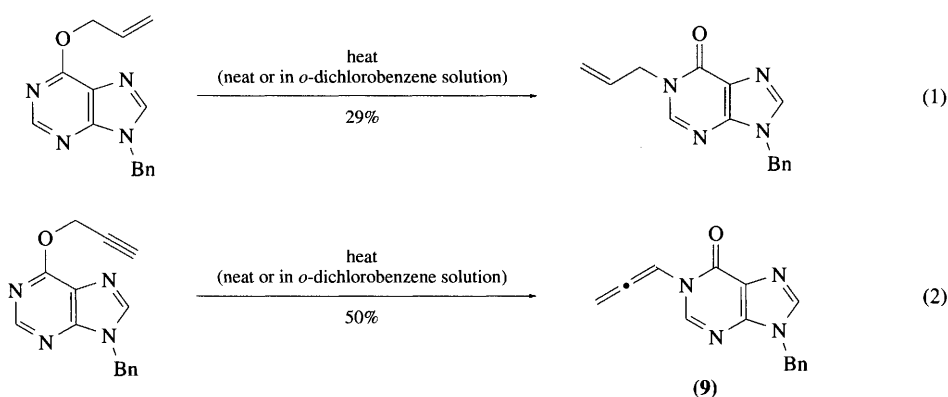
Scheme 4

Further examples of the Dimroth rearrangement of substituted purines have been recorded. Thus in 0.2 N NaOH at 100°C, 1-ethyladenine (8) produced *N*(6)-ethyladenine (91%), hypoxanthine (2%) and 1-ethylhypoxanthine (2%). The minor products are formed by hydrolysis of first formed imidazole carboxamides and recyclization (Scheme 5). Comparison of reaction rates in the Dimroth rearrangements of 1-ethyladenine perchlorate and 1-ethyl-9-methyladenine perchlorate in water at pH 6.92 and 8.70 (ionic strength 1.0) at 70°C revealed that nonsubstitution at N-9 decreases the rearrangement rate by a factor of 4–30 under those conditions <90CPB3326>. The same authors have measured the reaction rates of the Dimroth rearrangements of the marine sponge base 1,9-dimethyl-8-oxoadenine (A) (see Section 7.11.11.2), 1,9-dimethyladenine (B) and 8-bromo-1,9-dimethyladenine (C) in water at various pH values and ionic strengths. In all cases attack of OH^- on the protonated species at the 2-position was faster than that of the neutral species by a factor of 100–1400. The relative ease of the undergoing Dimroth rearrangements was $\text{C} > \text{B} > \text{A}$ <90CPB1536, 90CPB2591>.

In another study, 1-hydroxyalkyladenines in water at near neutrality underwent hydrolytic deamination to the corresponding hypoxanthines in addition to the Dimroth rearrangement to give *N*(6)-hydroxyalkyladenines. The relative rate of deamination compared to the Dimroth rearrangement was found to increase as the pH decreased <86CPB1094>. The same authors also report Dimroth rearrangements of 1-methyladenines <85CPB3635> and 6-trichloromethyl-9-methylpurine <85E248>. The normal O–N Claisen rearrangement has also been observed in purines. Thus allyloxy- and propargyloxypurines undergo thermal O→N [3,3] rearrangement either neat or in *o*-dichlorobenzene. The latter conditions lead to formation of the novel allenyl benzyhypoxanthine (9) <86T4873> (Equations (1) and (2)).



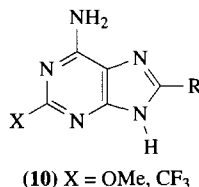
Scheme 5



7.11.5.2.2 C-Alkylation and arylation

Few direct *C*-alkylation reactions have been recorded and *C*-alkyl-substituted purines have largely been obtained by substitution reactions from halogeno or alkylthiopurines. Thus reaction of 3,7-dimethyl-6-methylthio-2-oxopurine with sodium alkyls gave *C*(6)-alkyl derivatives in yields of 25–95% [87S278]. 6-Purine malononitrile was similarly prepared by reaction of 6-chloropurine with malononitrile although other active methylene derivatives failed to react [90H(31)321]. 6-Alkylpurines have also been prepared by a photoinduced reaction of 6-halopurines. Thus 6-iodopurine and metal enolates gave corresponding 6-alkylpurines [85JOC5069, see also 85JA2183]. Palladium-catalyzed cross-coupling reactions have also been used to prepare *C*-alkylpurines. Thus aryl-substituted chloropurines with potassium cyanide gave purine carbonitriles [90H(30)435] and similar *C*-alkylated purine nucleosides have been obtained from silylated halopurines and aluminum alkyls [92JOC5268] (see Section 7.11.7.4). The Gomberg–Bachman reaction has been observed to occur in purines to produce *C*-aryl derivatives. Thus, treatment of methoxy- or trifluoromethyladenines with isoamyl nitrite and either benzene or anisole gave corresponding arylated products (10; R = Ph, anisyl)

<87JHC859>. 8-Arylguanine (and guanosine and GMP) have been similarly prepared from guanine (or guanosine or GMP) and aryldiazonium ions at pH 8.5 or 10.5 in aqueous solution <82JOC448, 82H(18)64> (see Section 7.11.5.2.3).

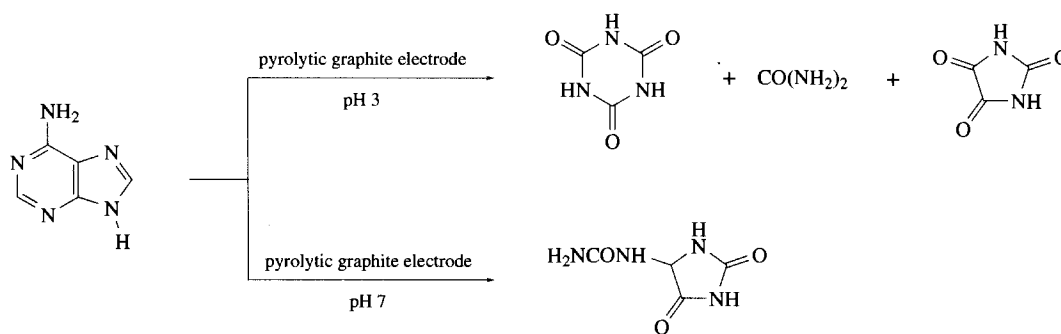


7.11.5.2.3 Reaction with diazonium ions

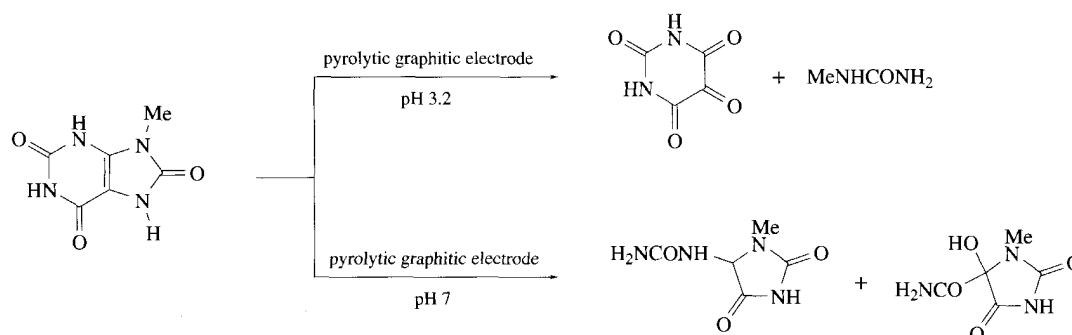
Further reactions of diazonium ions with purines have been reported. Thus guanine reacts rapidly at pH 10.5 in aqueous solution to give 8-arylazoguanines. 4-Bromobenzenediazonium ion reacts about 50 times more rapidly with guanine than with adenine, the latter producing 6-(3-(4-bromophenyl)-2-triazene-1-yl)purine. Guanosine reacts more slowly than guanine to give 8-arylguanines (see Section 7.11.5.2.2). 5-GMP, on the other hand, reacts slowly with aryldiazonium ions and only those compounds with strong electron-withdrawing groups yield *N*(2)-triazenes at ambient temperature and no 8-aryl or 8-arylo compounds were produced. However, 4-bromo- and 4-sulfobenzene diazonium ions react with GMP at higher temperatures to produce 8-aryl-GMP in low yields; the structures were confirmed by hydrolysis to corresponding 8-arylguanines <82JOC448>. The same authors <82H(18)67> also observed that whereas xanthine readily produced 8-arylo derivatives with aryldiazonium ions, xanthosine was unreactive. Inosine on the other hand gave 8-phenylinosine and purine gave 6-phenylpurine with benzene diazonium ions.

7.11.5.2.4 Oxidation of ring atoms

Reviews of changes in the oxidation state of DNA bases induced by oxidation <92MI 711-04>, aqueous solution redox chemistry <89CRV503>, and photoinduced oxidation <91MI 711-09> have appeared. Some new purine *N*(7)-oxides have been prepared for the first time from pyrimidine precursors (see Section 7.11.8.2). Hydroxylation of adenine to produce 8-hydroxyadenine using H₂O₂ under UV radiation or with ascorbic acid has been reported <93MI 711-04> (see Section 7.11.5.4). In contrast, electrochemical oxidation of adenine and hydroxyadenines in the pH range 3–11.2 gave initially 2-hydroxyadenine and further oxidation produced 2,8-dihydroxyadenine and other products. The major products of the reaction at pH 3 were urea, alloxan, and parabanic acid (imidazolidinetrione) and at pH 7, allantoin <91JCS(P2)1369> (Scheme 6). In contrast, the electrochemical oxidation of 7-methyluric acid examined in phosphate buffers (pH 3.2–11.2) at a pyrolytic graphite electrode produced (at pH 3.2) alloxan and methylurea, at pH 7.0 the major products were methylallantoin and 1-methyl-5-hydroxyhydantoin-5-carboxamide (Scheme 7). The enzymic oxidation of 7-methyluric acid appears to be similar to the electrochemical oxidation <93BSF146>.



Scheme 6



Scheme 7

Oxidation of several purines to alloxans and their identification as hydroxyquinoxalines by reaction of oxidation products with 4,5-dimethyl-*o*-phenylene diamine has been recorded <90YZ776>.

Absolute rate constants for the one-electron oxidation of guanine, guanosine, uric acid, xanthine, and hypoxanthine by various halogenated peroxy radicals in aqueous solution were determined using pulse radiolysis <92MI 711-05>. Pulse radiolysis has also been used to determine one-electron redox potentials of some purines. The potentials were measured at pH 13 by using *p*-methoxyphenol ($E = 0.4$ V), Trolox C ($E = 0.19$ V) and tryptophan ($E = 0.56$ V) as references. Guanosine had the lowest oxidation potential of the DNA bases examined <86JPC974>. Online electrochemical–thermospray–tandem mass spectrometry has been used to study intermediates and products formed in the oxidation of uric acid and 6-thioxanthine. Three previously unknown intermediates or products were identified <88ANC720>. A kinetic study of the ozonolysis of purine in aqueous solution <87MI 711-03> and a study of the ozonolysis of *N*(6)-benzoyl-9-(5-deoxy-2,3-isopropylidene- β -D-erythro-pent-4-enofuranosyl) adenine and related compounds <93TL5807> have been reported.

7.11.5.2.5 Halogenation

Purines have been chlorinated by reaction with acyl chlorides in DMF with MCPBA in moderate yields <89MI 711-03> and acycloguanosine and some derivatives were chlorinated with thionyl chloride <92KGS671>.

7.11.5.2.6 Metal complexes

(i) Platinum, palladium, and ruthenium

A triplanar platinum adenine complex $[\text{Pt}_3(\text{NH}_3)_3(9\text{-methyladenine})_2](\text{NO}_3)_6 \cdot 2\text{H}_2\text{O}$ is reported. The $2(\text{NH}_3)_3\text{Pt(II)}$ residue is bound to 9-methyladenine via N-7 and a *cis*-(NH_3)₂Pt(II) unit is bound through N-1. The two adenine rings are oriented head to head in the solid state whilst in solution equilibrium between two rotamers (head to head and head to tail) exists <93ICA31>.

Several mixed ligand complexes have been described including complexes with pyrimidine or imidazole derivatives, for example $\text{Pt}(\text{purine})\text{NMe-imidazole} \cdot \text{Cl}_4$. Spectral examination indicated a 6-coordinate geometry <89MI 711-04, 92MI 711-06>. Mixed ligand complexes of Pt(II) and Pt(IV) with 2,6-diaminopurine and 6-thioguanine have also been prepared. The binding of the ligand to the metal ion varied according to pH. Thus in 6-thioguanine complexes the ligand acts as a monodentate ligand coordinating through the C(6)-SH group in acid whereas in basic medium as a bidentate ligand binding through C(6)-SH and N-7 to give a five-membered chelate ring. In acid 2,6-diaminopurine forms mononuclear complexes with binding at N-7 and in basic solution binuclear hydroxo-bridged complexes with Pt(IV) and the ligand is monodentate coordinating through N-7 <85POL1617>.

The preferential binding of the antitumour drug cisplatin (*cis*-diamminechloroplatinum-II) to GpG and ApG sequences in DNA has prompted the use of *ab initio* calculations with relativistic pseudopotentials to evaluate three important parameters for the Pt–adenine model complex $[\text{Pt}(\text{NH}_3)_3 \text{adenine}]_2^+$. These are the force constant for the Pt–N-7 bond bending out of the adenine

plane, the energy profile for the torsion about Pt—N-7 and a set of fractional atomic charges that reproduce the *ab initio* potential for a number of space points placed around the adduct.

A comparative study of the tetrammine complex $[\text{Pt}(\text{NH}_3)_4]^+$ has shown that for platinum, adenine is a better σ donor than ammonia but it has weak π capacity <93JCC45>. Mixed-ligand complexes of *cis*-dichloroethionine-Pd(II) with purines and purine nucleosides have also been prepared. In the complexes of purines and their corresponding nucleosides, the ligand binding site is N-7 whereas in the case of pyrimidines and their nucleosides it is N-3 <90ICA129>.

The reaction of $\text{Pd}(\text{Me}_4\text{en})\text{Cl}_2$ ($\text{Me}_4\text{en} = \text{NNN}'\text{N}'$ -tetramethylethylenediamine) with inosine and IMP was studied as a function of the Cl^- concentration and pH. A 1:1 complex is produced <92ICA187>.

Ruthenium(III) complexes of adenine, guanine, and hypoxanthine are formed by reaction of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ with the bases in acid medium. Ru binds to adenine at N-9 and guanine at N-7. Similar complexes were obtained from 5'-AMP, 3'-AMP, 2'-AMP, 5'-GMP, and 5'-IMP with $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ in methanol. In the adenine nucleotide derivatives, the metal binds to N-1 or N-3. In IMP and GMP the coordination is through N-7 <91MI 711-11>.

Various organomercury complexes of theophylline and theobromine have been characterized by IR, ^1H , and ^{13}C NMR spectroscopy <87JCR(S)186> and similar products with theophylline, 6-thioguanine and 6-thiolpurine, and caffeine were prepared <92JJC(A)972>.

(ii) Transition metals

Various metal complexes of 6-chloropurine (L), for example $[\text{CuI}_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$, $(\text{HL})_2[\text{MCl}_4]$ ($\text{M} = \text{Pd}, \text{Cd}$), $(\text{HL})_2[\text{PtCl}_6]$ and $(\text{HL})[\text{AuCl}_4]$, have been obtained in acid medium. In the copper complex, the ligand is bidentate with an N-3—N-9 bridge to copper <92M9>.

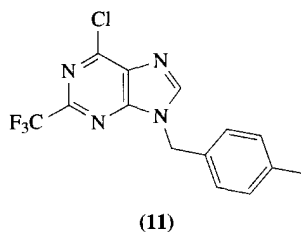
The complexes of 3d transition metal ions Co, Ni, and Cu with 9-methylpurine and its 2- and 8-methyl derivatives have been studied in aqueous solution spectrophotometrically and over a wide range of ligand concentrations. Cu^{2+} forms a 1:2 metal–ligand complex more readily than the other ions <83ICA25>. The stability constants of these complexes were also determined at 298.2 K. All methyl substituents reduced the complexing ability of 9-methylpurine, the 6-methyl group having much the greatest destabilizing effect. The equilibrium data are explained by competitive attachment of metal ions to N-1 or N-7 of 9-methylpurine <83ICA63>. An expansion of this work to cover purines with amino, methoxy, and methylthio groups at C-2 and C-8, C-6, or C-8 confirmed that binding at N-1 and N-7 occurs with comparable strength when C-6 is unsubstituted. In contrast, with adenine derivatives, N-7 coordination is favored <85ICA105>. When seven 9-methylpurine derivatives were equilibrated between CCl_4 or CHCl_3 and aqueous solutions containing either Ni(II)HClO_4 or $N(6),N(6)$ -dimethyladenosine, the equilibrium constants for complex formation with Ni(II) and association with $N(6),N(6)$ -dimethyladenosine were calculated. The results suggest that stacking association of 9-methylpurines with $N(6),N(6)$ -dimethyladenosine reduced the complexing ability of 9-methylpurine <85ICA197>.

Complexes $\text{M}_2(\text{OH})_4\text{LQ}$ ($\text{M} = \text{Mn}, \text{Co}, \text{Ni}, \text{Cu}, \text{Zn}, \text{Cd}$) ($\text{L} = \text{adenine}, \text{Q} = \text{thymine}$) were prepared in aqueous ethanol at pH 7. The complexes are polymeric and spectral studies suggest that adenine is coordinated through N-3 and N-7 <92SRI379>. Copper purine complexes have also been studied by ^1H and ^{15}N NMR spectroscopy. In the anionic form of the purine ligand with all four N atoms deprotonated, N-7 and N-9 resonances are selectively broadened by Cu^{2+} ions while N-1 and N-3 are not much affected. Proton relaxation data also show that the metal ions bind exclusively to the imidazole ring portion of the negatively charged purine ligand; the neutral ligand binds at N-7, N-9 and N-1 <92ACS446>.

7.11.5.3 Reactions with Nucleophiles

7.11.5.3.1 Reduction

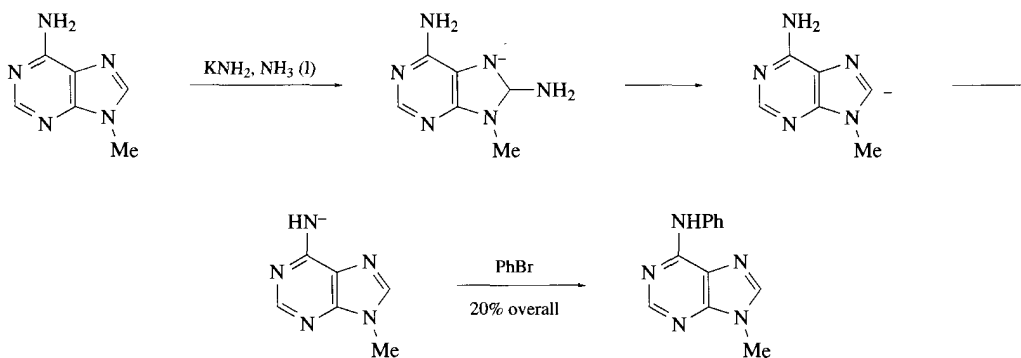
The dihydropurine 6-chloro-7,8-dihydro-9-(4-methylbenzyl)-2-trifluoromethylpurine has been prepared in 85% yield by reaction of compound (11) with sodium borohydride in refluxing THF <86JOC5435>.



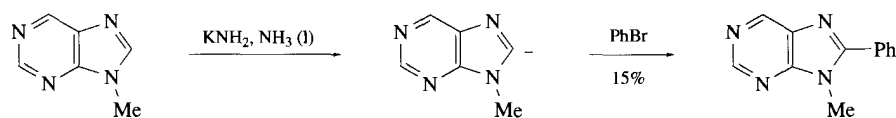
7.11.5.3.2 Amination and hydrolysis

A series of eleven 1-aminopurinium mesitylene sulfonates were prepared in good yields by treatment of the corresponding purine with *O*-(mesitylenesulfonyl) hydroxylamine <85RTC302>.

Further studies on the reaction of purines with potassium amide in liquid ammonia have been carried out. Thus 9-methylpurine, 6-chloro-9-methylpurine and 2',3'-*O*-isopropylidene nebularine with potassium amide in liquid ammonia gave 4-(substituted amino)-5-formamidopyrimidines. The ring opening involves adduct formation at C-8. Nebularine, adenosine and 2',3'-*O*-isopropylideneadenosine failed to react. Proof of anion formation at C-8 in the case of 9-methylpurine came via scavenging with bromobenzene to give 8-phenyl-9-methylpurine. Scavenging of 9-methyladenine with bromobenzene however gave 6-anilino-9-methylpurine <83JOC850> (Schemes 8 and 9). The same authors similarly showed that ring opening occurs with some 2,6-disubstituted purines with potassium amide in liquid ammonia <83JOC1207>.



Scheme 8



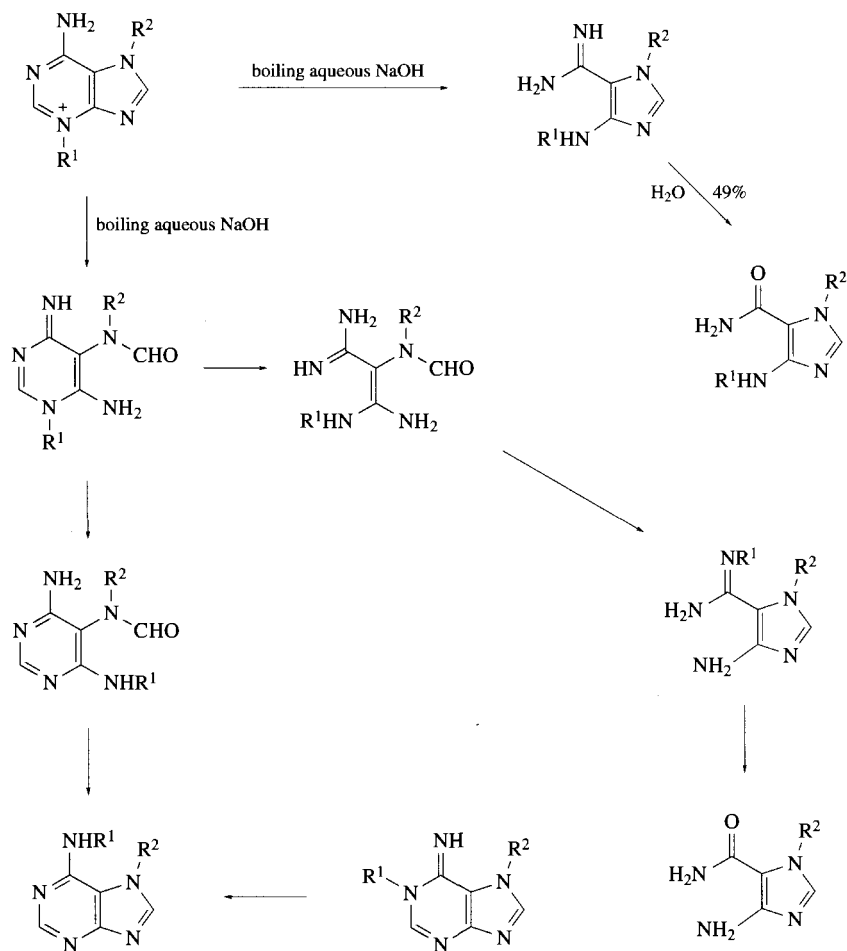
Scheme 9

Ring opening of several purines can also occur with aqueous sodium hydroxide. Thus dialkyladenine salts gave alkyl(alkylamino)imidazole carboxamides with boiling aqueous sodium hydroxide <88CPB107> (Scheme 10). The effects of N-3 and N-9 substituents on the stability of the adenine ring have also been examined. A bulky substituent slowed down ring opening whilst an electron-withdrawing group accelerated it <89CPB3243>.

1-Alkoxy-9-alkyladenines similarly open to produce imidazoles <89CPB1504>. The rates of ring cleavage of various adenine salts to give imidazoles at various pH values have been published. The fastest cleavage occurred with the *N*(1)-*p*-nitrobenzyloxy derivative <84CPB4842>.

7.11.5.4 Reactions with Free Radicals

Transformation reactions of purines and purine nucleoside and nucleotide radical cations and E- and OH-adducts have been reviewed <89CRV503>.



Scheme 10

The reaction of purines and purine nucleosides with the OH radical has been studied using pulse radiolysis. Thus the radical reacts with C(6)- and N(9)-substituted purines by addition ($k = 1.3 \times 10^8 - 8.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) via a polar transition state ($\rho^+ = -0.9$) to give isomeric radicals by attachment to C-4 and C-8 and possibly elsewhere. The C-4 adduct dehydrates to a radical with oxidizing properties and this is influenced by C-6 substituents ($\rho^+ = -0.3$). The C-8 adduct transforms to an imidazole, and C-6 substituents have little effect on the ring opening ($\rho^+ = -0.3$) (87JPC4138). In addition, the same authors have studied, also by pulse radiolysis, the reaction of the OH radical with N(6),N(6)-dimethyladenosine. Reaction occurs by addition of OH to C-4 (35%), C-5 (19%), and C-8 (30%) and by hydrogen abstraction from the methyl or ribose groups (16%). The adducts undergo transformation, for example the C-4 and C-5 adducts dehydrate ($k = 4.2-4.9 \times 10^5 \text{ s}^{-1}$) to give radical cations and the C-8 adduct produces an imidazole ($k = 9.5 \times 10^{-4} \text{ s}^{-1}$). The dehydration reactions are inhibited by protonation of the radicals and by OH^- but the ring opening reactions are enhanced by OH^- (87JA7441). Pulse radiolysis has also been used to study the reaction of free radical purine adducts with nitroxyl radicals (86MI 711-01).

A comparative study has been made of the hydroxylation of adenine by hydrogen peroxide with or without radiation to produce 8-hydroxyadenine. H_2O_2 with UV radiation provides the OH radical which then, with adenine, gives 8-hydroxyadenine as the major product with formation of an additional unstable second compound. 8-Hydroxyadenine may also be prepared using H_2O_2 and ascorbic acid without irradiation and no formation of free radicals (93MI 711-04). High yields of 9-alkylated purines with an N-9:N-7 ratio $>95:5$ have been obtained by radical SRN1 chemistry. In particular, a substituted nitroalkyl derivative $\text{R}_1\text{R}_2\text{C}(\text{NO}_2)\text{X}(\text{Cl}, \text{Br})$ reacts in a photostimulated (100 W fluorescent light under argon) reaction, with 6-chloropurine or 2-amino-6-chloropurine, to afford the 6-chloro-9-nitroalkylated purine derivative (94MI 711-02).

7.11.6 REACTIVITY OF NONCONJUGATED RINGS

The chemistry of the non-conjugated purines, such as xanthine and uric acid derivatives, has been largely covered in the preceding sections. Among the limited interesting new research to emerge is the results of oxidation of some of these compounds. Thus electrochemical oxidation of 7-methyluric acid was studied in phosphate buffers at pH 3.7–11.2 using a pyrolytic graphite electrode. Products produced at pH 3.2 were alloxan and methylurea. At pH 7 methylallantoin and 1-methyl-5-hydroxyhydantoin-5-carboxamide were obtained <93BSF146> (Schemes 6 and 7). Absolute rate constants for 1-electron oxidation of uric acid, xanthine and hypoxanthine by various halogenated peroxy radicals in aqueous solution were also determined using pulse radiolysis <92MI 711-05>. The redox chemistry of uric acid, 3,7-dimethyluric acid and 7,9-dimethyluric acid were similarly studied at a pyrolytic graphite electrode in aqueous solution. Identical oxidations were given by type VIII peroxidase and hydrogen peroxide <85MI 711-03>.

Xanthine, hypoxanthine, and other purines obtained by the reaction of DNA with nitrous acid were separated by HPLC <91MI 711-08>. Xanthine, and possibly hypoxanthine, were also detected in four CM2 chondrites from Antarctica, in amounts varying from 420 to 430 ng g⁻¹. In these experiments, no pyrimidines were found, helping to confirm the reliability of the results <90MI 711-03>.

7.11.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.11.7.1 Alkyl Derivatives

The reaction of a methyl group at the 6 or 8 position of 9-phenylpurine with benzaldehyde and ethyl benzoate in the presence of sodium hydride gave styryl and phenacyl purines. Conversion of Me into CHO was achieved by treatment with selenium dioxide in dioxan to give the purine carboxaldehyde <92CPB227>.

7.11.7.2 Cyanopurines

9-Aryl-6-cyanopurines, prepared from the 6-chloro derivatives and potassium cyanide, were converted into 9-aryl-6-acetyl-, 6-propionyl- and 6-benzylpurines by reaction with Grignard reagents <90H(30)435>.

7.11.7.3 Aminopurines

7.11.7.3.1 Alkylation

Methylation of *N*(6)-methoxyadenine with methyl iodide in dimethylacetamide gave mainly ring-methylated products. However, the *N*(6),*N*(9)-dimethyl derivative was produced in low (9%) yield <83CPB4270>.

7.11.7.3.2 Displacement reactions

Hydroxyalkyladenines have been hydrolyzed to the corresponding hypoxanthines <86CPB1094>. Reaction of methoxy- or trifluoromethyladenines with isoamyl nitrite and benzene or anisole gave via the Gomberg–Bachman reaction corresponding phenyl or anisyl products <87JHC859> (see Section 7.11.5.2.2).

9-Ethyl-1-(2-hydroxyethyl)adenine hydrobromide afforded the corresponding 1-(2-(1*H*-imidazol-1-yl)ethyl)hypoxanthine derivative in 52% yield by heating with imidazole in boiling DMF for 30 min <92CPB3201>. Deamination also occurred with pyridine or thiophenol in boiling DMF to produce the hypoxanthine with subsequent replacement of the 6-OH group by the nucleophile. The corresponding free base failed to give the deaminated product with imidazole in boiling DMF.

Electrochemical oxidation of adenine and hydroxyadenines in aqueous solution at pH 3–11.2 using a pyrolytic graphite electrode gave after extended oxidation, a diimine species which undergoes a series of reactions to give various ring-opened products <91JCS(P2)1369> (see Section 7.11.5.2.4).

Adenine and adenosine were converted into hypoxanthine and inosine respectively on a copper-montmorillonite support, adsorption being accompanied by oxidation <91N121>. 7-Benzyl-2-isobutyryl-3-methylguanine lost the 3-methyl group when heated in toluene with 2-3-5-tri-*O*-acetylribosyl bromide <85MI 711-05>.

7.11.7.4 Halopurines

Halogenopurines continue to be major intermediates for the synthesis of a wide variety of substituted purines, usually by halogen-displacement reactions including the use of palladium-catalyzed cross-coupling reactions which have become more widely used. Thus palladium-catalyzed cross-coupling reaction of 6-chloro-9-phenylpurine with potassium cyanide gave the 6-purine-carbonitrile <90H(30)435>. 6- and 2-Halo-9-phenylpurines also reacted with terminal alkynes in DMF when catalyzed with bis(triphenylphosphino)palladium chloride to produce 6- and 2-alkynylpurines which are a useful source of corresponding methyl ketones by treatment with mercuric sulfate and sulfuric acid <88CPB1935>. Silylated halopurine nucleosides also have been reacted with aluminum trialkyls with palladium-catalyzed coupling to afford *C*-alkylpurine nucleosides <92JOC5268>.

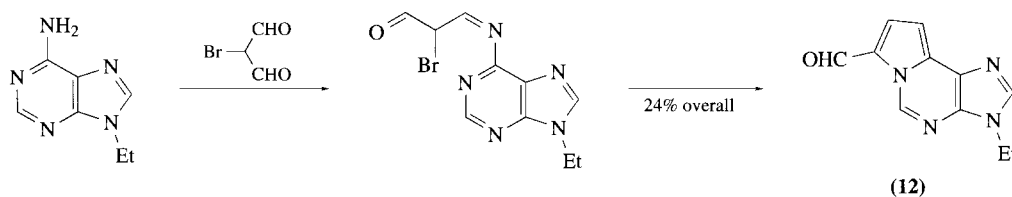
2-Chloro-9-phenylpurine reacts with a variety of nucleophiles including *O*-alkyl, *O*-aryl, SR, and NHR to produce the 2-substituted purines. The compound also reacts with benzylocyanide and ethyl cyanoacetate to give the corresponding purine-2-CHR(CN) derivative but failed to react with other active methylene derivatives, ketones, or potassium cyanide. In contrast, 9-phenyl-2-methylsulfonylpurine reacted readily with active methylene compounds, ketones, and potassium cyanide <87CPB4972>.

A series of 9-phenylphosphonic acids were prepared by condensation of a substituted diethylphosphonate with sodium 6-chloroguanine <92EUP465297>. 6-Chloropurine also reacts with malononitrile to give the 6-CH(CN)₂ derivative which after catalytic reduction to purine-6-CH(NH₂)CN was used as a source of pyrazolo- or pyrimidinopurines <90H(31)321>. A variety of novel functionalized 6-alkylated purines have been prepared in high yield by the photoinduced reaction of various metal enolates with 6-chloropurine <85JA2183, 85JOC5069>. An SRN1 reaction mechanism was implicated in these reactions. Halopurines have also been used as a route to various cyclic purine adducts. Thus reaction of 6-chloropurine with 3-alkyl-, 1,3-oxazolidines, or 3-methyl-1,3-thiazolidine gave cyclic products <84JHC333> (see Section 7.11.7.5). Cyclic products (oxazolopurines) were also produced by reaction of 8-chlorotheophylline with epoxides via nucleophilic addition and intramolecular nucleophilic substitution <92TL6307> (see Section 7.11.7.5).

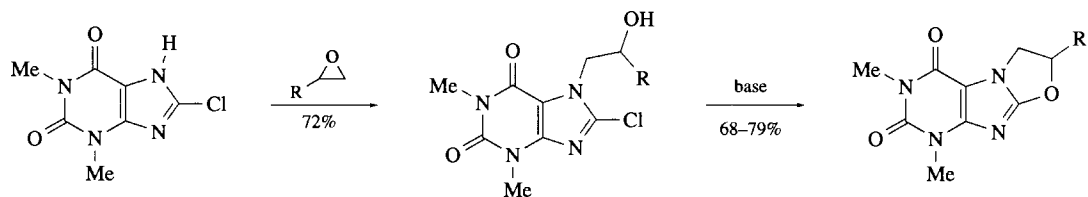
7.11.7.5 Purines with a Fused Heterocyclic Ring System

7.11.7.5.1 Five-membered fused rings

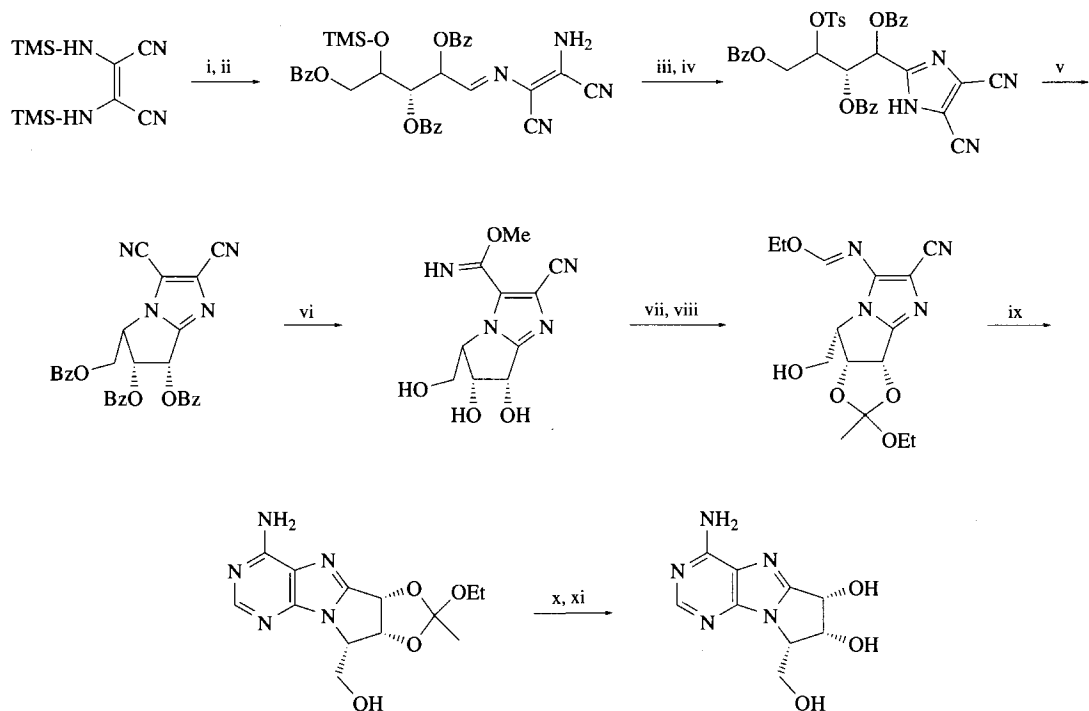
The reaction of purines and pyrimidines with malondialdehyde or bromalonaldehyde (prepared by bromination of malonaldehyde) has led to the formation of various products including 1:1 enamines <84JA3370> and five-membered fused-ring compounds. Thus 9-ethyladenine with bromalonaldehyde gave a 24% yield of the imidazopurine (**12**). A mechanism of formation of compound (**12**) is outlined in Scheme 11 <84JOC4021>. Similar products were obtained from various aminopyrimidines. Oxazolo[2,3-*f*]purines have been prepared by reaction of 8-chlorotheophylline with epoxides (Scheme 12) <92TL6307>. An unusual class of compounds in which a carbohydrate moiety is fused to a purine in the 8,9-position has been obtained <91TL7503> by reaction of 2,3,5-tri-*O*-benzoyl-*D*-ribofuranosyl acetate with trimethylsilylated diaminomaleonitrile and cyclization of the resultant acyclic product to an imidazole then, after deblocking, to a purine (Scheme 13). A more direct preparation of an imidazopurine (**13**) involves reaction of *N*(6)-(2-hydroxyethyl)-*N*(6)-methyladenine with thionyl chloride (Scheme 14) <84JHC333>.



Scheme 11

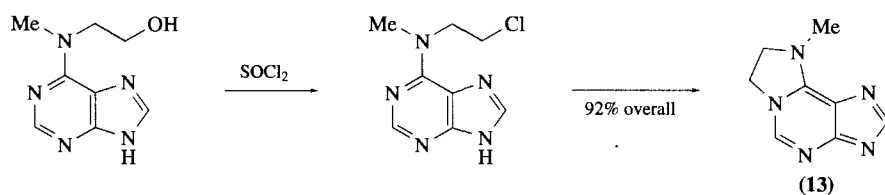


Scheme 12



i, 2,3,5-tri-*O*-benzoylribosyl acetate, TMS-I, CH_2Cl_2 , 0°C ; ii, NaHCO_3 ; iii, NBS, EtOAc, 30°C ; iv TsCl, pyridine; v, NaH, DMF, 70°C ; vi, NaOMe, MeOH; vii, 1.5 M NaOH, 80°C ; viii, $(\text{EtO})_3\text{CH}$, DMF, 140°C ; ix, NH_3 , MeOH; x, 0.2 M HCl, H_2O , MeOH; xi, NH_3

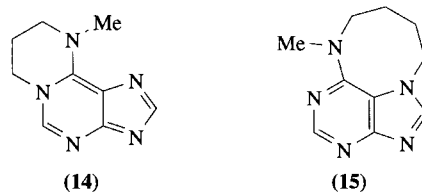
Scheme 13



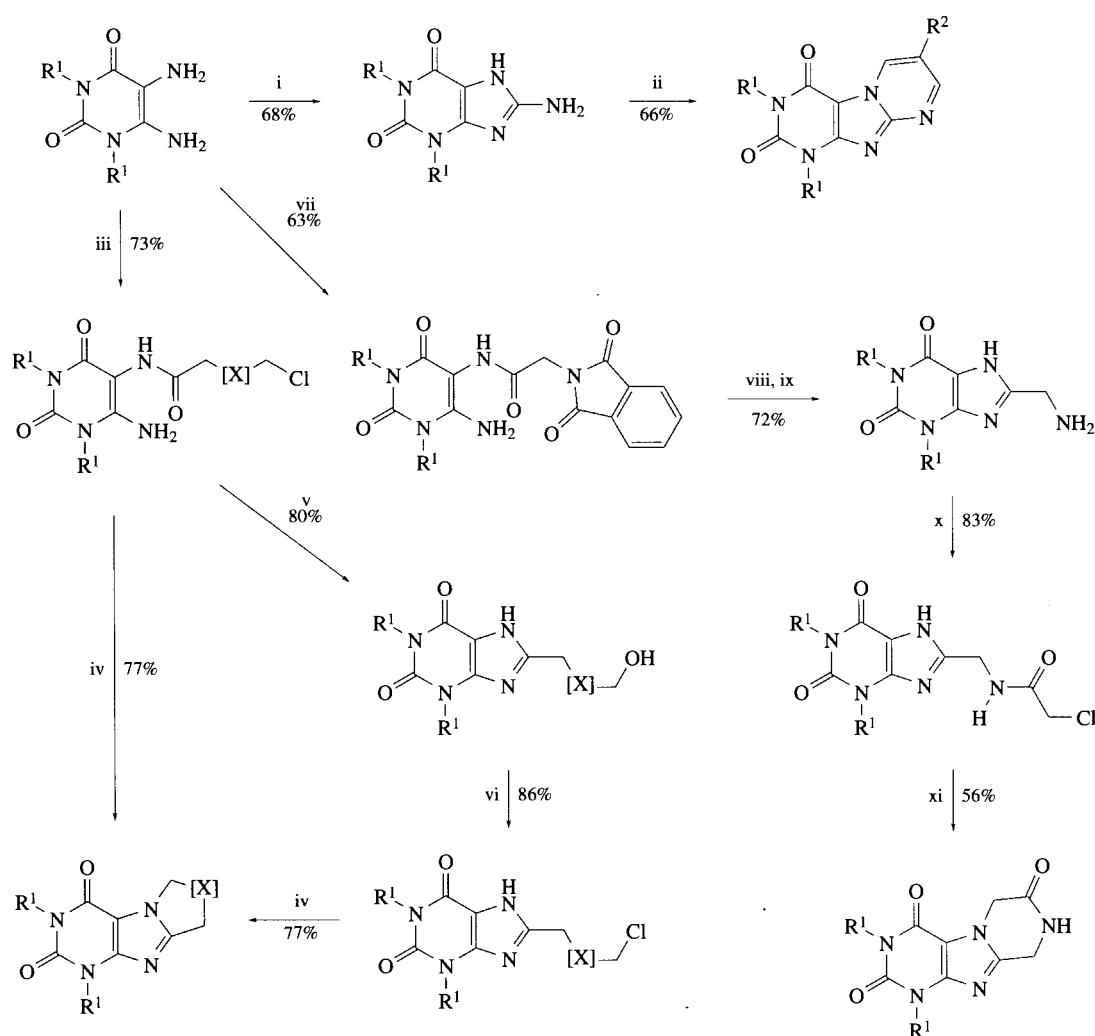
Scheme 14

7.11.7.5.2 Six-membered or more fused rings

Reaction of a series of *N*(6)-methyl-*N*(6)-hydroxyalkyladenines with thionyl chloride produced corresponding chloroalkyladenines which cyclized with sodium hydride to produce the six-membered pyrimidinopurine fused ring system (14) or larger ring systems, including the eight-membered fused-ring compound (15), according to the length of the alkyl chain (84JHC333) (see Section 7.11.7.5.1).



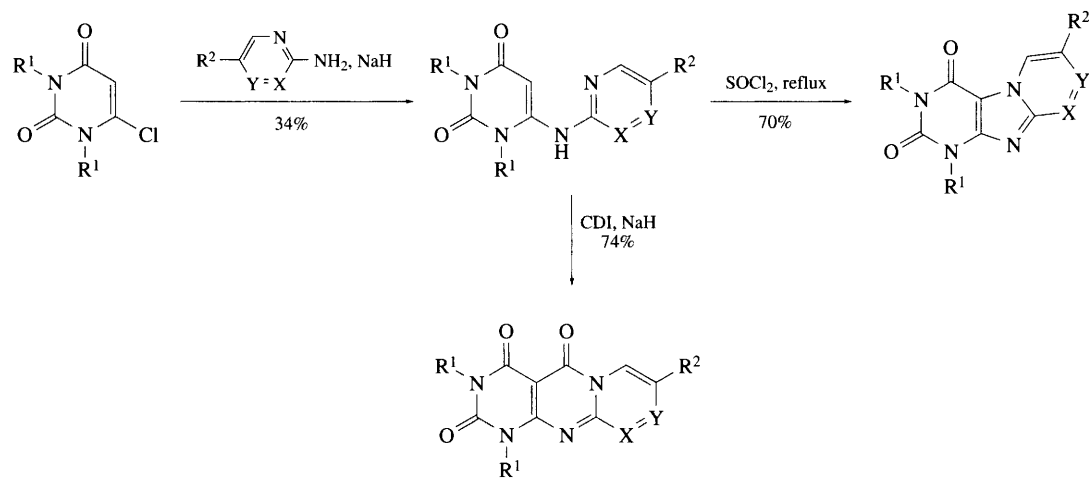
The syntheses of 1,3-dipropyl-1*H*,3*H*-pyrazino-, pyrido-, pyrimido-, and pyrrolo[2,1-*f*]purine-2,4-diones starting from 5,6-diamino-1,3-dipropylpyrimidine-2,4-dione and 6-chloro-1,3-dipropylpyrimidine-2,4-dione have been described (Scheme 15) [94JHC81]. A new route to 1,3-dipropyl-1*H*, 3*H*-pyrido- (or pyrazino-) [1',2'-1,2]pyrimidino[4,5-*d*]pyrimidino-2,4,5-triones has also been developed (Scheme 16).



i, NH_2CN ; ii, $\text{CH}_2(\text{CHOEt})_2$, HCl for ($R^2 = \text{H}$), $\text{BrCH}(\text{CHO})_2$ for ($R^2 = \text{Br}$); iii, $\text{ClCH}_2\text{XCH}_2\text{COCl}$; iv, MeONa ;

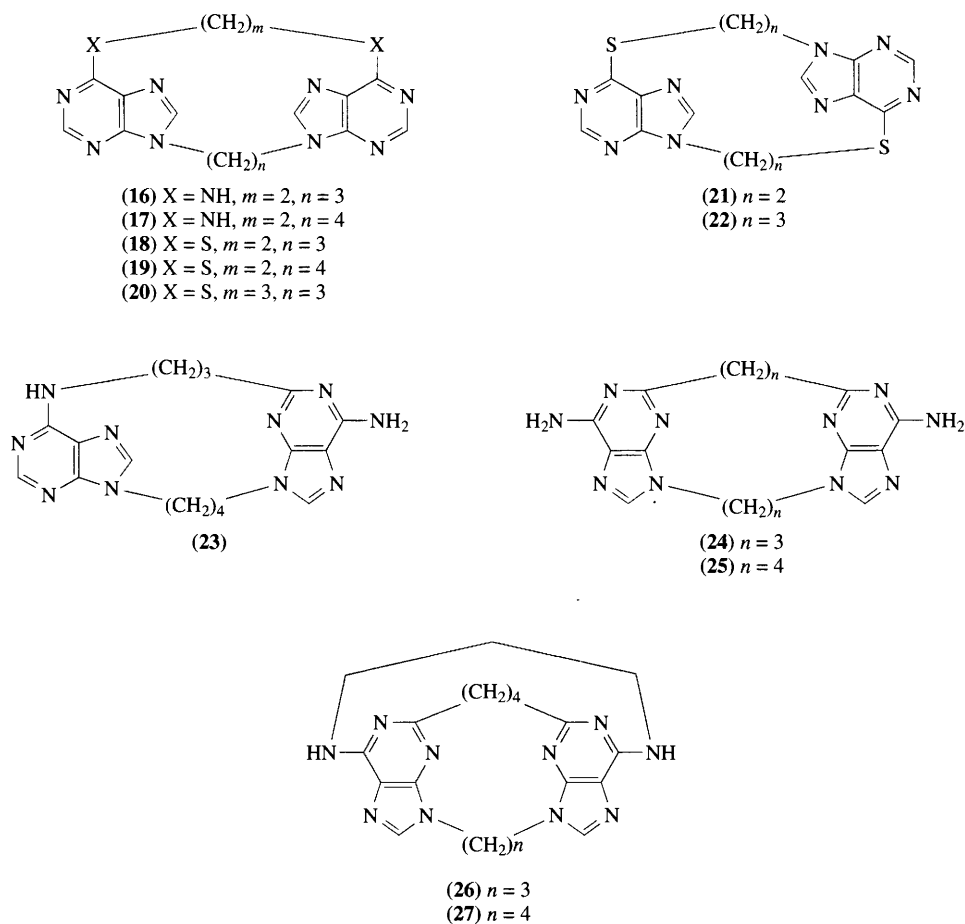
v, Ph_2O , reflux; vi, SOCl_2 ; vii, ; viii, 1 *N* NaOH ; ix, 20% NaOH , reflux; x, ClCH_2COCl ; xi, NaH , DMF

Scheme 15



Scheme 16

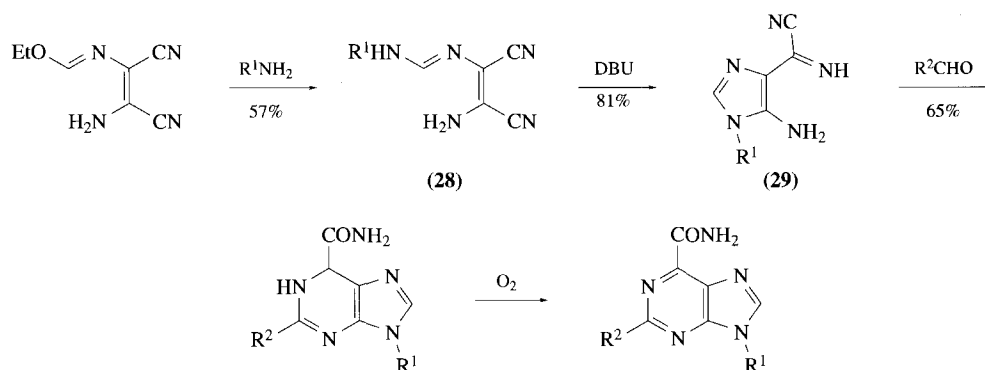
A series of 12 large fused-ring systems (purinophanes) has been prepared by the reaction of adenine or 6-thiopurine with various dibromoalkanes and sodium hydride. The products have structures (16)–(27) which vary according to the alkane and the method of preparation <88JA2192>. Stacking geometries of the rings were determined by x-ray analysis and/or ^1H NMR spectroscopy. All the purinophanes showed large hypochromism when compared to the two molar monomeric reference bases <88JA2192>.



7.11.8 RING SYNTHESIS

7.11.8.1 Synthesis from Acyclic Precursors: Abiotic Synthesis

The preparation of purines under conditions which purport to have occurred on the primitive planet and to have implications for the formation of living systems continue to be announced. Thus, oligomerization of hydrogen cyanide (1 M) in the presence of added formaldehyde (0.5 M) produced an order of magnitude more of 8-hydroxymethyladenine than adenine or other biologically significant purines <89SCI1102>. The result suggests to the author that on prebiotic earth nucleoside analogues may have been synthesized directly in more complex mixtures of hydrogen cyanide and other aldehydes, and prompts the question – was adenine the first purine? In comparison, it has been argued that in extant nucleic acids pyrimidines are postenzymic substitutes for purine analogues, namely xanthine and isoguanine, which are seen as sibling products in a pre-enzymic *de novo* purine nucleotide biosynthetic pathway <88PNA(85)1134>. Purines and pyrimidines have also been shown to form in new Oparin–Urèy-type primitive earth atmosphere experiments. Thus by reacting methane, ethane, and ammonia under electric discharges, adenine, guanine, and 5-aminoimidazole-4-carboxamide together with isocytosine were identified. The total yields were 0.0023% but the adenine formation occurred at much lower concentrations of hydrogen cyanide than recorded in earlier experiments <84MI 711-04>. Abiotic synthesis of purines and other nucleic acid bases has been recorded in similar experiments including use of electric discharges <86MI 711-02, 86MI 711-03> and under conditions simulating volcanic ash gas clouds <84MI 711-03>. Purine derivatives have also been synthesized from diaminomaleonitrile <84JHC333> (see Section 7.11.7.5.1). In a later synthesis ethoxymethylidenemaleonitrile was reacted with some hydroxy- or methoxy-alkylamines to give the corresponding amidines (28) which cyclized to aminoimidazoles (29) with DBU. The imidazole (29) with aldehydes or ketones produced 6-carbamoyl-1,6-dihydropurines which in some cases were oxidized to the corresponding 6-carbamoylpurines (Scheme 17) <92JCS(P1)2119>.



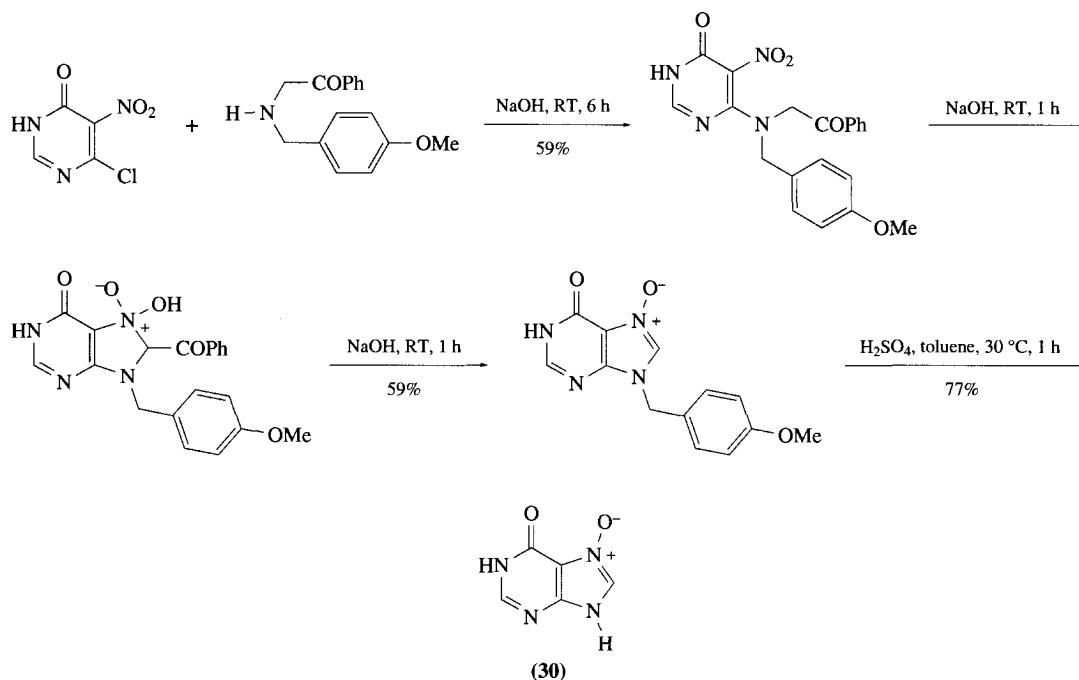
Scheme 17

7.11.8.2 Synthesis from Diaminopyrimidines

The Traube synthesis still remains valuable as a route to the synthesis of specific purines. The method has been used to record the first synthesis of hypoxanthine-*N*(7)-oxide (30) by reaction of 6-chloro-5-nitro-4(3*H*)-pyrimidinone with *N*-(4-methoxybenzyl)phenacylamine (Scheme 18) <92CPB612>. The same authors also report analogous syntheses of 8-methylguanine-7-oxide and its 9-arylmethyl derivatives, and guanine-7-oxide and some 9-substituted derivatives <92CPB343, 92CPB1315>.

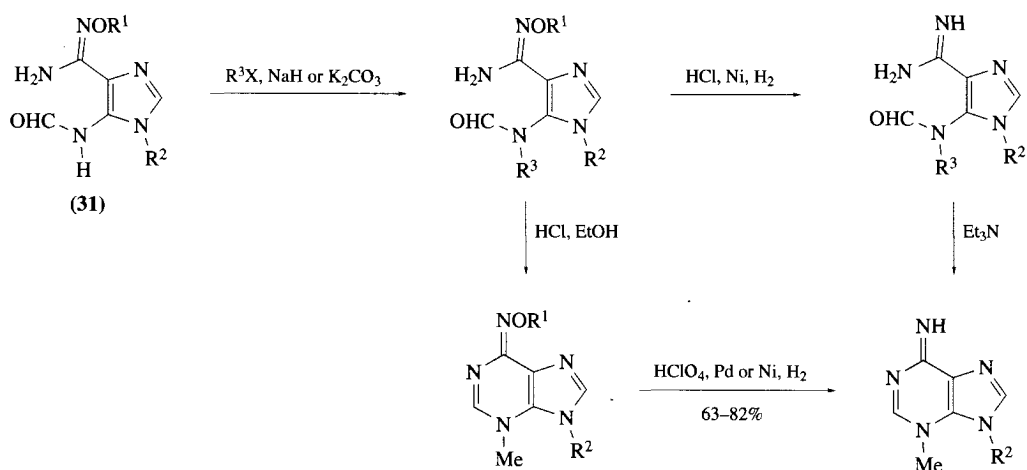
7.11.8.3 Synthesis from Imidazoles

In the 1990s the standard synthetic route to purines by cyclization of an appropriate 5(4)-aminoimidazole has been increasingly used. The general method is well illustrated by the synthesis



Scheme 18

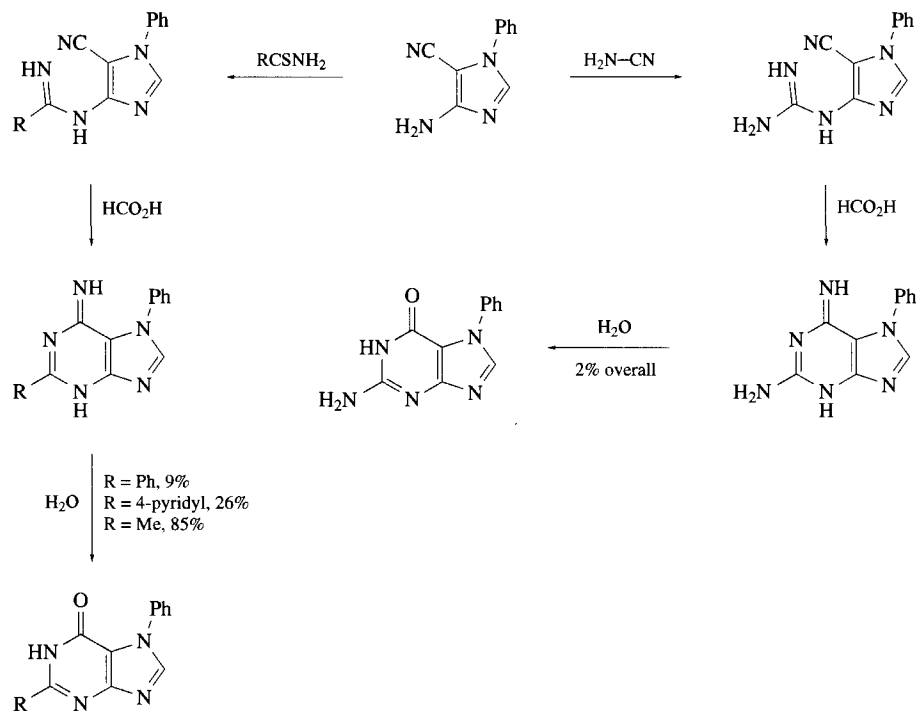
of *o*-hydroxyethylbenzyladenine, hypoxanthine, and guanine from appropriate 5-aminoimidazole-4-carboxamides <93JCS(P1)2555>. A series of 3,9-dialkylated adenine salts has been synthesized from *N*-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines (**31**) by cyclization with alkali (Scheme 19) <89CPB1504, 89CPB3435>. The imidazole derivatives are prepared by ring opening of 1-alkoxy-9-alkyladenines.



Scheme 19

2-Deuterated-3,9-dialkyladenines have been similarly prepared from appropriate aminoimidazole carboxamidines by deuterioformylation with DCO₂D and cyclization of the resulting deuterioformamidoimidazoles with base <90CPB99>. Comparison of the ¹H NMR spectra of the deuterated and nondeuterated derivatives has permitted a distinction to be made between C-2 and C-8 proton signals in a series of 3,9-dialkylated adenine salts.

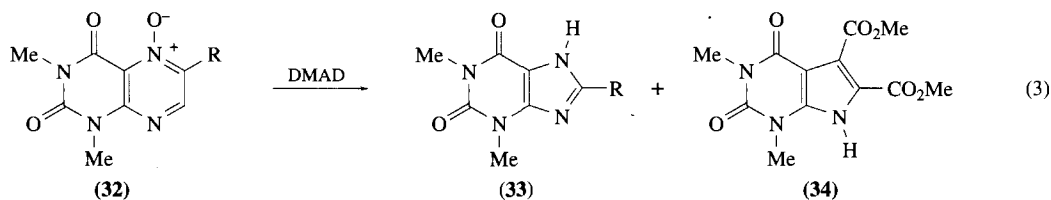
The method has also been applied <88S242> to the synthesis of 9-benzyl-4-(2-methylhydrazino)purine by reaction of the formimidate of 1-benzyl-4-cyano-5-formimidoimidazole with methylhydrazine and catalysis by TFA in a variation of a 9-cyclohexyladenine synthesis described earlier <84CHEC-I(5)499>. Nitroimidazoles have also been used as useful precursors of aminoimidazoles for purine synthesis <89CC551, 92JCS(P1)2779, 92JCS(P1)2789, 95SL203>. 7-Phenylguanine and 2-substituted-7-arylhypoxanthines have been synthesized by cyclization of 4-amino-5-cyano-1-phenylimidazole with cyanamide and various thioamides, using formic acid as a catalyst (Scheme 20) <87LA957>. 3-Methylguanosine has been similarly prepared from 1- β -D-ribofuranosyl-5-methylaminoimidazole-4-carboxamide and cyanogen bromide with sodium ethoxide <85CPB2339>.



Scheme 20

7.11.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

The aryl-substituted pteridine-5-oxide derivative (32) with dimethylacetylene dicarboxylate (DMAD) in a 1,3-dipolar cycloaddition reaction gave a mixture of the 8-aryldimethylxanthine (33) and the pyrrolopyrimidine (34) (Equation (3)) <85H(23)2317, 88MI 711-06>.



7.11.10 CRITICAL COMPARISON OF SYNTHETIC ROUTES

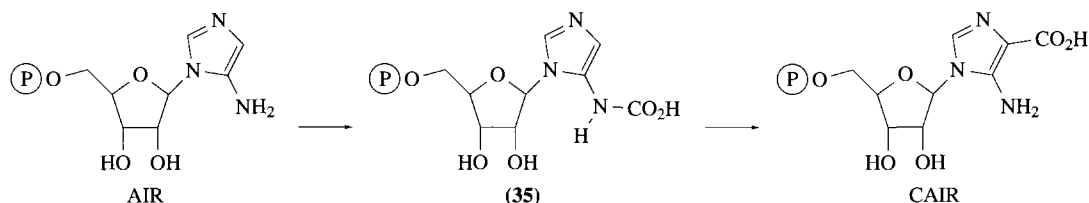
With very few exceptions, by far the most important synthetic routes to the purine ring system remain the Traube synthesis from pyrimidines and the synthesis achieved by cyclization of an appropriate aminoimidazole. One of the more active areas of synthesis since the mid-1980s has been the acyclonucleosides, i.e. purines, especially guanine, with a 9-substituent which possesses some of

the skeletal features of ribose or 2-deoxyribose (see Section 7.11.5.2.1). Such compounds, which are of course of interest as antiviral agents, are normally prepared by alkylation of the purine generally as a metal or metallo (e.g. trimethylsilyl) derivative using an alkyl halide or similar reagent. However, such alkylations almost always lead to mixtures of isomeric N-9 and N-7 (and possibly other) substituted purines which inevitably require extensive separatory processes in order to obtain pure materials. Accordingly, there has been considerable interest in attempting to discover methods which would lead to much better regioselectivity in the alkylation procedure. Some limited progress has been made by the use of phase-transfer catalysis and further improvements in this methodology are readily foreseen. High yields of some specific 9-nitroalkyl substituted purines have been achieved by radical SRN1 chemistry from 6-chloropurine or 2-amino-6-chloropurine and a nitroalkyl halide with photostimulation using a 100 W fluorescent lamp in argon. The ratios of N-9 : N-7 substituents are claimed to be $>9:1$ (94MI 711-02). Whether such reactions prove to be of general application, however, remains to be seen. Still the best route to the unambiguous synthesis of substituted purines is the use of aminoimidazoles. This method appears to be slowly gaining in popularity and there is little doubt that it will be even more widely used in future synthetic work. Palladium-catalyzed cross-coupling reactions have also proved useful for the synthesis of a wide variety of substituted purines, generally by displacement of halogen in a halopurine under much milder conditions than those that pertain during the normal type displacement reaction. Thus replacement of a chlorine atom in 6-chloropurine by cyanide normally requires long heating with cupric cyanide in high boiling solvents (84CHEC-I(5)499) but occurs under mild conditions with palladium catalysis (90H(30)435) (see Section 7.11.7.7) and substantial progress in this particular area is envisaged in the future.

7.11.11 NATURALLY OCCURRING PURINES

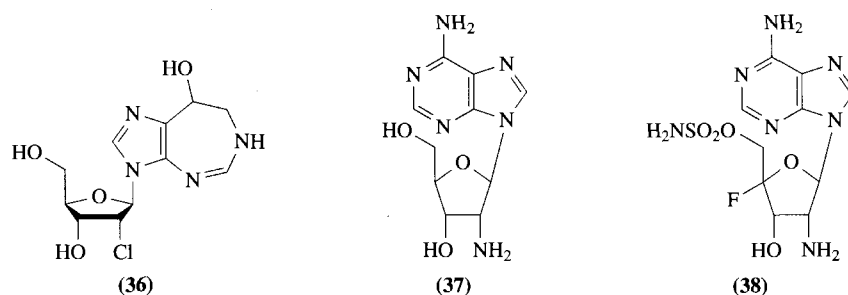
7.11.11.1 Biosynthesis

A new intermediate in purine nucleotide *de novo* biosynthesis in *E. coli*, namely *N*(5)-carboxy-aminoimidazole ribotide (**35**) has been identified together with two new enzymatic activities involving the carboxylation of the 5-amino group of 5-aminoimidazole ribotide (AIR) and the rearrangement of the *N*-carboxy derivative to the *C*-carboxy derivative (CAIR) (Scheme 21) (94B2269).



Scheme 21

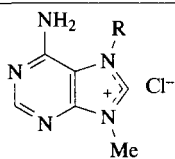
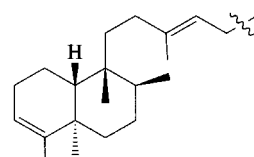
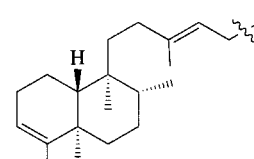
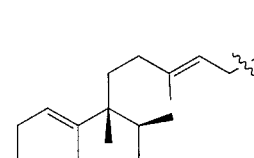
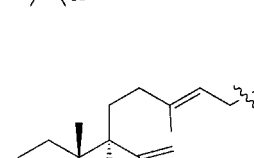
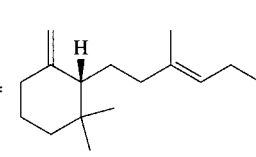
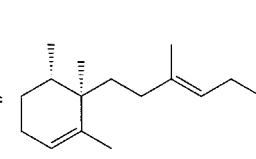
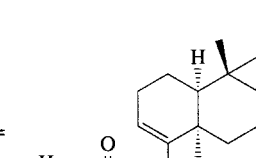
The biosyntheses of the naturally occurring purine nucleoside antibiotics, 9- β -D-arabino-furanosyladenine (Ara-A), 2'-chlorodeoxycoformycin (**36**), 2'-amino-2'-deoxyadenosine (**37**) and nucleocidin (**38**) from adenine or adenosine have been examined by radiolabelling and the results are reviewed (89MI 711-05).



7.11.11.2 Methylated Purines

Marine sponges have continued to be a rich source of a variety of substituted methylated purines. Compounds include the agelasines A–F, a series of twelve 9-methyl-7-substituted adenines in which the 7-substituent is a terpenyl unit (see Table 2) which have been isolated from pacific sponge *Agelas* species. Similar compounds include the agelasimines A (39) and B (40) (*N*(3),*N*(6)-dimethyl- and *N*(1),*N*(3)-dimethyladenines, respectively) with 7-terpenyl substituents isolated from *Agelas maur-etiana*. They are related to 1,9-dimethyl-8-oxo-6-iminopurine (41) which was isolated along with 1-methyladenine as *N*(6)-acetyl derivatives from the English Channel sponge *Hymeniacidon sanguinea* Grant <85MI 711-04> and synthesized <90CPB2146, 90CPB3503> from 9-methyladenine by bromination and reaction of the resultant 8-bromo derivative with alkali followed by methylation, or alternatively methylation followed by hydrolysis (Scheme 22).

Table 2 New purine derivatives from marine sponges: agelasines A–F and ageline B.

		
A	R =	
B	R =	
C	R =	
D	R =	
E	R =	
F	R =	
	R =	
		(Ageline B)

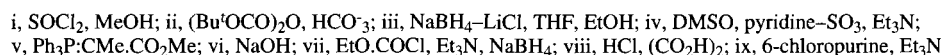
Isolation: <84TL2989, 84TL3719, 86BCJ2495>. X-ray crystal data: <84TL935>. Biology and pharmacology: <88CJC45, 89MI 711-07>. Review: <90CPB2146>.

Models of the agelasimines A and B, namely 7-benzyl-*N*(3),*N*(6)-dimethyladenine and 7-benzyl-1,2-dihydro-1,3-dimethyladenine, respectively, have been synthesized from 3-methyladenine, the key steps involved being regioselective methylation of 7-benzyl-3-methyladenine and 7-benzyl-1,2-dihydro-3-methyladenine <93H(35)143>.

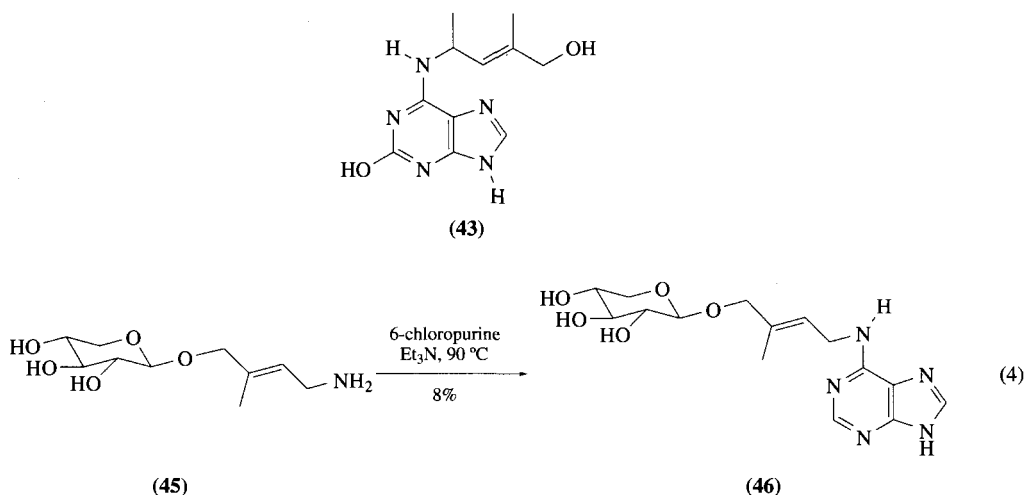


Cytokinin chemistry and biology has been reviewed <90MI 711-04, B-94MI 711-03>.

O-Xylopyranosyl zeatin (**46**), a new *O*-glycosylcytokinin, has been isolated from *Phaseolus vulgaris* <87PNA(84)3714> and synthesized (8% yield) <87JCR(S)110> by reaction of the *O*-xylosylamine (**45**) with 6-chloropurine (Equation (4)).

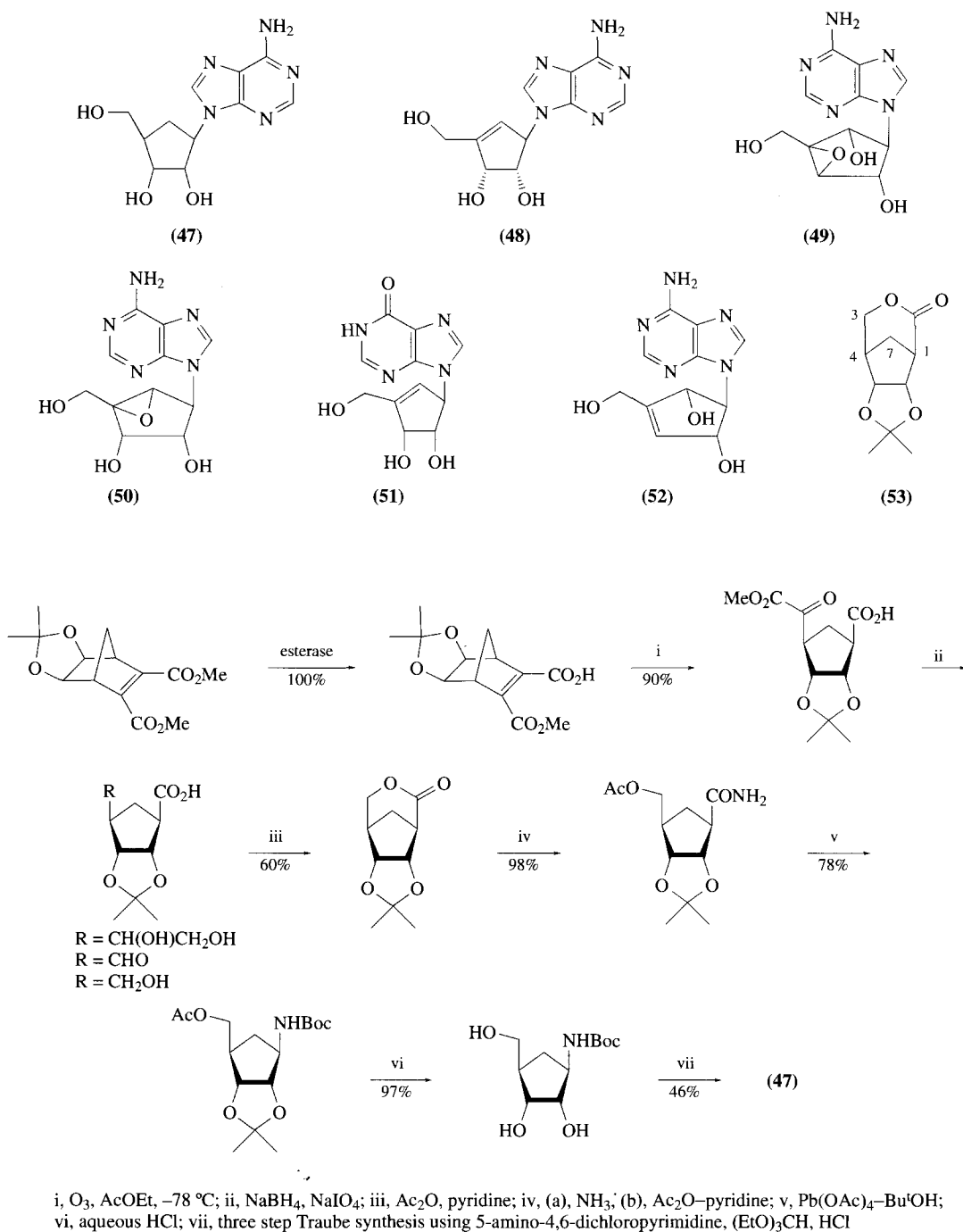


Scheme 23



Interest has continued in the purine nucleoside antibiotics including the novel naturally occurring carbocyclic (cyclopentyladenine or hypoxanthine) nucleoside analogues aristeromycin (**47**) and the closely related neplanocins A, B, C, D, and F; (**48**), (**49**), (**50**), (**51**), and (**52**), respectively. The carbocyclic nucleosides have been reviewed (Table 1). Full syntheses of (–)aristeromycin and (–)neplanocin A have been recorded from Ohno's lactone (**53**) (Schemes 24 and 25, respectively) [⟨83JA4049⟩](#) although the former required the use of an esterase. The synthesis of neplanocin A has been improved by an improved synthesis of Ohno's lactone (Scheme 26) [⟨93LA1313⟩](#). The synthesis of neplanocin A has also been achieved by an alternative novel route from different starting materials (Scheme 27) [⟨92JCS\(P1\)2245⟩](#). Neplanocin F (**52**) isolated as a minor constituent from *Ampullariella regularis*, has also been synthesized (Scheme 28) [⟨92JOC2071⟩](#). Many other carbocyclic purine nucleosides have been described [⟨92JMC3372, 92MI 711-09⟩](#), including analogues of xylofuranosylpurines [⟨84JMC1358⟩](#) and 2'-deoxyribofuranosides [⟨84JMC1416⟩](#). The carbocyclic analogue of 5-amino-4-imidazole ribofuranoside has been used as a route, by standard ring-closure methods, to analogues of guanosine, isoguanosine, and 3-methylxanthosine [⟨92MI 711-07⟩](#).

The adenine nucleoside antibiotic sinefugin (**54**), first isolated from *S. griseolus* has now been synthesized free from its C-6' epimer (Scheme 29) [\(83JA7638\)](#). The compound has a variety of

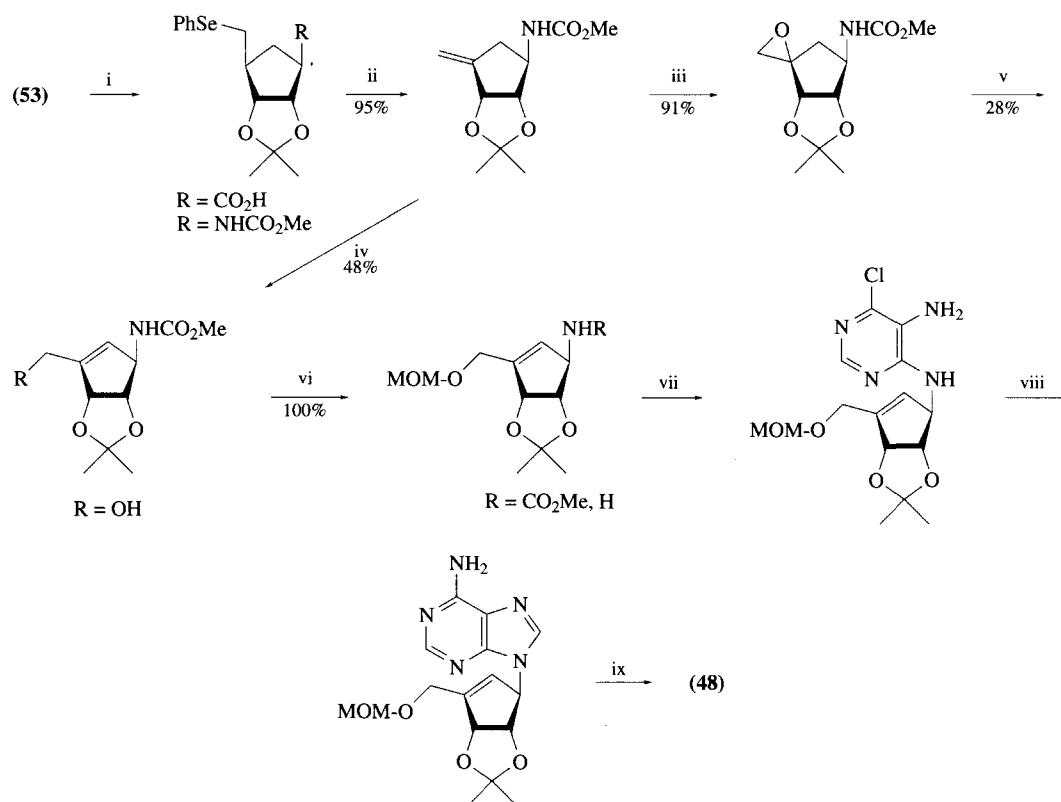


Scheme 24

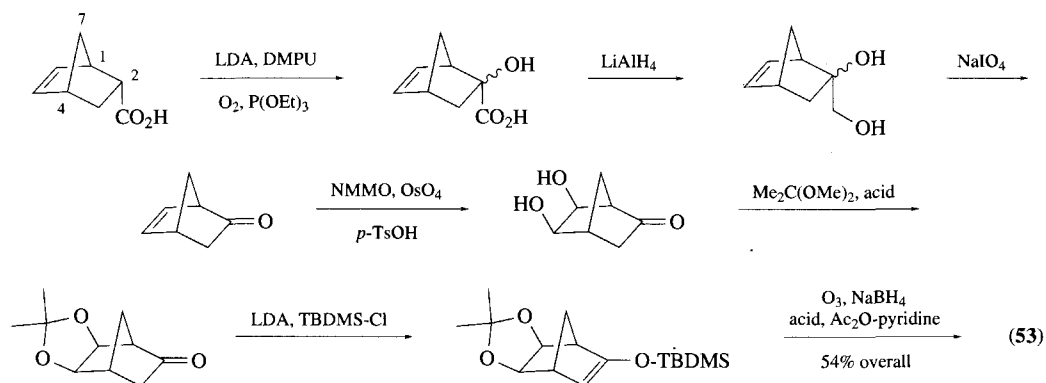
biological activities including antifungal, antiviral, and antiparasitic and this has been attributed to its ability to inhibit methyltransferase enzymes.

7.11.11.5 Miscellaneous

Purines and pyrimidines have been detected in the Neogene sediments in a 1600 m thick stratigraphic sequence in the Shingo Basin. Adenine, guanine, and pyrimidines were detected at the

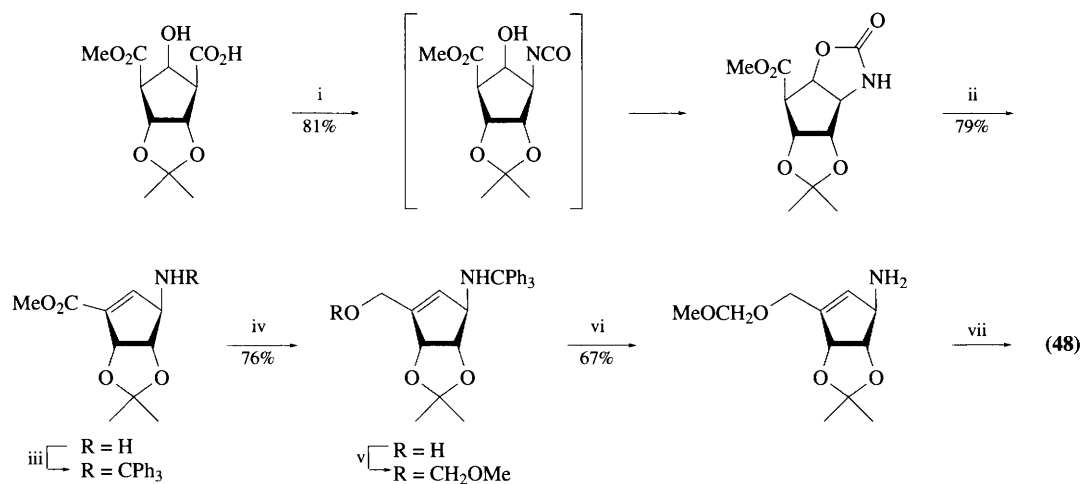


Scheme 25



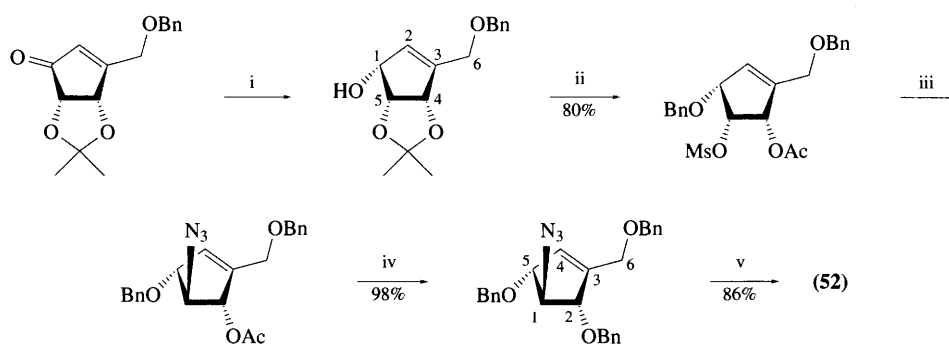
Scheme 26

100 ng g⁻¹ level in the top level of the sequence and at 10 ng g⁻¹ in the remainder of the sediments <88MI 711-07>. Positive evidence for the presence of guanine and tentative evidence for xanthine and hypoxanthine in two CM2 chondrites (Yamato-74662 and Yamato-791198) from Antarctica has been recorded <90MI 711-03>. Two other chondrites (Yamato-793321 and Belgica-7904) contained no detectable amounts of purines or pyrimidines.



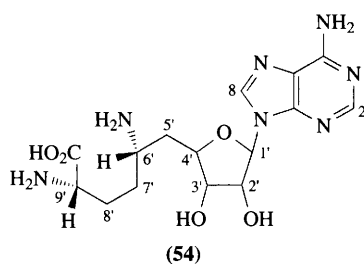
i, $(PhO)_2P(O)N_3$, dmap, THF, 48 h; ii, KF, TsF, pyridine, THF; iii, TrCl, DMF, Et_3N ; iv, Bu^i_2AlH , toluene, $-78^\circ C$, 6 h; v, $MeOCH_2Cl$, Pr^i_2NEt , DMF; vi, *N*-hydroxybenzotriazole, CF_3CH_2OH , 3 h; vii, Traube synthesis using 5-amino-4,6-dichloropyrimidine, $HC(OEt)_3$

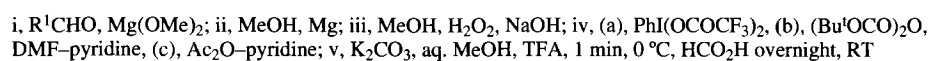
Scheme 27



i, Allylic reduction; ii, NaH, DMF, $PhCH_2Br$, 40% TFA, Ac_2O-NEt_3-dmap , $NaOMe-MeOH$, $MeSO_2Cl-Et_3N$; iii, LiN_3-DMSO ; iv, $NaOMe-MeOH$, $NaH-PhCH_2Br$, H_2 -Lindlar catalyst, MeOH, RT; v, Traube synthesis using 5-amino-4,6-dichloropyrimidine, $HC(OEt)_3$, Ac_2O

Scheme 28





Scheme 29

7.12

Bicyclic 5-6 Systems: Other Four Heteroatoms 2 : 2

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and

AYMAN W. ERIAN

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7.12.1 INTRODUCTION

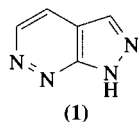
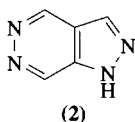
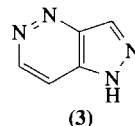
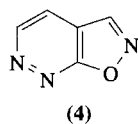
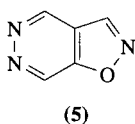
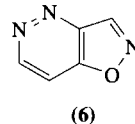
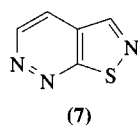
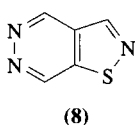
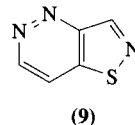
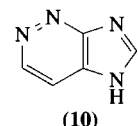
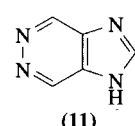
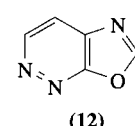
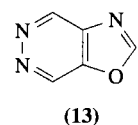
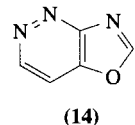
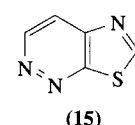
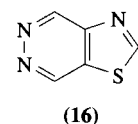
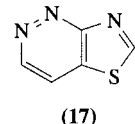
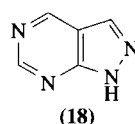
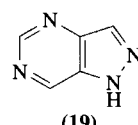
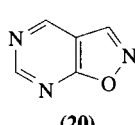
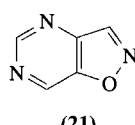
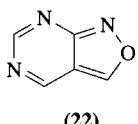
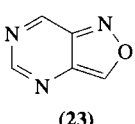
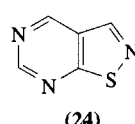
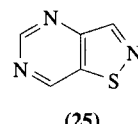
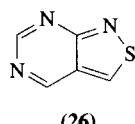
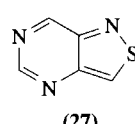
A large number of ring systems in which a five-membered ring with two heteroatoms is fused to a six-membered ring also with two heteroatoms and without a heteroatom at the ring junction are possible. The parent ring systems of known derivatives are shown in structures (1)–(39). The most investigated of these are the pyrazolopyrimidines (18) and (19), and, to a lesser extent, the pyrazolopyridazines (1)–(3). The biological activities of derivatives of these ring systems are the reason for the interest in their chemistry. The purines (40) also have a five-membered ring with two heteroatoms linked to a six-membered ring with two heteroatoms but because their chemistry is vast they are dealt with separately in Chapter 7.11. Systems (41)–(44) in which atom Y is a divalent atom are also aromatic and charge separated forms (e.g. 45) can also be treated as 10π electron systems. Systems (46)–(50) are also known and their synthesis is described briefly.

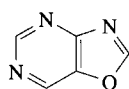
The whole subject matter has never been collectively reviewed although the chemistry of some individual ring systems has been reviewed (82MI 712-01, 87AHC(41)319, 90AHC(48)223, 92AHC(55)129). Earlier work on many of the systems discussed in this chapter was discussed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (84CHEC-I(4)497). In all the systems (1)–(39) both the five-membered ring and the six-membered ring contain nitrogen. Thus, the name azoloazines is used to refer collectively to these ring systems.

7.12.2 THEORETICAL METHODS

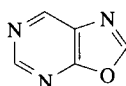
LCAO data for electron densities on pyrazolo[3,4-*d*]pyrimidine (18) are shown in structure (51). Hückel molecular-orbital (MO) calculations of π -electron density for pyrazolo[3,4-*d*]pyrimidine (18) reveal N-2 to be the most electron-rich atom (69CJC1129). The same conclusion was reached using other LCAO calculations. Because simple molecular orbital calculations exaggerate electro-negativities of nitrogen atoms (58JCS2973), true charge densities are smaller than calculated but their relative values are unaffected (56JCS272).

The four most important tautomers of pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (52a–d) were studied using *ab initio* LCAO–MO methods (91CPL(181)123). Calculation indicates that structure (52a) is the predominant form both in nonpolar and polar environments. The second most stable species, the oxo hydroxy tautomers (52b) and (52c), have relative energies of 38.7 kJ mol^{–1}. For the dioxo to oxo-hydroxy transition, the calculated energy gap corresponds to an equilibrium constant

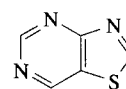
1*H*-Pyrazolo[3,4-*c*]pyridazine1*H*-Pyrazolo[3,4-*d*]pyridazine1*H*-Pyrazolo[4,3-*c*]pyridazineIsoxazolo[5,4-*c*]pyridazineIsoxazolo[4,5-*d*]pyridazineIsoxazolo[4,5-*c*]pyridazineIsothiazolo[5,4-*c*]pyridazineIsothiazolo[4,5-*d*]pyridazineIsothiazolo[4,5-*c*]pyridazine5*H*-Imidazo[4,5-*c*]pyridazine3*H*-Imidazo[4,5-*d*]pyridazineOxazolo[5,4-*c*]pyridazineOxazolo[4,5-*d*]pyridazineOxazolo[5,4-*c*]pyridazineThiazolo[5,4-*c*]pyridazineThiazolo[4,5-*d*]pyridazineThiazolo[4,5-*c*]pyridazine1*H*-Pyrazolo[3,4-*d*]pyrimidine1*H*-Pyrazolo[4,3-*d*]pyrimidineIsoxazolo[5,4-*d*]pyrimidineIsoxazolo[4,5-*d*]pyrimidineIsoxazolo[3,4-*d*]pyrimidineIsoxazolo[4,3-*d*]pyrimidineIsothiazolo[5,4-*d*]pyrimidineIsothiazolo[4,5-*d*]pyrimidineIsothiazolo[3,4-*d*]pyrimidineIsothiazolo[4,3-*d*]pyrimidine



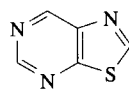
(28)

Oxazolo[4,5-*d*]pyrimidine

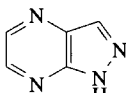
(29)

Oxazolo[5,4-*d*]pyrimidine

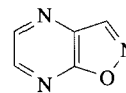
(30)

Thiazolo[4,5-*d*]pyrimidine

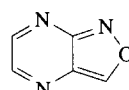
(31)

Thiazolo[5,4-*d*]pyrimidine

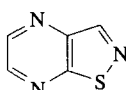
(32)

1*H*-Pyrazolo[3,4-*b*]pyrazine

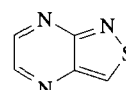
(33)

Isoxazolo[4,5-*b*]pyrazine

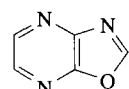
(34)

Isoxazolo[3,4-*b*]pyrazine

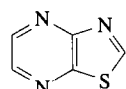
(35)

Isothiazolo[4,5-*b*]pyrazine

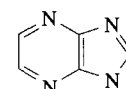
(36)

Isothiazolo[3,4-*b*]pyrazine

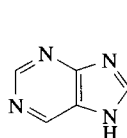
(37)

Oxazolo[4,5-*b*]pyrazine

(38)

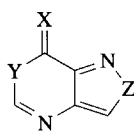
Thiazolo[4,5-*b*]pyrazine

(39)

1*H*-Imidazo[4,5-*b*]pyrazine

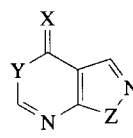
(40)

Purine

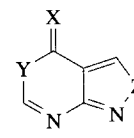


(41)

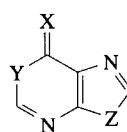
X = O, S, N, Se; Y = O, S



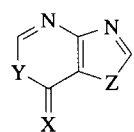
(41a)



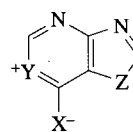
(42)



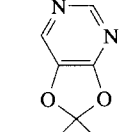
(43)



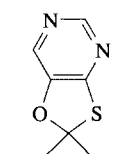
(44)



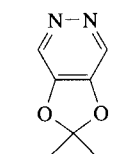
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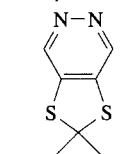
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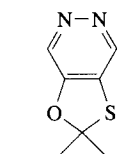
(47)



(48)



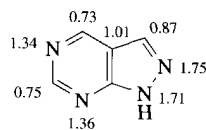
(49)



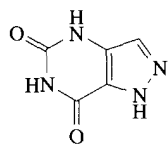
(50)

of 1×10^7 <91MI 712-01>. INDO calculations show that 1,2-disubstituted derivatives of allopurinol (**53**) are the least stable. The anion of allopurinol (**53**) is believed to exist as a mixture of tautomeric forms <79JCS(P1)2795>.

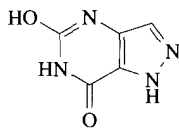
A quantum chemical study of formycin A (**54a**) and its 2-amino (**54b**) and 2-fluoro (**54c**) derivatives was performed using the semiempirical MNDO and AM1 methods as well as an *ab initio* STO-3G



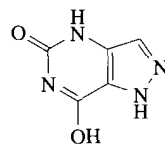
(51)



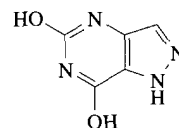
(52a)



(52b)

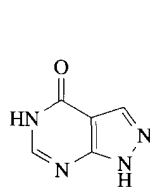


(52c)



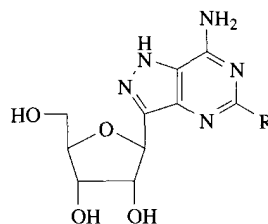
(52d)

method. Calculations were performed on a reduced model in which the ribose moiety was substituted by a hydroxymethyl group. Results indicate that formycin A can be protonated on N-4 or N-6 depending on the tautomeric form (1*H* and 2*H*) <89MI 712-01>. The quantum chemical study of N-6 protonated molecules shows that a second protonation can take place on N-3 and N-1 depending on tautomeric form. Results indicate that the protonation of formycin A and its derivatives at N-6 leads to a change in tautomeric preference from 2-*H* to 1-*H* <89MI 712-01>. The relative energies of amino-imine tautomers of 1*H* and 2*H* formycin A protonated at N-6 were calculated. The amino form and the 1*H* form were more stable, based on data obtained by MNDO, AM1, and *ab initio* STO-3G methods <89MI 712-02>.



(53)

(allopurinol)



(54a) R = H (formycin A)

(54b) R = NH₂

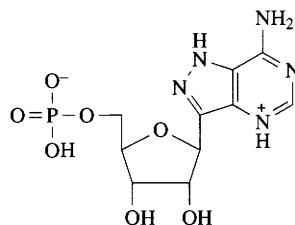
(54c) R = F

7.12.3 EXPERIMENTAL STRUCTURAL METHODS

7.12.3.1 X-ray Diffraction

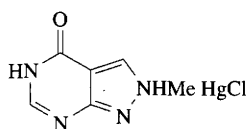
X-ray crystal structures of several biologically active azolopyrimidine derivatives has been determined in order to understand their biological properties. The structures of formycin A (54a) and its 5'-monophosphate (55) have been reported <73B1196, 74AX(B)1511, 88B5819>. It was shown that the base is planar with the largest deviation from the plane of 0.0023 Å at C-3. The molecules were shown to exist as the 1*H* tautomers and nitrogen is the hydrogen donor site in any plausible hydrogen bonding scheme. X-ray crystallographic comparison between this form for the base and isomeric 2*H* tautomer indicated that the 1*H* form has C(7a)-C(7) and C(3a)-C(3) bonds longer than the corresponding bonds in the 2*H* tautomer. Also bond angles between N(1)-C(7a)-C(3a), C(3a)-C(3)-N(2), and N(2)-N(1)-C(7a) are larger. For formycin A monophosphate (55) it is believed that N-4 is protonated. This assertion is supported by observation of widening of the angle C(3a)-N(4)-C(5) by 3.2°. However, the data is inconclusive as difference Fourier maps could not locate hydrogen at either N-4 or N-6. The furanose ring of formycin A monophosphate is in the C(3')-endo form with a pseudorotation angle *P* = 20.3° and is packed in a way similar to that of adenosine monophosphate. In the crystal structure there are four formycin monophosphate molecules and six water molecules per unit cell <89BBR(161)910>. Each formycin monophosphate participates in thirteen intramolecular hydrogen bonds which act to stabilize the crystal. The crystal

structure of the nucleoside 2',3'-dideoxyformycin A has been determined and shows a *syn* conformation about the glucoside bond, stabilized by an intramolecular hydrogen bond between the O-5' and N-3 atoms <89BBR(161)910>.



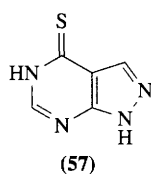
(55)

An x-ray study of allopurinol (**53**) indicates that it exists in the 1*H* form. It is apparent that hydrogen bonding patterns in the crystal lattice may be responsible for the preferred protonation site in the solid state. Intramolecular N(1)-H-N(7) and N(5)-H-O(4) contacts for allopurinol and N(2)-H-O(4) contacts for allopurinol cation are observed. The crystal structure of the methyl mercury complex (**56**) indicated that N-1 and N-5 are respective coordination sites. Similar structures have been proposed for allopurinol copper complexes <87ZN(B)195>.

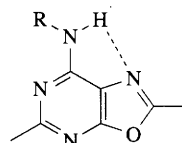


(56)

X-ray diffraction data for pyrazolo[3,4-*d*]pyrimidine-4-thione (**57**) reveals a space group P2/c with four molecules in a unit cell of parameters $a = 13.90(5)$ $b = 12.00(3)$, $c = 3.83(7)$, $A, B = 102.00(2)$. The molecules are linked together by a network of hydrogen and van der Waals bonds <74AX(B)1598>. The molecular structure of 4-methoxy-1-D-ribofuranosyl-pyrazolo[3,4-*d*]pyrimidine has been established by x-ray diffraction <83AX(C)1441>. Also, x-ray diffraction was used to establish the site of ribosylation of 3-methyl-1*H*-pyrazolo[4,3-*d*]pyrimidine-5-one <84JMC986, 84JMC1119>. The crystal and molecular structure of *N*-(2,5-dimethyloxazolo[5,4-*d*]pyrimidine-7-yl)- β -phenyl- β -alanine and *N*-(2,5-dimethyloxazolo[5,4-*d*]pyrimidine)-7-yl-sarcosine (**58**) were also determined by x-ray methods. The molecules are almost planar and an intramolecular hydrogen bond between N-3 and the exocyclic amino nitrogen exists <86AKZ114>.



(57)

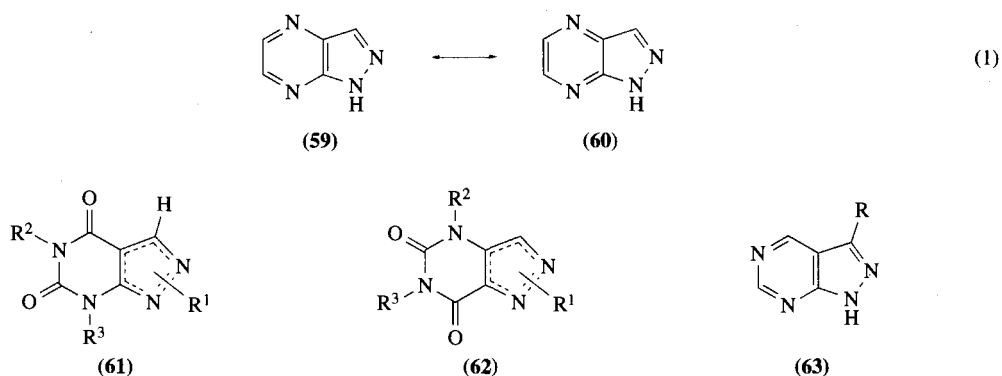


(58)

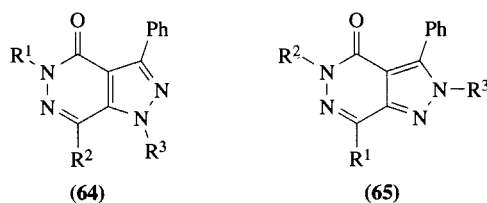
7.12.3.2 Proton NMR Spectroscopy

Much proton NMR data has not been unequivocally assigned. In azolopyrazines the pyrazine ring H-2 and H-3 protons show a coupling constant of 3.5 Hz, which is much smaller than the corresponding coupling constants in the nonannulated pyrazines, and this may be taken as evidence for bond fixation. Thus, compound (**59**) has a minimal contribution of resonance form (**60**) (Equation (1)) to its actual structure <67TL2029, 82AJC2299>. In the isomeric pyrazolo[3,4-*d*]pyrimidine and pyrazolo[4,3-*d*]pyrimidine diones ((**61**) and (**62**)) proton H-3 in (**61**) is shifted downfield compared to that in structure (**62**). This shift, which is due to the carbonyl group in the pyrimidine moiety, has been used to discriminate between the isomeric pairs (**61**) and (**62**) <84CHEC-I(4)497>. On the

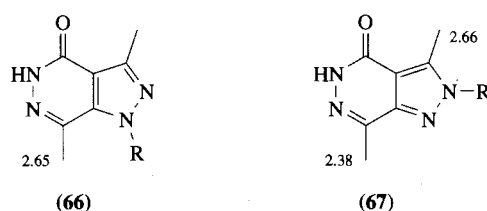
other hand proton H-4 in a series of 5-phenylpyrazolo[3,4-*d*]-pyrimidines (**63**) was found to appear at almost the same chemical shift (δ 8.9 ppm) $\langle$ 92JCS(P1)239 $\rangle$.



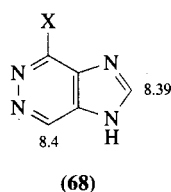
The ^1H NMR spectra of the isomeric 3-phenylpyrazolopyridazines (**64**) and (**65**) shows a downfield shift of the *ortho* protons in the phenyl ring in the isomers (**64**) but not in the isomers (**65**). These findings reflect the coplanarity or noncoplanarity of the aromatic rings. This steric effect is characteristic of *ortho*-substituted biphenyls and analogous heterocyclic compounds $\langle$ 66JOC1878, 78JHC813 $\rangle$.



An analysis of the ^1H NMR spectra of the pyrazolopyridazinones (**66**) and (**67**) shows that the most interesting difference between these isomers is that the chemical shift values for the 3-methyl substituents are deshielded more in the isomers (**66**). The methyl group at C-7 shows instead a diamagnetic displacement. It is conceivable that these chemical shifts may vary with the position of the double bond in the two cycles. A deshielding shift can be expected when the methyl groups are attached to a double bond which is conjugated with the carbonyl group $\langle$ 78JHC813 $\rangle$.



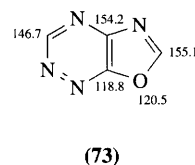
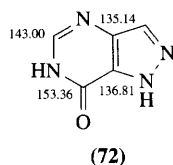
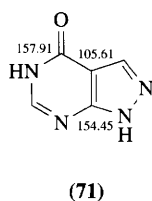
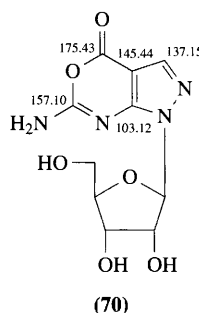
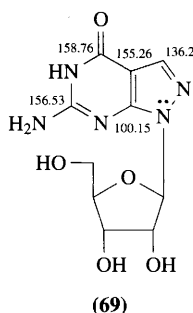
For imidazopyridazines (**68**), unambiguous assignment of H-2 and H-7 proton resonance could be achieved by analysis of C-H coupling constants in the ^{13}C NMR spectrum. The high field signal was assigned to H-2 while the one appearing at the lower field was assigned to H-7, which is in accordance with previous assignments for the parent ring system $\langle$ 69JHC93 $\rangle$. The spin-lattice relaxation times of base protons in imidazopyridazine nucleosides have been used to assign both configuration and glycosylation sites in these molecules $\langle$ 84JHC481 $\rangle$.



The position of ^1H NMR chemical shifts of H-3 and H-6 in alkyl allopurinols has been used to determine the site of protonation. Attachment of a proton to the pyrazole moiety causes only a small shift in the H-3 signal whereas attachment of a proton to N-5 causes a large deshielding of H-6 $\langle 79\text{JCS(P1)2795} \rangle$.

7.12.3.3 Carbon-13 NMR Spectroscopy

Again data has not been unequivocally assigned. Some of the published data should be reinterpreted by considering the factors affecting chemical shifts. Reported ^{13}C NMR data for 6-amino-1-ribofuranosyl allopurinol is shown in structure (69) $\langle 90\text{JHC787} \rangle$. In the authors' opinion, data for C-3a and C-7a should be interchanged as in this molecule C-3a is shielded by pyrazole nitrogen lone pair resonance which would deshield C-7a. Similar arguments apply to ^{13}C NMR spectra of compound (70) $\langle 90\text{JHC787} \rangle$. Accordingly, the data for allopurinol is interpreted in structure (71) $\langle 73\text{JHC431, 84CHEC-I(4)497} \rangle$. It is interesting that in compound (72) C-3a appears at 135.14: the shift of δ 25 ppm is a result of the attachment of this carbon to a nitrogen atom $\langle 87\text{AHC(41)319} \rangle$. In the ^{13}C NMR spectrum of compound (73), it seems also that values for C-3a and C-7a should be interchanged $\langle 90\text{TL1155} \rangle$: the appearance of C-7a at 118.8 cannot be readily understood. Carbon-13 NMR spectra of the isomeric pyrazolo[3,4-*d*]pyridazin-ones (66) and (67) show only minor differences between respective carbons: C-3a appears at 114.0 in the derivatives (66) and 111.0 in the isomers (67) indicating delocalization of the nitrogen lone pair at this carbon $\langle 78\text{JHC813} \rangle$.

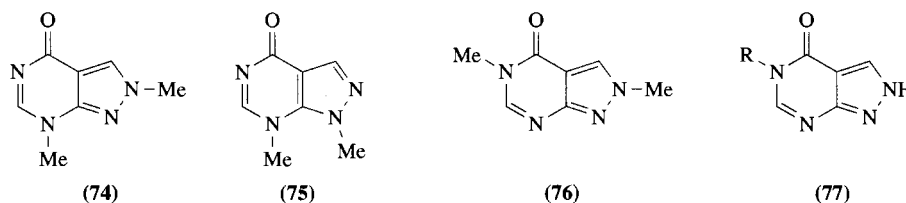


7.12.3.4 UV Spectroscopy

3- β -D-Ribofuranosyl-7-aminopyrazolo[4,3-*d*]pyrimidines as well as formycin A (54a) have been used as fluorescent probes in biological systems $\langle 74\text{MI 712-01, 79MI 712-01} \rangle$. The cationic forms of APPH $^+$ (4-aminopyrazolo[3,4-*d*]-pyrimidine cation), *N*(2)-methyl APPH $^+$ and *N*(7)-methyl APPH $^+$ exhibit intense fluorescence in aqueous alcoholic solutions at room temperature. The first two exhibit excitation spectra which differ from the absorption spectra and point to the existence of a tautomeric equilibrium in the ground state. From the shape of the excitation spectra and comparisons with methylated analogues in fixed tautomer forms, it follows that the emission of APPH $^+$ originates exclusively from the species *N*(2)-H, *N*(7)-H $^+$, the other forms being nonfluorescent. The proportion of the emitting species, calculated from the excitation wavelength dependence of the quantum yield, is in good agreement with data for the ground state. The emission spectrum of APPH $^+$ in aqueous medium consists of two bands with λ_{max} 360 nm and 430 nm which exhibit identical excitation spectra, but are quenched to different extents by H $_3$ O $^+$. The results indicate that the long wavelength emission band of APPH $^+$ originates from the rare tautomeric species *N*(7)-H

formed in the excited state by photodissociation of the *N*(2)-H proton from the species *N*(2)-H, *N*(7)-H⁺ <80ZN(C)878>.

The UV spectra of isomeric pairs of pyrazolo[3,4-*d*]pyrimidine-4,6-diones and pyrazolo[4,3-*d*]pyrimidine-5,7 diones show that the isomers with a [4,3-*d*] ring fusion absorb at longer wavelengths (red shift) compared to the [3,4-*d*] isomers <82IJC(B)585>. The *p*-quinonoid structure of the pyrimidine moiety in compounds (74) and (75) causes a bathochromic shift of 20–25 nm, relative to compounds (53) and (76). The close values of $\lambda_{\max}$ for 7-methyl (77; R = Me) and 2,7-dimethyl allopurinol (74) suggest that the former is present in aqueous solutions as the *N*(2)-H tautomer <79JCS(P1)2795>.

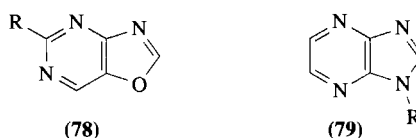


A band at 250–280 nm has been observed in the UV spectrum of diazodiazines and may be considered characteristic of these ring systems <58JA421, 67TL2029, 90TL1155>. Some systems revealed in addition to this band another band at 300–360 nm.

7.12.3.5 Mass Spectrometry

Mass spectra of 1*H*-pyrazolo[3,4-*d*]pyrimidine as well as its 1- and 4-substituted derivatives follow two main fragmentation pathways. One is formation of a pyrazolo[3,4-*d*]pyridinium cation from the molecular ion, caused by elimination of the C-4 substituent: fragmentation of the pyrimidine ring of the resulting ion leads to a pyrazolyne radical ion by loss of hydrogen cyanide. The other pathway leads to the formation of a diazatropylum type ion caused by the migration of the 4-substituent with loss of a hydrogen radical. The mass spectral fragmentation of the 4,5-dihydro-4-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine is loss of the C-4 substituent <76MI 712-01>.

The mass spectrum of formycin (54a) showed M⁺ and MH⁺ ions due to the protonated base moiety of the molecule <78MI 712-01>. The mass spectra of 5-substituted oxazolo[4,5-*d*]pyrimidines (78) proceeds via loss of the C-5 substituent <82KGS1255>. The main fragmentations of substituted imidazo[4,5-*b*]pyrazines (79) <89KGS532> and oxazolo[5,4-*d*]pyrimidines <85KFZ685> have been determined.



7.12.4 THERMODYNAMIC ASPECTS

7.12.4.1 Melting Points

Strong intermolecular attractions exist between molecules of unsubstituted ring systems having NH. This is indicated by the fact that all isolated unsubstituted derivatives are solids with high melting points (>190°C). This is understandable in terms of the formation of strong hydrogen bonds with nitrogen atoms of other molecules <56JA242, 56JA784, 67TL2029, 72JHC967, 74TL3893>. Only the melting point of the hydrate of 1*H*-pyrazolo[4,3-*d*]pyrimidine has been measured (107°C). It is most likely that the nonhydrated form would melt at a temperature comparable to that reported for the isomeric 1*H*-pyrazolo[3,4-*d*]pyrimidine (m.p. 107°C).

Ring systems having no NH groups melt at much lower temperatures. For example, oxazolo[4,5-*d*]pyrimidine (28) melts at only 110°C <90TL1155>. As may be anticipated, replacement of hydrogen in NH azoloazines by alkyl groups leads to a decrease in melting points <58JCS2973>. Replacement

of hydrogen by halogen has little effect on melting points. However, amino and oxo derivatives melt at much higher temperatures than the parent, reflecting the stronger intermolecular bonds in these derivatives <58JA421, 58JCS2973>.

7.12.4.2 Solubility

Azoloazines are generally soluble in water, ethanol, acetone, and other polar solvents but sparingly soluble in nonpolar solvents.

A comparison of the general solubility of the pyrazolo[3,4-*d*]pyrimidines and the corresponding purines reveals that in general the pyrazolo[3,4-*d*]pyrimidines are less soluble in water than the purines. It is interesting to note that although 4-aminopyrazolo[3,4-*d*]pyrimidine (4APP) is approximately 1/25 as soluble in boiling water as adenine, 4-methylaminopyrazolo[3,4-*d*]pyrimidine is five times more soluble than the corresponding purine isomer in aqueous solution at 100°C. This would seem to indicate intermolecular hydrogen bonding of 4APP in the crystal lattice is uncommonly high and in some way is associated with the 4-amino group and the two nitrogens of the pyrazole ring. Methylation of the 4-amino function destroys the ability of the molecule to arrange itself in such a favorable pattern for intermolecular hydrogen bonding. Thus, 4-methylaminopyrazolo[3,4-*d*]pyrimidine is strongly attracted by water molecules which compete favorably for the site of hydrogen bonding. This postulate receives experimental support from the fact that 4-MeAPP crystallizes from an aqueous solution in the form of a dihydrate which loses the last molecule of water only under rather drastic conditions <56JA784>.

At 15–40°C the solubility of allopurinol (**53**) in the presence of polyvinylpyrrolidone increased with increasing concentration of the polyvinylpyrrolidone while differential heats of solution decreased and free energy of partitioning increased. This indicates that allopurinol forms a complex with polyvinylpyrrolidone <74JPP84>.

7.12.4.3 Chromatographic Behavior

Almost all chromatographic investigations have been made on allopurinol (**53**), in order to develop detection methods <77JC195, 80JC286, 83JC75, 84JC205>. Thus, HPLC methods for detecting allopurinol and oxyallopurinol in human serum have been reported. Allopurinol in the eluents was detected electrochemically by a polarographic detector operating in the oxidative mode. This method is based on the ability of allopurinol to form insoluble anodic films with mercury <84JC205>. Another method which is in common use is UV detection at 254 nm <86MI 712-01>.

A precise, accurate, selective, and sensitive HPLC method for the detection of 2-ethyl-4,6,8-trimethylimidazo[1,2-*b*]pyrazolo[3,4-*d*]pyrimidine in monkey plasma is based on the use of two reversed-phase C18 Hypersil columns placed in series and UV detection at 315 nm. The method is linear over a concentration change of 0.05–3.0 $\mu\text{g ml}^{-1}$ and the detection limit is 0.05 $\mu\text{g ml}^{-1}$ <89JC493>.

7.12.4.4 Aromaticity

All the fully conjugated azoloazines (**1**)–(**39**) as well as oxo, thioxo, and imino derivatives of the azoloazines (**41**)–(**44**) are aromatic: they tend to undergo substitution rather than addition reactions. Reported bond lengths and bond angles for a variety of azoloazines indicate that all bond lengths are between those of a single bond and a double bond. However, shortening of single bonds in the tetrazaindenes is more than that in oxygen derivatives and in the triazaindene derivatives.

Reported ^1H NMR and ^{13}C NMR data also indicates ring current effects in both the six-membered ring and the five-membered ring and these effects are very similar to those in the corresponding nonfused rings.

Ultraviolet absorption spectra have been used for many years in a qualitative way to indicate similarities in the bonding patterns of different compounds. The recorded UV spectra of azoloazines are characterized by a band at 250–280 nm which is ascribed to a $\pi\text{--}\pi^*$ transition and which finds similarity in indole as well as other aromatic carbocyclic and heterocyclic compounds <84CHEC-1(4)497>.

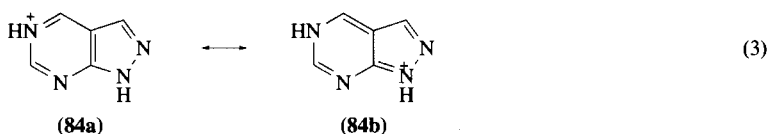
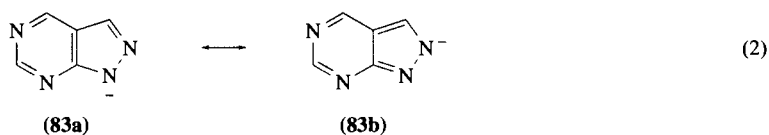
7.12.4.5 Tautomerism

7.12.4.5.1 Prototropic tautomerism

For nonfunctionally substituted fully conjugated azoloazines, only pyrazoloazines and imidazoazines exhibit this type of tautomerism. Four tautomeric forms are possible for pyrazolo[3,4-*d*]-pyrimidine (**18**, **80–82**) (Scheme 1). In the solid state as well as in neutral media, this compound exists as structure (**18**). In basic media the anion (**83a, b**) is the predominant species (Equation (2)). In acidic solutions the cation (**84a, b**) predominates (Equation (3)) <58JCS2973>.

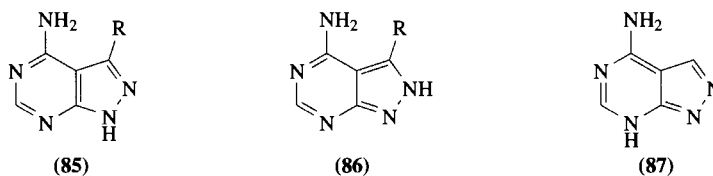


Scheme 1



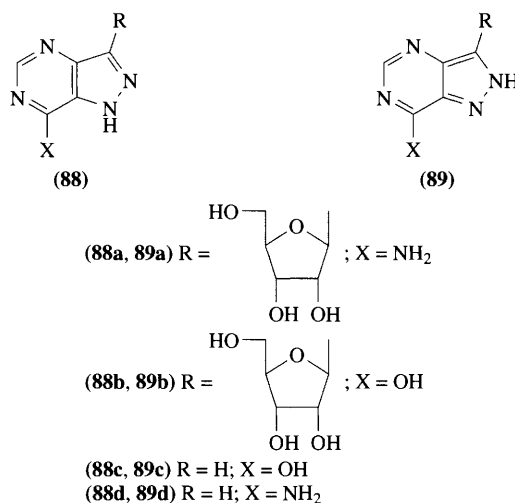
7.12.4.5.2 Tautomerism of amino derivatives

The tautomerism of 4-aminopyrazolo[3,4-*d*]pyrimidines as well as aminopyrazolo[4,3-*d*]pyrimidines has been investigated. 4-Aminopyrazolo[3,4-*d*]pyrimidines exist in water in two tautomeric forms: 1*H*-4-amino (**85**) and 2*H*-4-amino (**86**) [K (**86/85**) = 0.1 at 100°C; ΔH = 9.0 kcal, mol⁻¹]. Interconversion of these two forms is catalyzed by acid or base <77JA7257, 80ZN(C)878, 82MI 712-02>. Together with these two predominant species there are smaller proportions of the 7*H*-4-amino (**87**) (1×10^{-3}) and the 5*H*-4-amino isomer (2×10^{-4}). The species (**87**) exists only as an amino tautomer whereas the 5*H*-4-amino species in water has a partial imino structure (amino/imine = 10) <77JA7257>.



Luminescence spectra of formycin B (**88b**), its aglycone (**88c**) and various *N*-methyl derivatives at room temperature and at 77K indicated that they consist of two tautomeric species (**88**) and (**89**) both of which emit at 300 nm at 77K. They can be distinguished by location of emission maxima <82MI 712-02>. Photolysis induced tautomerization <82MI 712-02>. The tautomeric equilibrium between (**88c**) and (**89c**) has a constant ratio [$N(2)\text{-H}/N(1)\text{-H}$ = 0.2] and the energy difference in ethanol is estimated to be 1 kcal mol⁻¹. The tautomeric interconversion is catalyzed by H⁺ (3×10^9 M⁻¹ sec⁻¹) and by OH⁻ (5×10^5 M⁻¹ sec⁻¹). No other catalytic pathway such as water catalysis or

tautomerization via tautomeric cations contributes significantly to the interconversion: protonation on the pyrazole ring of formycin does not occur significantly <80JA3897>.



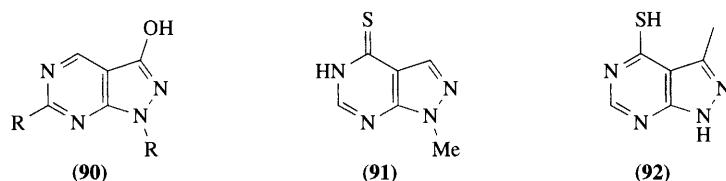
The dynamic tautomerism in the derivatives (88) was investigated by ¹³C NMR spectroscopy <73JHC431>. As the temperature is increased from -14 to 145°C, the signal of the bridgehead C-7a in compound (88c) moves downfield whereas the signal for C-3 moves upfield. These findings are consistent with a change in proton population at N-1 and N-2. Energetically the most favorable resonance structure places the proton on N-1. As the temperature is increased, the population of the N-2 tautomeric form (89) is increased causing the observed shifts at C-3 and C-7a <68JA697, 68JA4232, 71JA1880, 73JA2791>. The experiments conducted on the pyrazolo[4,3-*d*]pyrimidine-7-one, and pyrazolo[3,4-*d*]pyrimidine-4-one indicate that the broad line width observed for C-3 and C-7 in derivatives (88a-c) is the direct result of tautomeric averaging of the proton between N-1 and N-2 <73JHC431>.

The dynamic tautomerism of formycin A (54a) was investigated by a temperature jump method and the mechanism of tautomerism discussed <78JA3957>.

7.12.4.5.3 Tautomerism in oxo and thioxo derivatives

The IR spectrum of allopurinol (53), the 6-thioxo and the 6-oxo derivative reveal strong carbonyl absorption and an absence of any absorption for enol forms <76ACHS533>. The hydroxypyrazolo[3,4-*d*]pyrimidine derivatives (90) exist mainly in the hydroxy form as shown by the absence of a carbonyl band in the IR spectrum <61JOC451>. 4,7-Dioxypyrazolo[3,4-*d*]pyridazines exist in dioxo form <77JHC375>.

The tautomerism in few azoloazines with potential thiol groups has been investigated. 1-Methylpyrazolo[3,4-*d*]pyrimidine-6-thione (91) exists in the thione form as indicated by x-ray crystallography <73CR(C)1007, 74AX(B)1598>. Although the isomer (92) is suggested to exist as such in polar solvents one would expect predominance of the thione form whose charge separation should be stabilized by solvent <87AHC(41)319>.



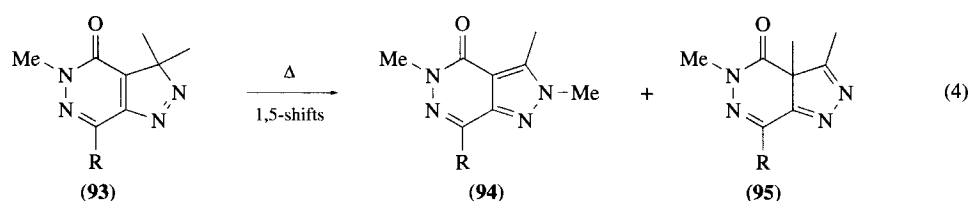
7.12.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.12.5.1 General Considerations

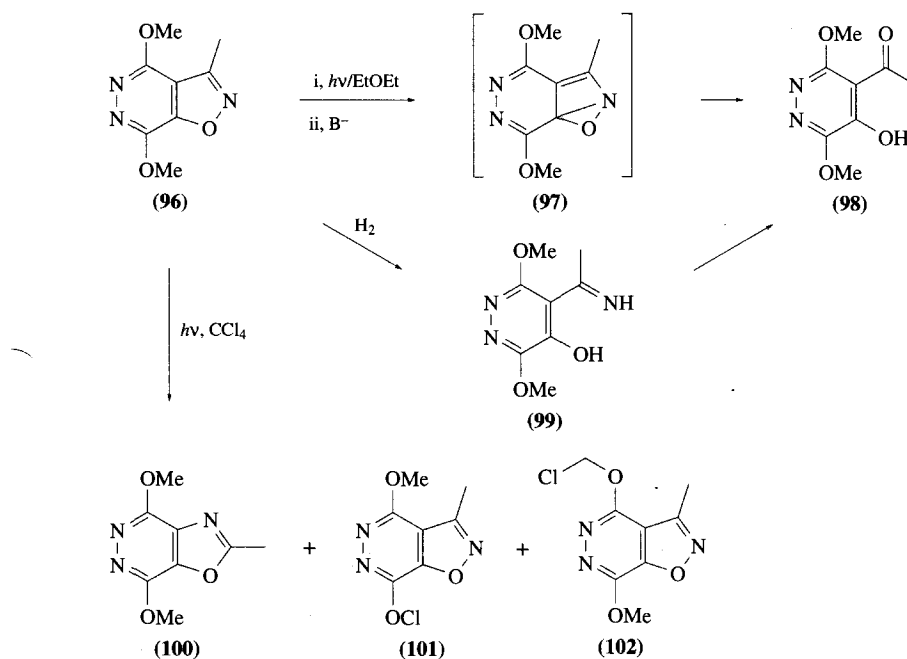
These systems are aromatic in the sense that there is a tendency for reaction by substitution rather than by addition. Only one of the two heteroatoms on each ring contributes a lone pair of electrons to the ring; the other has its lone pair localized. Electrophilic reagents thus attack ring nitrogen and electrophilic substitution at carbon is rare. In contrast, good leaving groups at π -deficient carbons are readily replaced by nucleophiles. Nucleophilic substitution of hydride ion also occurs quite readily.

7.12.5.2 Thermal and Photochemical Processes that are Unimolecular

Thermal 1,5-sigmatropic rearrangement of the methyl groups in 3,3-dimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (**93**) gives the N-2 methylated product (**94**) and the C-3a methylated product (**95**) (Equation (4)) <91JHC425>.



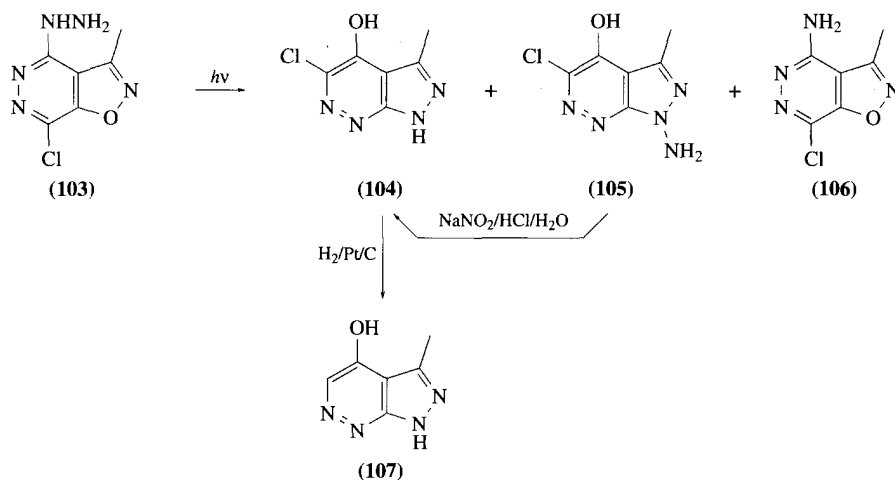
The dimethoxy isoxazolo[4,5-*d*]pyrimidine derivative (**96**) showed solvent-dependent photochemistry (Scheme 2). Thus, irradiation in ether followed by alkaline hydrolysis gives compound (**98**) which is believed to be formed via the intermediate (**97**). The structure of the product (**98**) was established by synthesis via reductive cleavage of compound (**96**) to give the imine (**99**) and subsequent hydrolysis. Photolysis of compound (**96**) in carbon tetrachloride afforded a mixture of the products (**100**)–(**102**) <85JHC1561>.



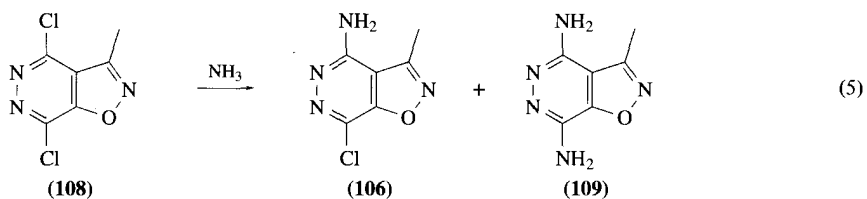
Scheme 2

The UV irradiation of derivative (**103**) affords a mixture of products (**104**–**106**). Structures (**104**) and (**105**) were established by conversion to compound (**107**) (Scheme 3). The structure (**106**) was

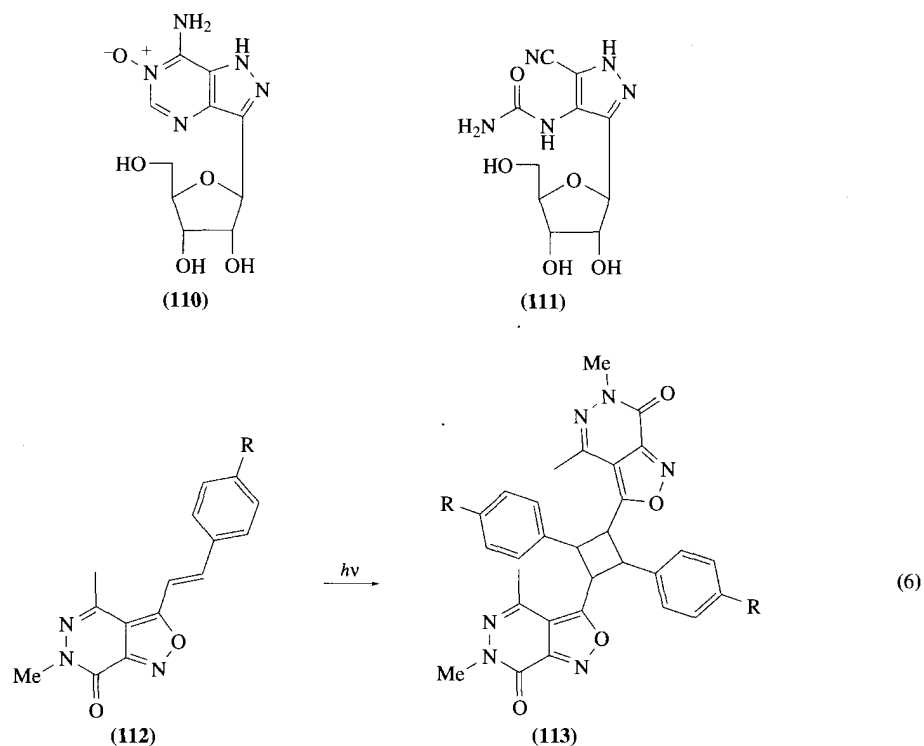
established by reaction of the dichloro derivative (108) with ammonia to give compounds (106) and (109) (Equation (5)) <85JHC1561>.



Scheme 3



Formycin-*N*(6)-oxide (110) rearranged to give the urea derivative (111) on irradiation at > 290 nm in aqueous solution <84JCS(P1)2421>. Irradiation of compound (112) gives the dimer (113) (Equation (6)) <86H(24)3467>.



7.12.5.3 Electrophilic Attack at Nitrogen

7.12.5.3.1 Protonation

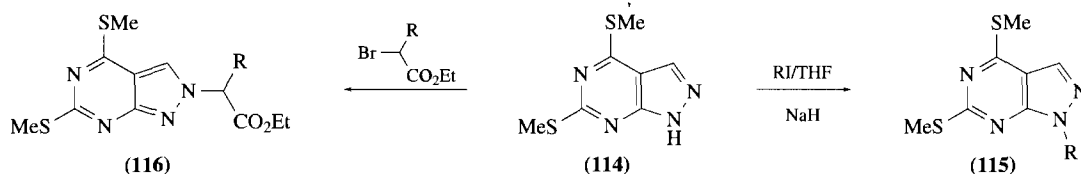
Azoloazines having NH functions are weakly acidic and are also basic. *N*-Alkylated derivatives act only as bases. Carbon-13 NMR studies on 1-isopropyl-4-amino-pyrazolo[3,4-*d*]pyrimidine and isomeric 2-isopropyl derivative indicate that N-5 and N-7 are the respective protonation sites <77JA7257>. Allopurinol as well as its derivatives have been shown by UV and NMR to form mono- and diprotonated species in sulfuric acid solutions <75KGS838>.

The protonation site in 6-(2,4-dimethoxyphenyl)-5*H*-imidazo[4,5-*d*]-pyridazine and in 2-(2,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*d*]pyridazine has been determined by ¹³C NMR. Both ring systems are protonated at the pyridazine nitrogen. In the [3,4-*c*] system, protonation occurs at N-2 <89JCS(P1)1769>.

7.12.5.3.2 Alkylation and glycosylation

(i) Intermolecular alkylation and glycosylation

The site at which alkylation occurs depends on the alkylation reagent, the reaction conditions and the nature of the substituents on the azoloazine ring system. Thus, whereas alkylation of compound (114) by alkyl iodides in THF in the presence of sodium hydride gives the products (115), alkylation by ethyl α -bromoacetate or ethyl α -bromopropionate gives the products (116) (Scheme 4) <89S876>.

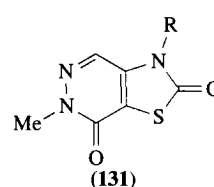
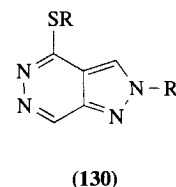
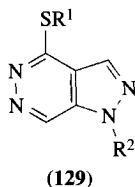
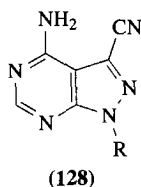
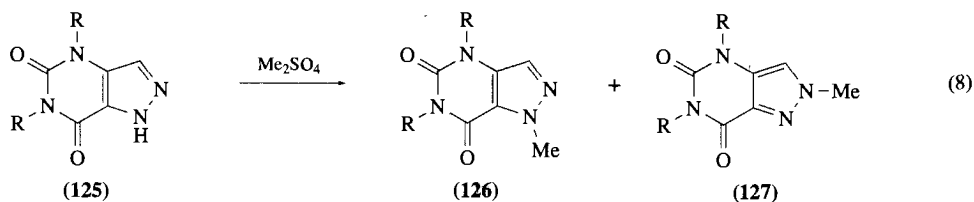
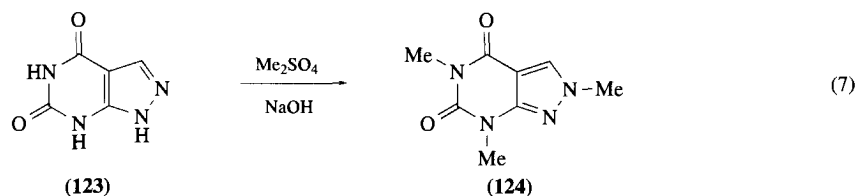
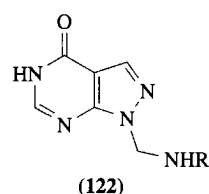
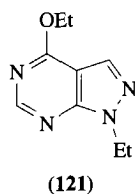
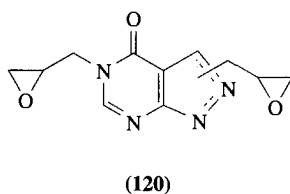
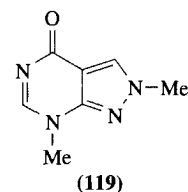
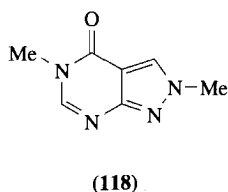
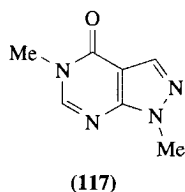


Scheme 4

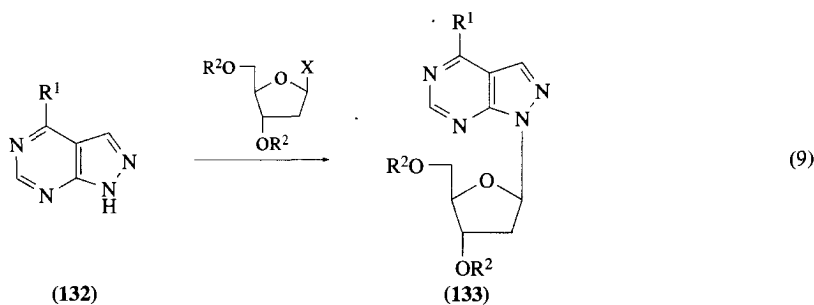
Alkylation of pyrazolo[3,4-*d*]pyrimidine-3-carbonitrile with DMF diethylacetal or with triethyl orthoformate gives the N-1 ethyl derivative <88KGS914>. Phase-transfer methylation of 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidines gives a mixture (2:1) of N-1 and N-2 methylated derivatives <85JOC1847>.

Methylation of allopurinol by methyl iodide in the presence of a base gives a mixture of 1,5-dimethyl (117), 2,5-dimethyl (118), and 2,7-dimethyl (119) derivatives <79JCS(P1)2795>. When N-1 is alkylated methylation affords the 1,5-dimethyl derivative <79AP(312)703>. Whereas alkylation of allopurinol with epichlorohydrin gives compound (120) <83EUP71904>, in addition to the expected dialkylation derivatives at N-1, N-2, and N-7 <83EUP71904>, alkylation with dimethylformamide dimethylacetate in a chloroform-methanol mixture gives the dialkylated derivative (121) <88KGS1526>. Reaction of allopurinol with formaldehyde and secondary amines (Mannich reaction) gives only the mono alkylated derivative (122) <86MI 712-02>.

When the pyrazolo[3,4-*d*]pyrimidine-4,6-dione (123) is methylated with dimethyl sulfate only the trimethyl product (124) could be isolated (Equation (7)) <58HCA1052>. With the dialkyl derivatives (125) a mixture of the isomers (126) and (127) is produced (Equation (8)) <65JOC199>. The reaction of compound (128; R = H) with α -bromoacetylacetone gives the derivative (128; R = CH₂COCH₂COCH₃) <90JMC980>. Alkylation of the pyrazolo[3,4-*d*]pyridazines (129; R² = H) with alkyl bromides gives a mixture of derivatives (129; R¹ = alkyl) and (130; R¹ = alkyl) <82JHC817>. 2-Oxo-3-substituted-6-methylthiazolo[4,5-*d*]pyrimidine-7(6*H*)-ones (131) are prepared by alkylation of compound (131; R = H) <79JAP79119490, 79JAP79119491>.

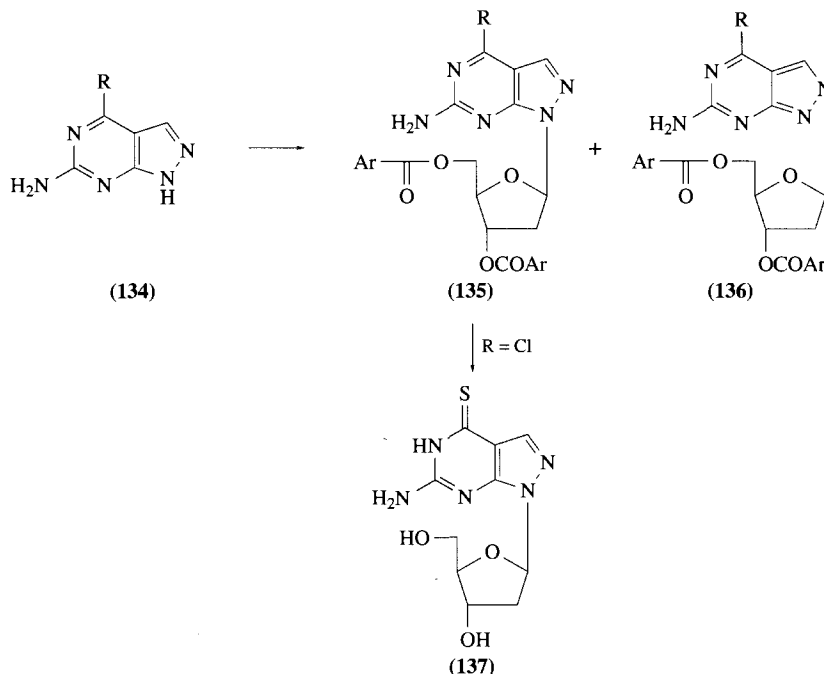


Nucleoside derivatives of azoloazines can be prepared by treatment of azolopyrimidines with halo sugars in the presence of alkali [85JCS(P1)2573, 87IJC(B)851, 87IJC(B)1054, 90JHC171]. For example, phase-transfer glycosylation of heterocycles (132) gives the nucleosides (133) (Equation (9)).



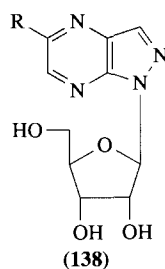
Phase-transfer glycosylation of compound (134; R = OMe) using 2-deoxy-3,5-di-*O*-*p*-toluoyl- α -12-erythropentofuranosyl chloride in aqueous potassium hydroxide gives the β -anomer (135), together with its α -anomer and the β -*N*(2) isomer (136) (Scheme 5). Similar phase-transfer glycosylation of compound (134; R = Cl) but without catalyst gives product (135; R = Cl) and its β -*N*(2)

isomer. The latter when treated with thiourea and sodium methoxide in methanol gave compound (137) <86HCA1602>. Phase-transfer glycosylation of allopurinol has also been reported <84TL5017>. Glycosylation of 7-aminopyrazolo[3,4-*d*]pyrimidine-3-one with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose in the presence of boron trifluoride gives the N-1 ribosyl derivative <90JHC439>.



Scheme 5

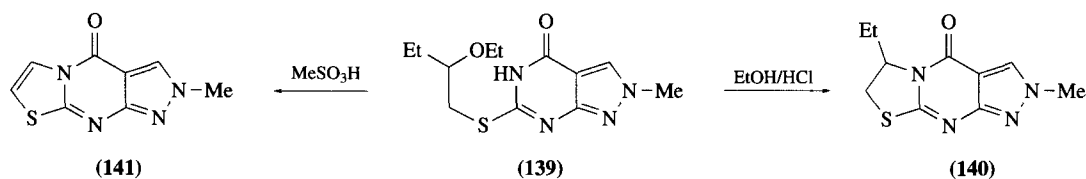
Silylation followed by treatment with acylated sugars is the more frequently utilized approach for the synthesis of azoloazine *N*-nucleosides <74JHC1033, 79MI 712-03, 81CB1610, 82JMC1040, 83JMC1601, 84JMC986>. Unexpectedly glycosylation of allopurinol gives N-2 glycosyl derivatives as the major products <83MI 712-01>. Melting 2,4-dinitrophenol with 5-ethoxy-1*H*-pyrazolo[3,4-*b*]pyrazine at 140–145 °C followed by treatment with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -*O*-ribofuranose at 140–145 °C gives the corresponding N-1 nucleoside, which is deprotonated by sodium methoxide in methanol to yield compound (138; R = OEt) <81JHC751, 82JMC1040>.



(ii) Intramolecular alkylation and acylation

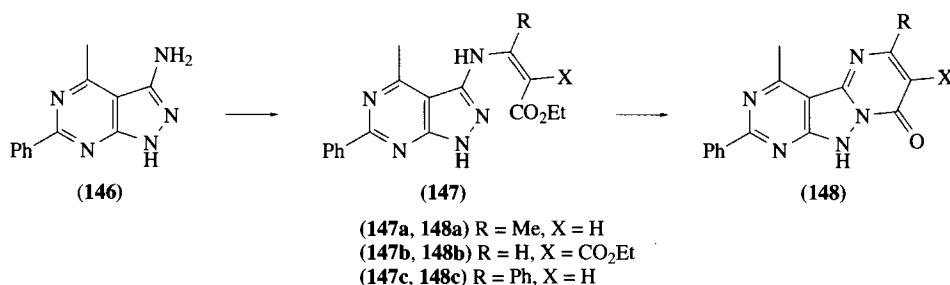
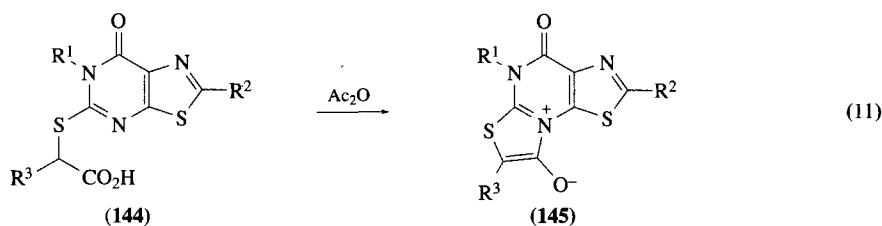
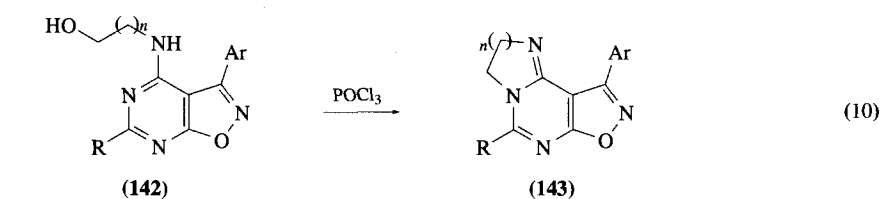
A variety of intramolecular alkylations at ring nitrogens leading to tricyclic systems have been reported. For example compound (139) cyclized on treatment with ethanolic hydrochloric acid to give the product (140). Cyclization of compound (139) using methyl sulfonic acid gives the derivative (141) (Scheme 6) <87LA1211>.

Cyclization of the alcohols (142) with phosphorus oxychloride gives the derivatives (143) (Equation (10)) <72AHC(14)1>. The meso-ionic derivatives (145) are produced by cyclodehydration of the acids (144) using acetic anhydride (Equation (11)) <83JJC243>. Reacting amine (146) with ethyl

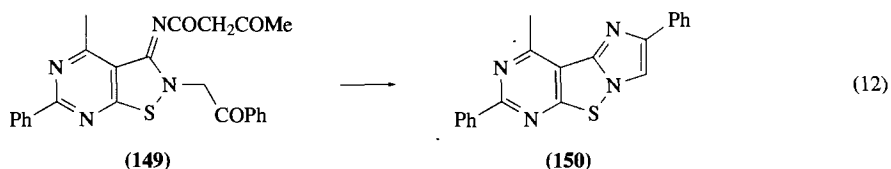


Scheme 6

acetoacetate, diethyl ethoxymethylenemalonate or ethyl phenylpropiolate gives the esters (**147a–c**) which readily cyclize under mild conditions into derivatives (**148a–c**) (Scheme 7) <89JCR(S)333>. The cyclization of (**149**) to (**150**) occurs in 36% yield (Equation (12)) <89JCR(S)333>.



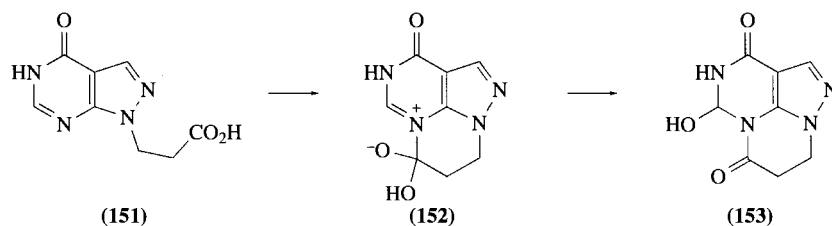
Scheme 7



Treatment of the acid (**151**) with DCC gives compound (**153**) most likely via the intermediate (**152**) (Scheme 8) <85JOC1847>.

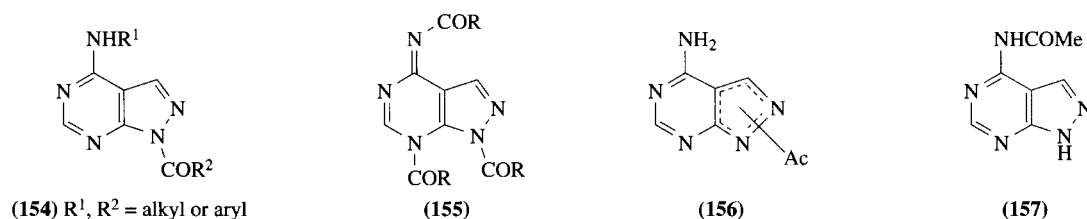
7.12.5.3 Reactions with organic acid derivatives

Acylation and arylation have not been thoroughly studied. Treatment of the amine (**85**; R = H) with an acid chloride gives the monoacylated derivative (**154**). The N-1 monoalkylated derivatives of compound (**85**; R = H) are monoacylated on the exocyclic amino function. Triacylation of

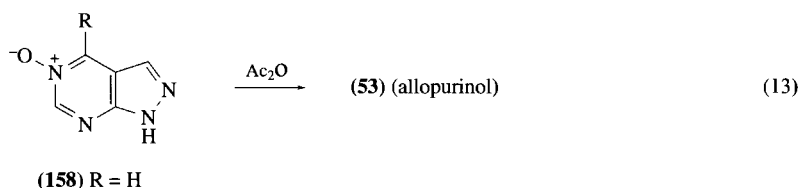


Scheme 8

compound (85; R = H) gives the derivatives (155) <75T587> and treatment with acetic anhydride gives the isomers (156) which are converted into the amide (157) in basic media <78JAN377>.

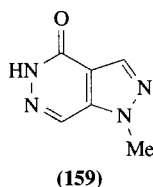


The *N*-oxide (158) reacts with acetic anhydride to yield allopurinol (53) (Equation (13)) <76CPB3120>.



7.12.5.3.4 Reactions with metal ions

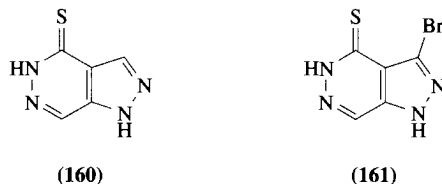
Methylmercury complexes of allopurinol (56) and 1-methylpyrazolo[3,4-*d*]pyridazine-4-one (159) have been isolated from aqueous solutions and characterized <87ICA181>. Copper complexes of allopurinol have also been prepared by reaction with copper salts and their structures were elucidated by x-ray crystal structural analysis <87ZN(B)195>.



7.12.5.4 Electrophilic Attack at Carbon

Little is reported on substitution at carbon atoms by electrophiles in these systems. As a result of their π -electron deficiency, azoloazines of the types discussed here are expected to be relatively unreactive toward electrophiles; when electrophilic substitution occurs, it normally takes place at

carbons of the five-membered ring. Thus, bromination of compound (160) affords the 3-bromo derivative (161) <82JHC817>. The bromination of 4-aminopyrazolo[3,4-*d*]pyrimidine gives the corresponding 3-bromo derivative <82KGS982>.

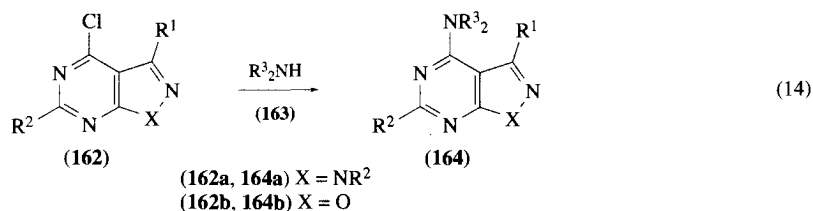


7.12.5.5 Nucleophilic Attack at Carbon

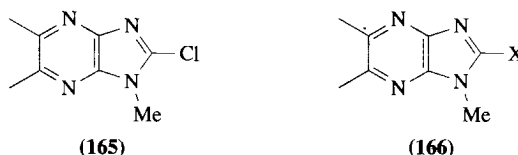
In contrast to their low reactivity towards electrophiles, azolodiazines are highly reactive toward nucleophiles. The displacement of good leaving groups is generally easy to accomplish and replacement of substituents on the six-membered ring is normally easier than replacement on the five-membered ring. On account of the small resonance energy in some of these molecules nucleophilic displacement sometimes leads to ring cleavage.

7.12.5.5.1 Reactions with nitrogen nucleophiles

Replacement of halogen, alkylthio, and alkoxy functions with nitrogen nucleophiles is normally effected under mild conditions especially when the substituent is on a highly π -deficient site of the molecule <59USP298469, 63YZ767, 66CR(C)1385, 68JHC13, 71BSF3537, 75KFZ10, 76GEP2430454, 76ZOR1132, 79JAP79119491, 82JHC1565, 86USP879240, 88MI 712-01>. For example, the 4-chloro substituents in the derivatives (162a,b) are readily replaced by secondary amines (163) to give the fungicidal compounds (164) (Equation (14)) <76GEP2430454, 88MI 712-02>.

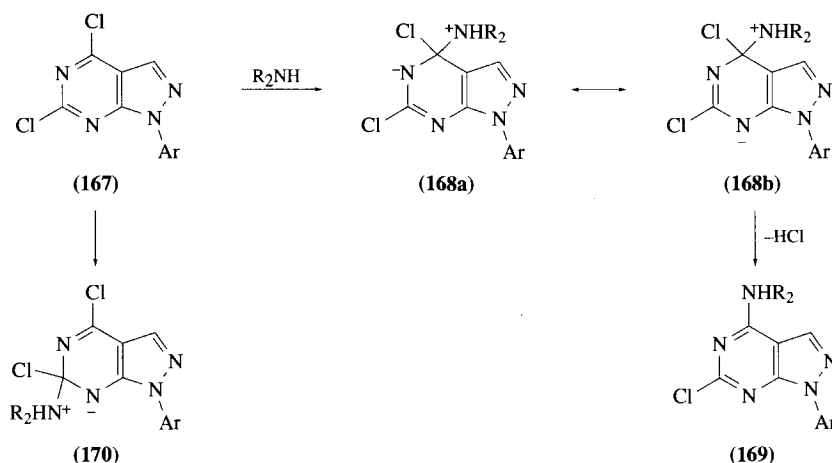


Replacement of halogen substituents on the azole moiety by amines and hydrazines can also be effected. For example, the compound (165) reacts with amines and amidines to yield the derivatives (166) <75KFZ10>.



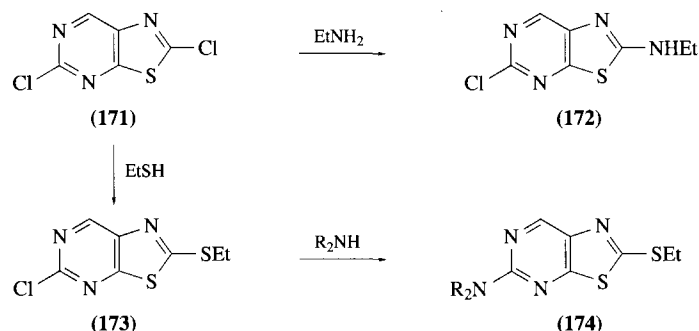
The relative reactivity of different sites in azolodiazines has not been fully investigated. However, in pyrazolo[3,4-*d*]pyrimidines halogen at C-4 is more readily replaced than halogen at C-6. It is evident that the intermediate for substitution at C-4 is stabilized by both nitrogen atoms. Thus, the dichloro derivatives (167) give the amines (169) on treatment with secondary amines (Scheme 9). The amines (169) are assumed to be formed via the intermediates (168a) and (168b) <82JHC1565>.

The intermediate **(170)** which can lead to a substitution at C-6 has only one resonance form which does not disrupt the aromatic sextet of the five-membered ring.



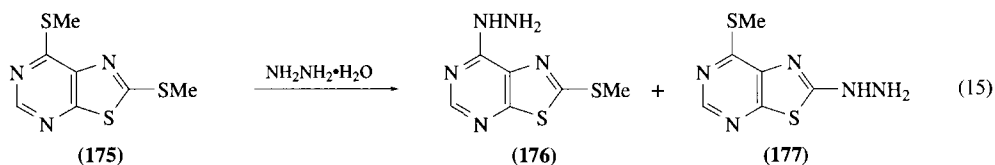
Scheme 9

In thiazolo[5,4-*d*]pyrimidines, the halogen at C-2 is more readily replaced than the halogen at C-6. Thus, reacting compound **(171)** with ethylamine gives compound **(172)** (Scheme 10). However, a halogen substituent at C-6 is more reactive than an ethyl thiol function at C-2. Treatment of compound **(173)**, produced by reaction of compound **(171)** with ethylthiol, with amine gives the derivatives **(174)** <68CPB745, 73JCS(P1)657>.



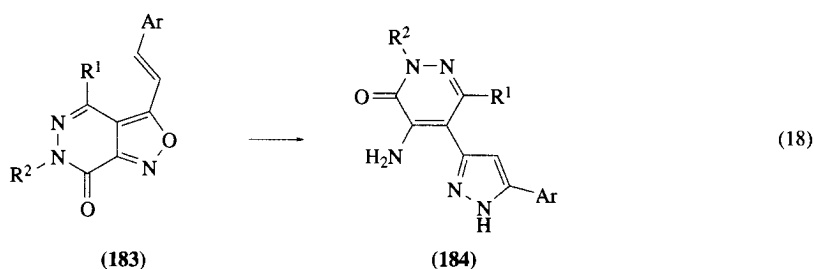
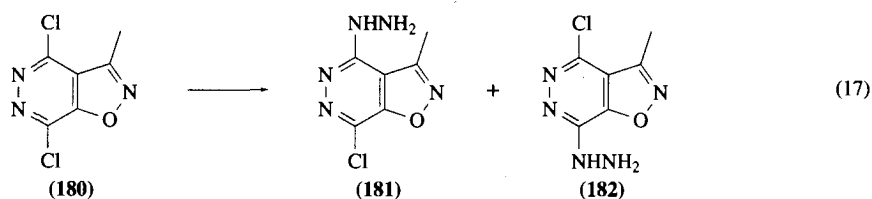
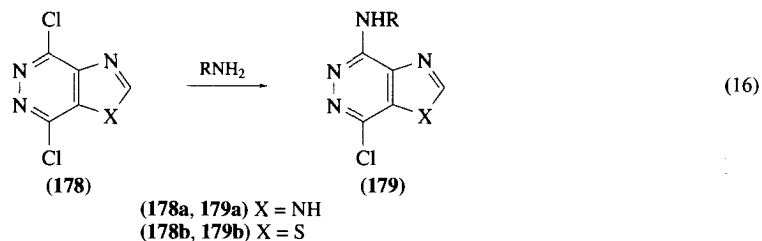
Scheme 10

Suzuki and co-workers <68CPB750> have correlated chemical shift values of protons attached to the carbon at different sites in thiazolo[5,4-*d*]pyrimidine with the ease of substitution of halogen in 2,5,7-trichlorothiazolo[5,4-*d*]pyrimidine. The order of reactivity of chlorine was thus concluded to be C-2 > C-5 > C-7 which is the order of chemical shift: protons at C-2 resonate at lower field than those at C-5, and C-7 protons resonate at highest field. It seems, however, that the reactivity at C-5 and C-2 is very similar as compound **(175)** reacts with hydrazine hydrate to yield a mixture of the isomers **(176)** and **(177)** (Equation (15)) <79IJC307>.



Reaction of compounds **(178a)** and **(178b)** with amines and hydrazines gives the derivatives **(179a)** and **(179b)**, resulting from substitution at C-4 (Equation (16)) <59USP298469, 63YZ767, 66CR(C)814, 66CR(C)1385, 68JHC13, 71BSF3537>. In contrast to this, study of the reactivity of compound **(180)** towards nucleophiles shows that positions 4 and 7 have similar reactivity. In fact this derivative **(180)** with a stoichiometric amount of hydrazine hydrate gives a mixture of the isomers **(181)** and

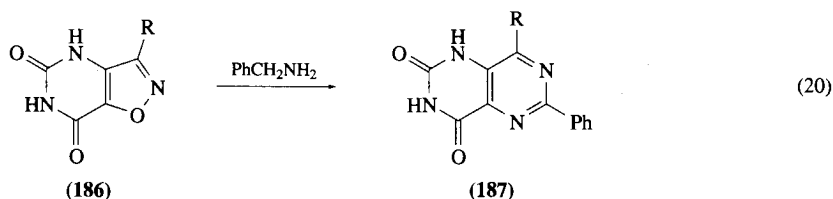
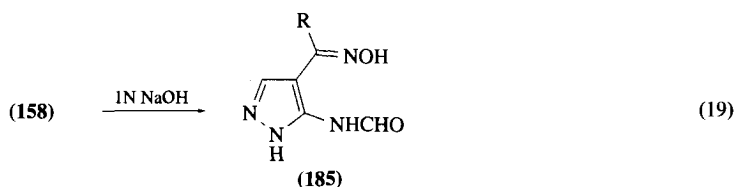
(182) (Equation (17)) <85JHC1561>. Treatment of derivatives (183) with hydrazine hydrate results in ring cleavage and formation of the pyrazolylpyridazin-6-one (184) (Equation (18)) <84H(22)1741, 86H(24)3143>. The reaction of 3-substituted 5,7-dimethylisoxazolo[3,4-*d*]pyrimidin-4,6-diones with benzylamine resulted in their rearrangement into pyrimido[3,4-*d*]pyrimidines <79CL155>.



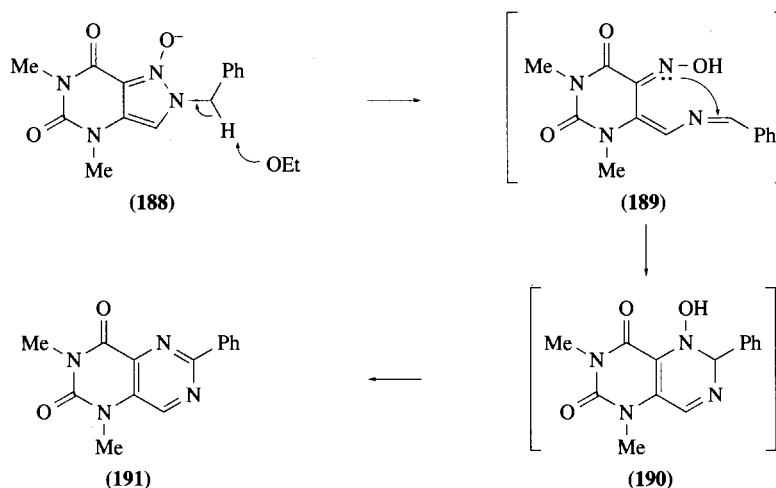
7.12.5.5.2 Reactions with oxygen nucleophiles

Halogens at activated sites in azoloazines are readily replaced by the action of alkoxide ions <69BSF4004, 69CPB2158, 72CPB1473, 72CPB1528, 78JHC1>. Similarly, methoxy groups are replaced by hydroxyl functions on treatment of methoxyazoloazines with alkali <85JOC1847>.

Reaction of azoloazines with oxygen nucleophiles leads, in several cases, to ring cleavage. Cleavage of both the azine and azole rings has been reported. The *N*-oxide (158) reacts with 1 N sodium hydroxide to yield the pyrazole derivative (185; R = H) (Equation (19)). Similarly, the reaction of isoxazolo[4,5-*d*]pyrimidines (186) with benzylamine gives the derivatives (187) (Equation (20)) <76CPB3120>.

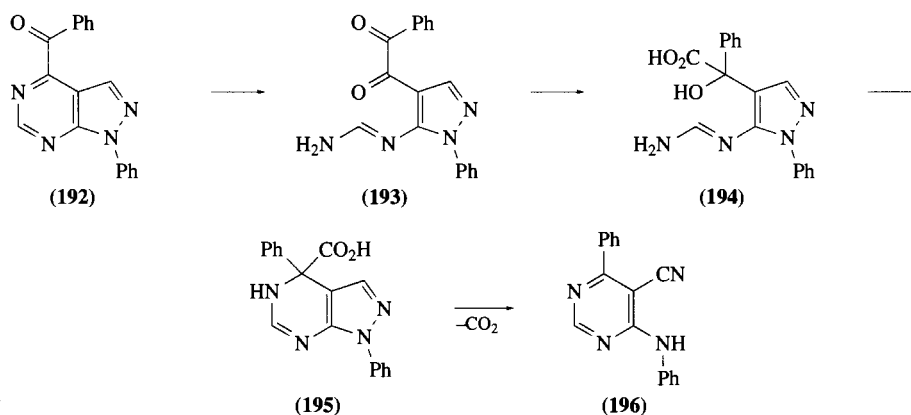


2-Benzyl-4,6-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*) dione-1-oxide (188) affords the pyrimidopyrimidine derivative (191), most likely via the intermediates (189) and (190) (Scheme 11) <78TL2295>.



Scheme 11

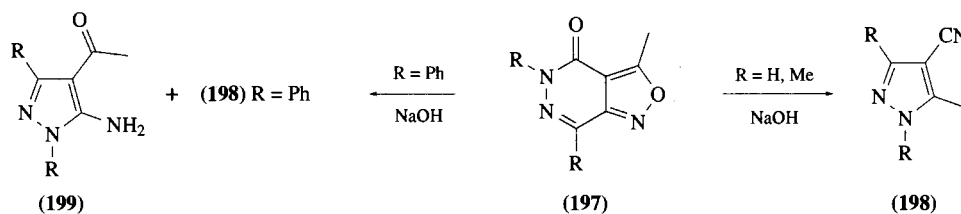
Treatment of compound (192) with sodium hydroxide in DMSO gives the pyrimidine (196). It is most likely that this product (196) is formed via addition of water to the C=N bond adjacent to the benzoyl group (Scheme 12). This affords the formamidine (193) which undergoes benzylic-like rearrangement to the acid (194) which cyclizes (194) → (195). Decarboxylation and N—N bond cleavage in the pyrazole moiety gives the final isolable product (196) <83CPB3951>.



Scheme 12

Treating the isoxazolopyridazine (197; R = H) with 2–4 N sodium hydroxide gives the cyano-pyrazoles (198) (Scheme 13). In contrast, the *N*-phenyl derivative (197; R = Ph) gives pyrazole (199; R = Ph) as a major product together with a small amount of compound (198; R = Ph) <85H(23)365>.

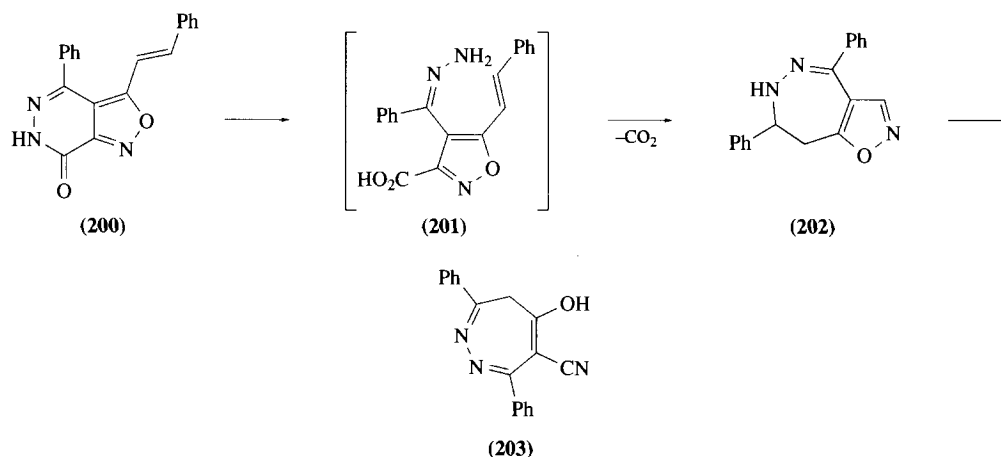
Treatment of compound (200) with alkali results in the formation of the 1,2-diazepine derivative



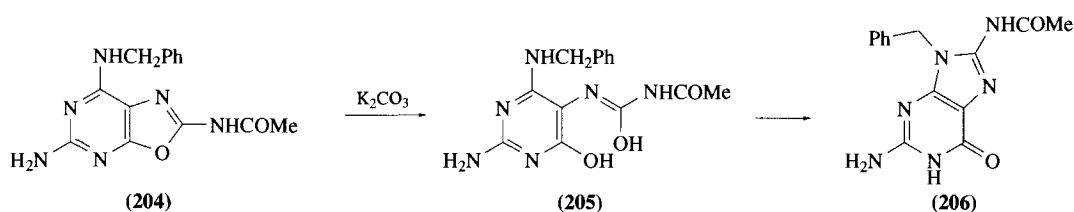
Scheme 13

(203) (Scheme 14). This product is probably formed via intermediacy of the species (201) and (202) <84H(22)1741>.

Oxazoloazines are very readily cleaved: treatment of compound (204) with potassium carbonate results in its rearrangement into compound (206) via intermediate (205) (Scheme 15) <84H(22)2439>.



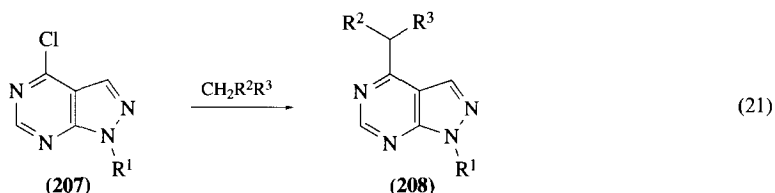
Scheme 14



Scheme 15

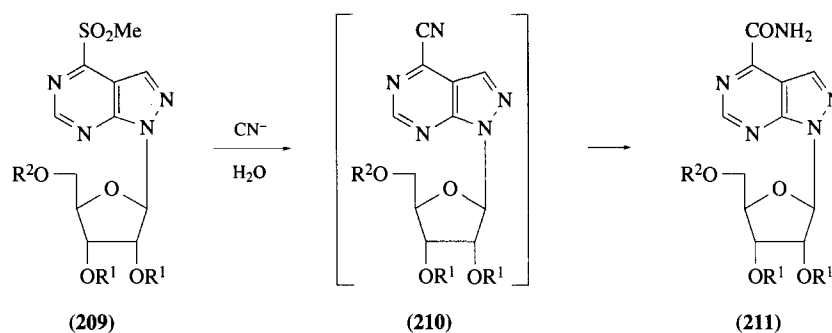
7.12.5.5.3 Reactions with carbon nucleophiles

A halogen substituent at C-4 of the pyrazolo[3,4-*d*]pyrimidine ring system is readily replaced by active methylene reagents <76S824, 76YZ1352>. For example, treatment of the derivatives (207) with active methylene reagents in the presence of sodium hydride results in the formation of derivatives (208) in 70–80% yield (Equation (21)). The methylsulfonyl derivative (209) is converted into the carboxamide (211) when treated with cyanide ion; intermediacy of the nitrile (210) seems most likely (Scheme 16) <82JMC1334>.

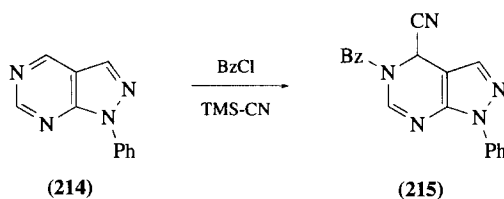
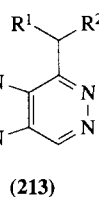
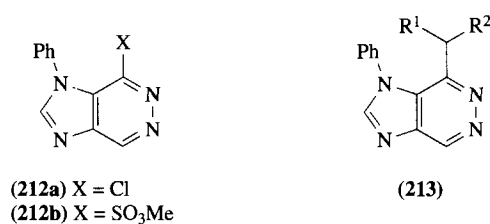


Halogen substituents in azolopyridazines are also replaced by active methylenes. Thus, the chloro derivative (212a) reacts with active methylene reagents in the presence of sodium hydride to yield derivatives (213) <89CPB13>.

The Reissert reaction of compound (214) using benzoyl chloride and trimethylsilylcyanide in the presence of catalytic amounts of anhydrous aluminum chloride gives the Reissert compound (215) (95%) (Equation (22)) <86CPB4569, 87CPB4803>.



Scheme 16

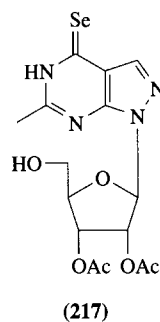
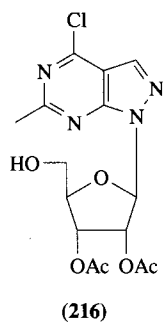


(22)

4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine reacts with aromatic aldehydes and sodium hydride to yield aryl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-yl-ketones. Use of DMF or DMSO in this reaction reduces time and reaction temperature <90CPB1147>. The *N*-oxide (158) reacts with Grignard reagents to yield derivatives (132) <76CPB3120>.

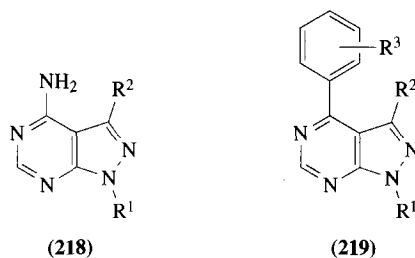
7.12.5.4 Reactions with other nucleophiles

The reaction of 4-halo-1*H*-pyrazolo[3,4-*d*]pyrimidines with sulfur reagents, for example, hydrogen sulfide, gives 4-thiolpyrazolo[3,4-*d*]pyrimidines <76JAP7611789>. The ribofuranosylpyrazolo[3,4-*d*]pyrimidine (216) reacts with selenourea followed by deacylation to give the nucleoside (217) <84JMC1026>. Disodium thiomaleonitrile reacts with 5,6-dichlorothiazolo[4,5-*b*]pyrazines to yield the tricyclic system [1,4]dithiino[2,3-*b*][1,3]thiazolo[4,5-*e*]pyrazine-6,7-dicarbonitrile <78USP4172133>.

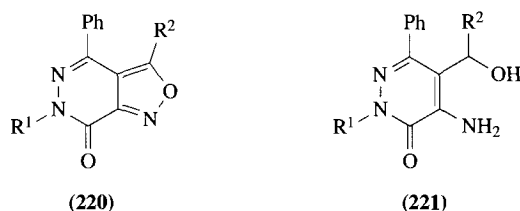


7.12.5.6 Reactions with Radicals, Oxidation and Reduction

4-Aminopyrazolo[3,4-*d*]pyrimidines (**218**) were converted into the corresponding 4-aryl substituted derivatives (**219**) on treatment with nitrites and subsequent boiling in an aromatic solvent. The isomer distribution (**219**) prepared by this route was as predicted for a radical intermediate. Unusual fragmentation product ions were isolated. These probably are as a result of the collapse of the radical intermediate <83JOC4605>.

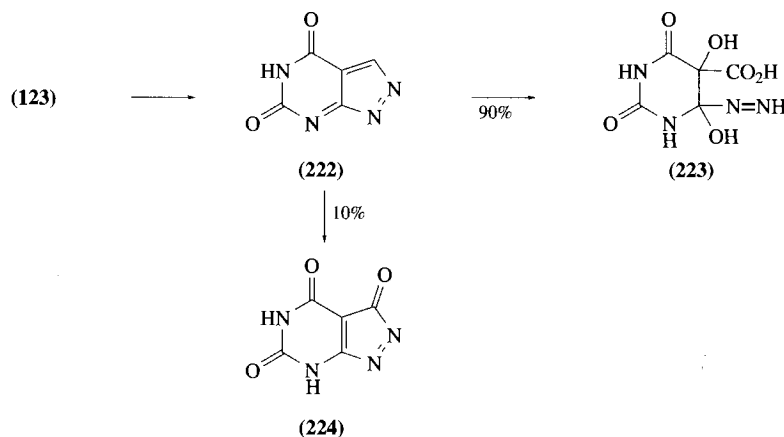


Reductive ring opening of derivatives (**220**) resulted in their conversion into the alcohols (**221**) in good yield <91H(32)1173>.



Halogen substituents in azoloazines can be readily replaced by hydrogen on treatment with palladium over carbon. For example, 4,6-dichloro-1-substituted imidazopyridazines are converted into 1-substituted imidazo[4,5-*d*]pyridazines on treatment with palladium-carbon in the presence of triethylamine <78JHC1>.

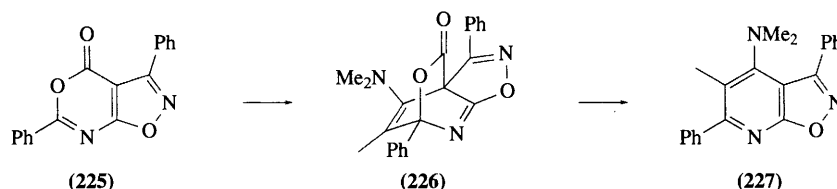
Oxidative cleavage of 7-oxo-6,7-dihydroisoxazolo[3,4-*d*]pyridazines by cerium(IV) dinitrate affords 5-aryl-4-nitro-3-oxo-2,3-dihydro-pyridazines <88IJC(B)1154>. The electrochemical oxidation of compound (**123**) at a pyrolytic graphite electrode exhibits three voltametric oxidation peaks over pH 1–12. The first pH-dependent peak is due to an irreversible oxidation process giving (**222**) which further reacts by two routes. The major route (90%) involves addition of water followed by further electrochemical oxidation and hydrolysis to give 5,6-dihydro-5,6-dihydroxy-5-carboxy-6-diazouracil (**223**). The minor route involves further electrochemical oxidation of intermediate (**222**) to give the trione (**224**) (Scheme 17) <76JEC171>.



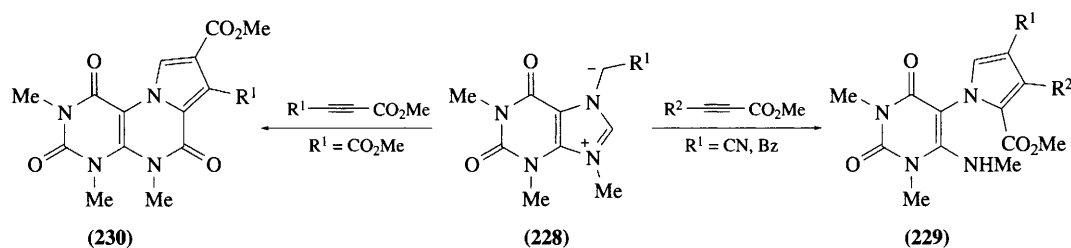
Scheme 17

7.12.5.7 Cyclic Transition State Reactions with a Second Molecule

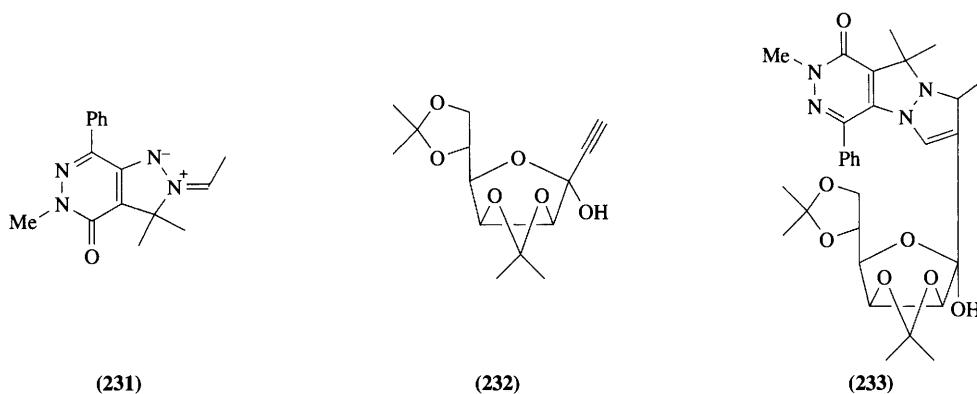
Azolooxazinones react with electron-rich alkynes to yield [4 + 2] cycloadducts that decompose by CO₂ elimination affording azolopyrimidines <87CB1427>. For example, reaction of compound (225) with 1-dimethylaminopropyne gives compound (227) via the cycloadduct (226) (Scheme 18). The ylides (228; R = CN, Bz) react with methyl alkynecarboxylic acid derivatives to yield products (229) whereas the derivative (228; R = CO₂Me) gives the tricyclic product (230) (Scheme 19) <82H(19)1845>. The reaction of the 1,3-dipole (231) with the alkynic sugar derivative (232) gives compound (233) <87CPB35, 93MI 712-01>.



Scheme 18



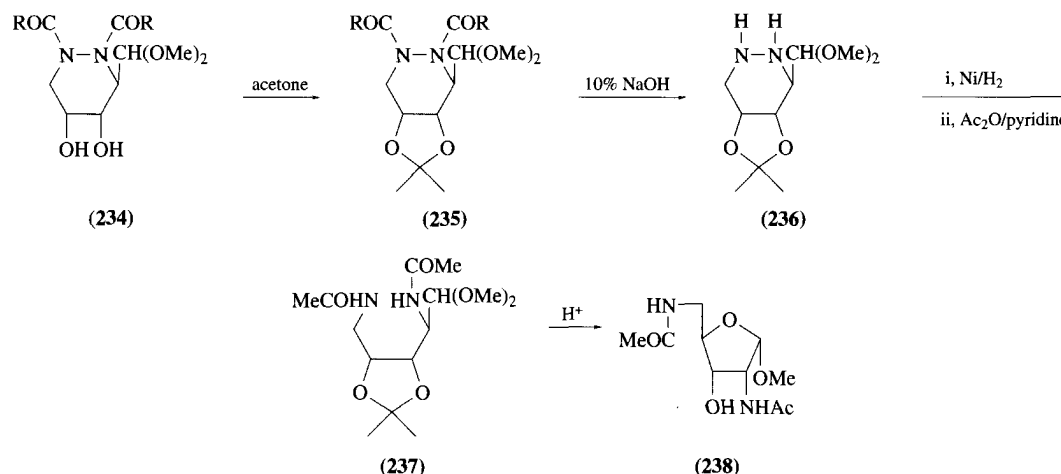
Scheme 19



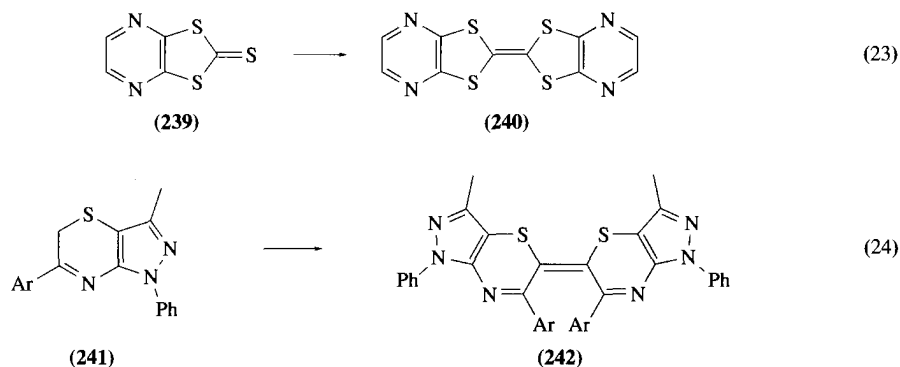
7.12.6 REACTIVITY OF NONCONJUGATED RINGS

Very little work has been done with this type of compound. It has been reported that compound (235), formed from (234) and acetone, is deacylated on treatment with 10% potassium hydroxide solution to yield compound (236) which on catalytic reduction in acetic anhydride–pyridine mixture gives derivative (237) (Scheme 20). The latter compound is hydrolyzed into compound (238) <80LA1307>.

Treatment of compound (239) with (EtO)₃P gives compound (240) (Equation (23)) <72JOC221, 85MCLC333>. The dimerization (241 → 242) has also been reported (Equation (24)) <89KGS265>.



Scheme 20

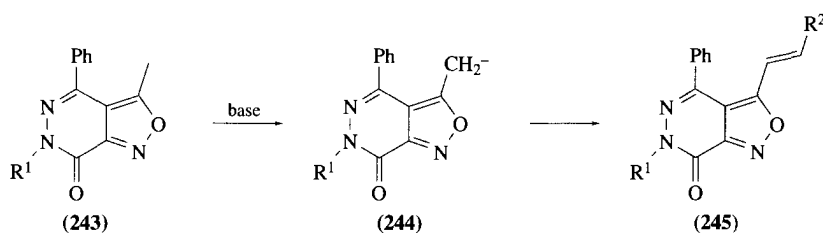


7.12.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

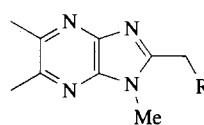
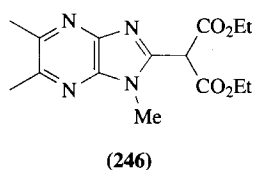
7.12.7.1 Alkyl and Substituted Alkyl Substituents

Alkyl substituents in aromatic azoloazines are reactive towards electrophilic reagents in basic media. Basic reagents readily abstract protons from such alkyl groups yielding resonance stabilized carbanions. Thus, treatment of the methyl derivatives (243) with aldehydes gives the alkenes (245) (Scheme 21) <84H(22)1741>. Ready formation of the resonance stabilized anions (244) is behind the activity of the methyl group.

Chlorination of compound (246) followed by decarboxylation gives the chloro derivative (247a) which when treated with suitable nucleophiles gives products (247b-d) <84AJC1057>.

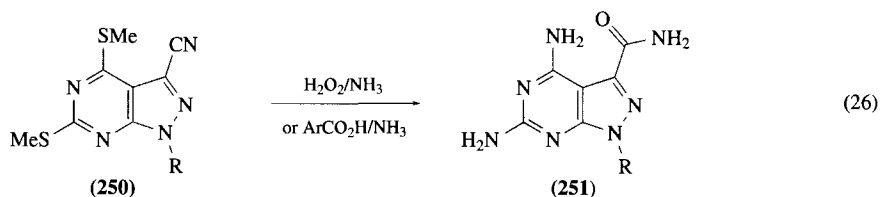
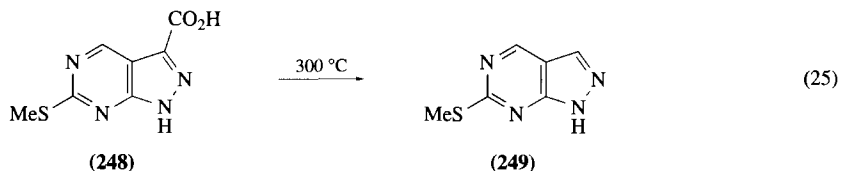


Scheme 21



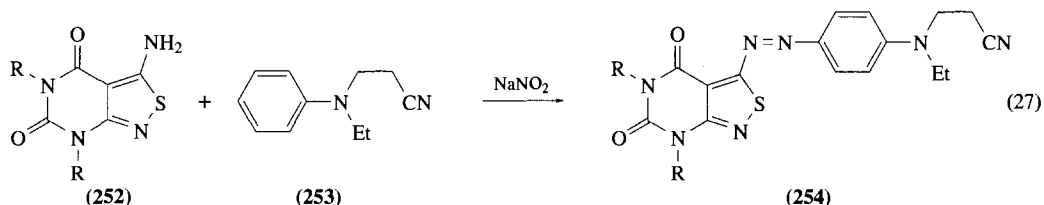
7.12.7.2 Carboxylic Acids and Carboxylic Acid Derivatives

On heating at 300 °C, the acid (**248**) is converted into compound (**249**) (Equation (25)) <74TL3893>. Treating the nitriles (**250**) with hydrogen peroxide and ammonia or with perbenzoic acid and ammonia results in their conversion into the derivatives (**251**) (Equation (26)) <87IJC(B)851>.

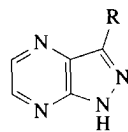


7.12.7.3 Amino, Diazo, and Hydrazo Substituents

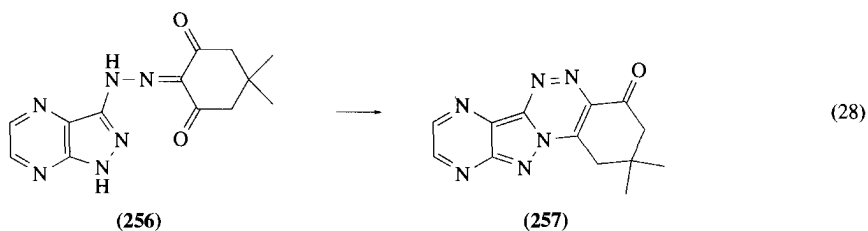
Amino functions in azoloazines can be diazotized and the resulting diazonium compounds undergo standard reactions <92GEP4213395>, for example, coupling diazotized (**252**) with amine (**253**) gives diazo derivatives (**254**) (Equation (27)) <75GEP2336978>.



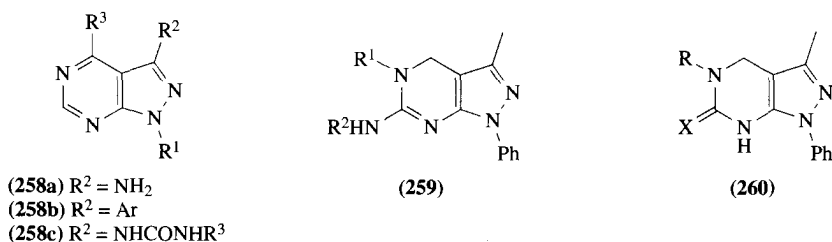
3-Aminopyrazolo[3,4-*b*]pyrazine (**255**; R = NH₂) is a useful synthon and can be transformed into a stable 3-diazo compound which upon treatment with 48% HBr is converted into the bromo derivative (**255a**) (84%). With hydroxylamine hydrochloride, the diazo compound is transformed into the azide (**255b**) (91%) and on irradiation in methanol compound (**255c**) is formed. The diazo compound also coupled with 5,5-dimethylcyclohexane-1,3-dione to yield the coupled product (**256**) which is converted into the polycyclic compound (**257**) on heating in DMF (Equation (28)) <82H(19)339>. Similar results have been obtained with 3-aminopyrazolo[3,4-*d*]pyrimidine (**258a**) <92JCS(P1)239>. Also, diazotization of 3-amino-4-methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine gives a stable diazo compound <92JCS(P1)239>.



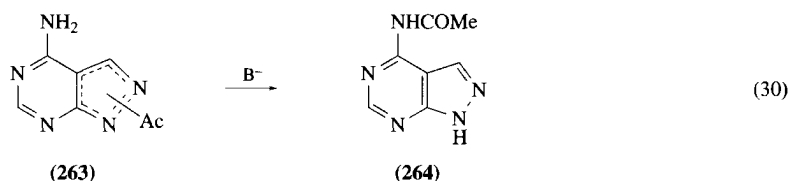
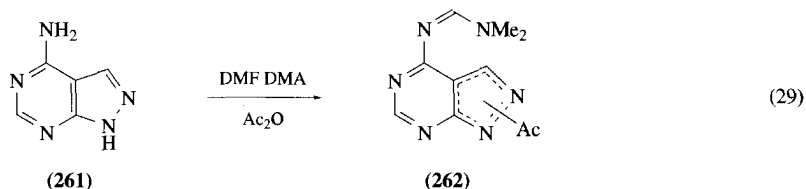
(255a) R = Br
 (255b) R = N₃
 (255c) R = H



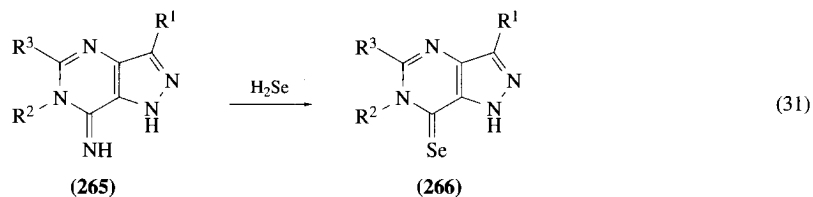
Diazotization of derivatives (258a) with alkyl nitrites in the presence of an acid catalyst in aromatic solvents gives the aryl derivatives (258b) <83JOC4605>. Compound (258a) also adds isocyanates to give the ureas (258c) <76JMC555>. The aza-Wittig reaction of amines (259) with CO₂ or CS₂ gives (260; X = O, S) <90S469>.



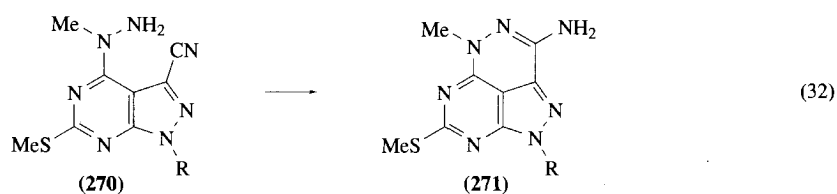
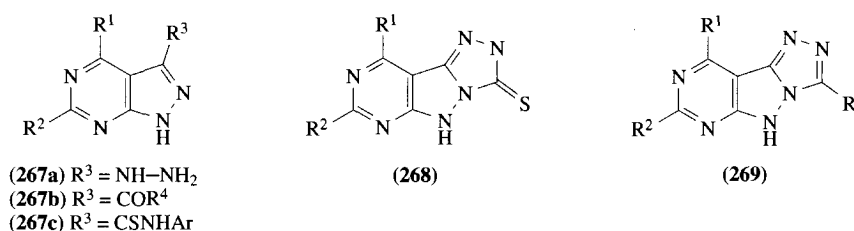
The reaction of compound (261) with DMF DMA in Ac₂O gives formamidines (262) (Equation (29)) <78MI 712-01> whereas reaction with acetic anhydride gives (263) which rearranges to the amide (264) on treatment with alkali (Equation (30)) <78JAN377, 87AHC(41)319>. 3-Amino-pyrazolo[3,4-*d*]pyrimidines also condense with ethyl ethoxymethylenecyanoacetates to yield corresponding condensation products that are cyclized into pyrimidopyrazolopyrimidines <89JCR(S)333>.



The imine (265) is converted into the selenium derivative (266) on treatment with excess H₂Se (5 days) (Equation (31)) <75CC319>.

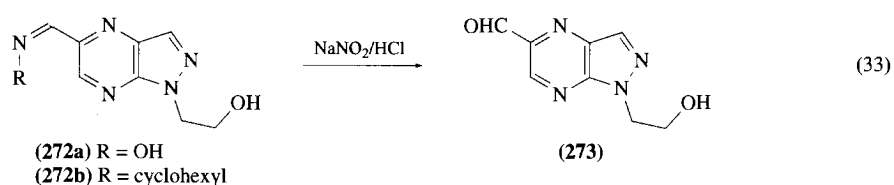


The 3-hydrazino derivative (**267a**) cyclized with carbon disulfide or triethyl orthoformate into the fused triazoles (**268**) and (**269**) respectively. Alternatively, hydrazine (**267a**) gave (**267b**) and (**267c**) on treatment with acid chlorides and with arylisothiocyanates <90CPB1147>. The tricyclic derivatives (**271**) are obtained by cyclizing the hydrazines (**270**) (Equation (32)) <89TL3287>.

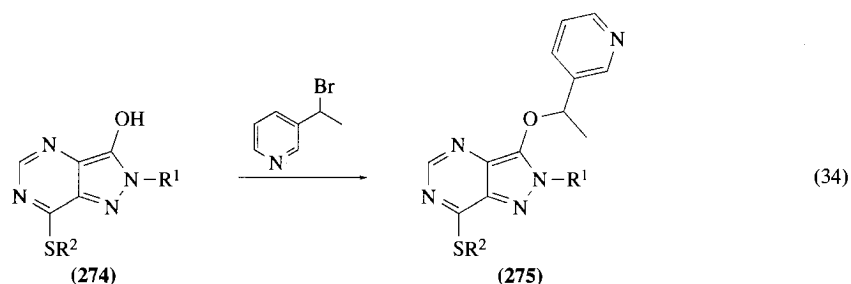


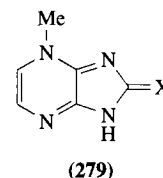
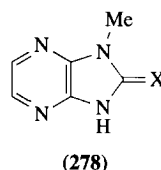
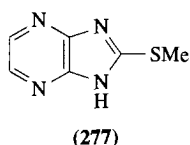
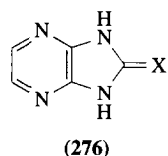
7.12.7.4 Aldehydes, Oxo, and Thioxo Substituents

Only one aldehyde derivative has been prepared. Treatment of 1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*b*]pyrazine-5-carboxylaldoxine (**272a**) with sodium nitrite and HCl gave the aldehyde (**273**) (92%) which is readily converted into the imine (**272b**) on treatment with cyclohexylamine (Equation (33)) <90JAP02172988>.

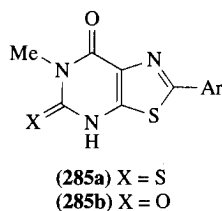
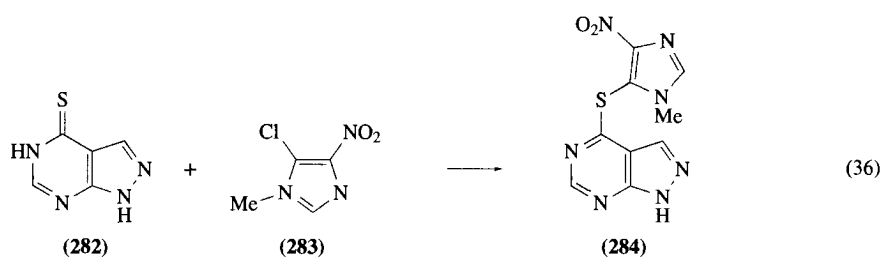
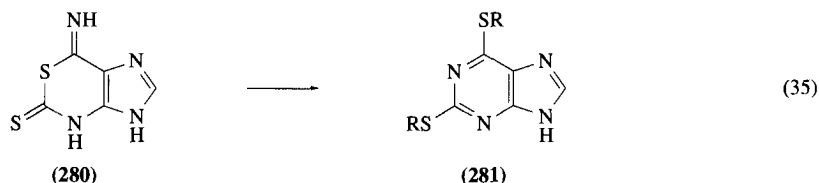


As mentioned earlier (see Section 7.12.4.5.3), tautomeric oxohydroxyazolopyrimidines exists mainly in the oxo form. Several *O*-alkylation reactions have been reported. The reaction of the derivatives (**274**) with α -bromo-3-ethylpyridine hydrochloride in the presence of potassium carbonate gives compounds (**275**) (Equation (34)) <88JAP63246377>. Reaction of compound (**276**; $\text{X} = \text{O}$) with methyl iodide or diazomethane gives *O*-alkylated products together with some N-1 and N-4 alkylated products (**277–279**) <82AJC2299>.





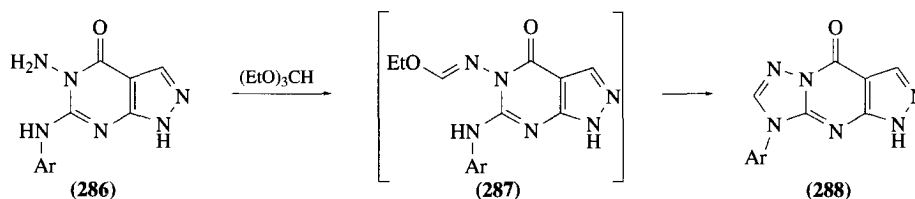
Attempted alkylation of compound (280) with dialkylsulfates resulted in rearrangement to the purines (281) (Equation (35)) <76JAP7616691>. The thione (282) is converted into compound (284) on reaction with the nitroimidazole (283) (Equation (36)) <76JAP7611790>. *S*-Alkylation of 1-phenyl-4-thiol-6-substituted pyrazolo[3,4-*d*]pyrimidines gives the corresponding *S*-alkyl derivatives <91AJC753>. Desulfurization of derivatives (285a) into (285b) is effected by action of 30% hydrogen peroxide in acetic acid <72AHC(14)1>.



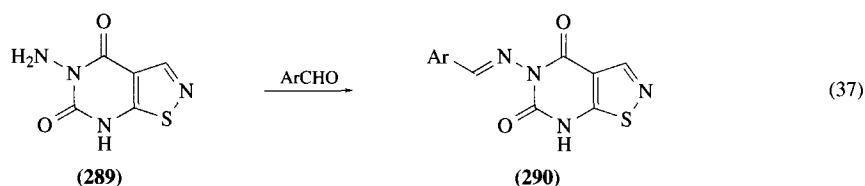
7.12.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

7.12.8.1 Amino Substituents

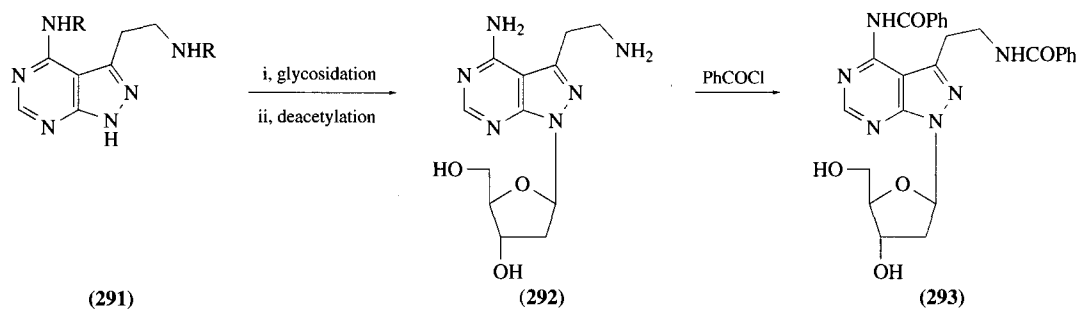
The *N*-amino functions in the derivatives (286) condense with triethyl orthoformate to yield the intermediate condensation products (287) which are readily cyclized by the action of *p*-toluene-sulfonic acid to yield the tricyclic systems (288) (Scheme 22) <92EJM73>. The isothiazolopyrimidines (290) are formed by condensation of compound (289) with aldehydes (Equation (37)) <83MI 712-02>.



Scheme 22



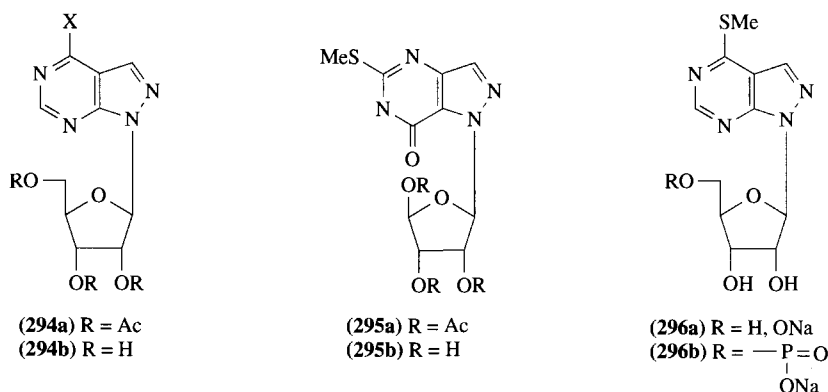
Glycosidation of derivatives (**291**; R = COCH₃) with 3,5-di-*O*-acetyl- β -D-deoxyribosyl chloride affords, after deacetylation, the nucleoside (**292**) (Scheme 23). The latter reacts readily with benzoyl chloride to give the benzoyl derivatives (**293**) <86JAP61109797>.



Scheme 23

7.12.8.2 Carbohydrate Substituents

Hydrolysis of protecting groups on the carbohydrate moiety of ribosylazoloazines has been extensively utilized to produce nucleosides <76ZOR900, 78ZOR651, 79MI 712-02>. For example, (**294a**) gives (**294b**) on hydrolysis and (**295a**) gives (**295b**) on aminolysis <76ZOR1132, 79MI 712-03>. Phosphorylation of compound (**296a**) gives the corresponding 5-monophosphate (**296b**) <83JMC1489>.



Deoxynucleoside phosphoramidates of 4-benzoylpyrazolo[3,4-*d*]pyrimidine-5-amines were prepared and utilized in automatic DNA synthesis yielding DNA fragments having an isosterically modified nucleoside base <91MI 712-02>.

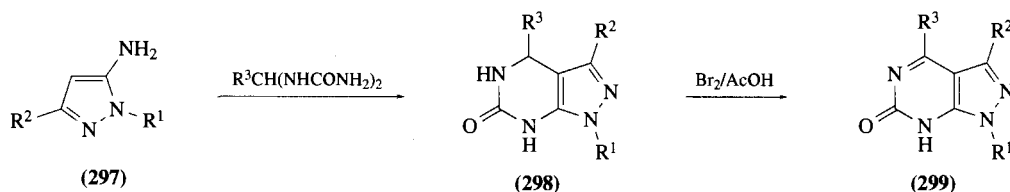
7.12.9 RING SYNTHESIS

7.12.9.1 Synthesis of Six-membered Rings by Formation of Two Bonds

7.12.9.1.1 From [3 + 3] atom fragments

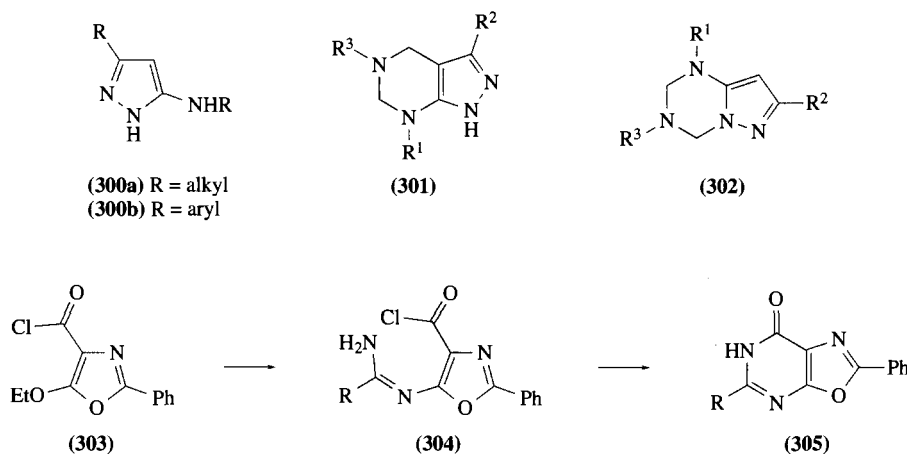
Few azoloazines have been prepared using this approach <65CB346, 71KGS535, 74KGS823, 74KGS1422, 75KGS95, 75S645, 86CCA483>. Boiling the aminopyrazoles (**297**) with *N,N*-diuredomethane in acetic

acid gives the derivatives (298) which are readily oxidized to the aromatic system (299) by the action of bromine in acetic acid (Scheme 24).



Scheme 24

Cyclocondensation of 3(5)-alkylaminopyrazoles (300a) with formaldehyde and primary amines gives the pyrazolo[3,4-d]pyrimidines (301). Similar treatment of arylaminopyrazoles (300b) with formaldehyde and primary amines leads to pyrazolo[1,5-a][1,3,5]triazines (302) <88JHC1387>. The oxazolopyrimidines (305) are obtained by reaction of the acid chloride (303) with amidines: the intermediate (304) is believed to be formed (Scheme 25) <83S837>.



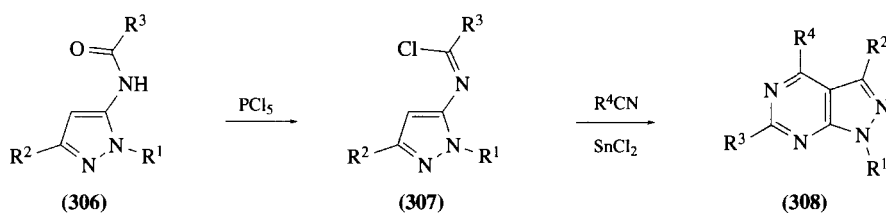
Scheme 25

7.12.9.1.2 From [4 + 2] atom fragments

(i) Pyrazolo[3,4-d]pyrimidines

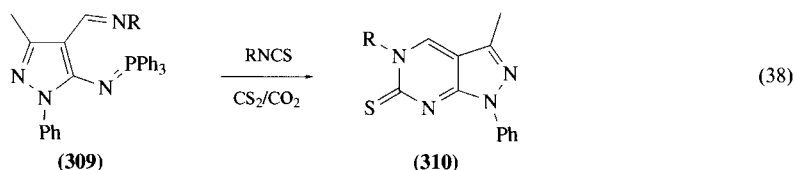
Acylaminopyrazoles (306), prepared by acylation of 1,3-disubstituted pyrazole-5-amines, react with phosphorus pentachloride to yield the chlorimidoyl chlorides (307) (Scheme 26). The latter condense with nitriles in the presence of stannic chloride to yield the pyrazolo[3,4-d]pyrimidines (308) <87S628, 88MI 712-02>. Very similar is the reported conversion of aminopyrazoles into derivatives (307) on treatment with chloromethanimines <75S645>.

The reaction of iminophosphoranes (309) with isothiocyanates in carbon disulfide and CO_2 gives

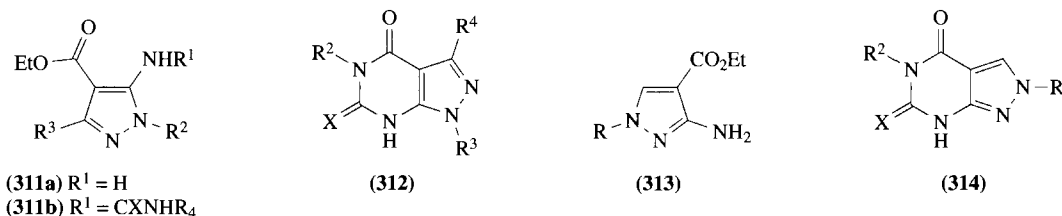


Scheme 26

the pyrazolo[3,4-*d*]pyrimidines (**310**) (Equation (38)) <88JOC4654>. Condensing 4-acylpyrazol-5-amines with urethane affords pyrazolo[3,4-*d*]pyrimidines <75JAP7514695>.

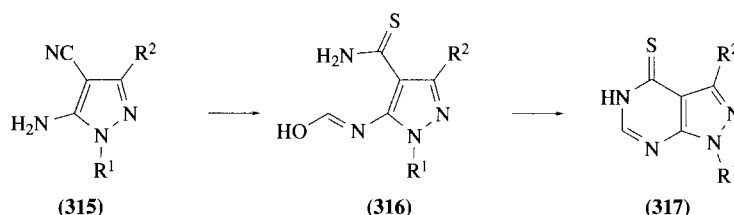


Vast numbers of pyrazolo[3,4-*d*]pyrimidines have been prepared by cyclocondensation of 3(5)-aminopyrazole-4-carboxylic acids with bidentate reagents. Intermediate substituted aminopyrazoles have been isolated in several cases. These reactions can also be considered as intramolecular cyclizations of substituted aminoazole carboxylic acid derivatives. The reaction of the amines (**311a**) with isocyanates and with isothiocyanates gives derivatives (**311b**) which undergo intramolecular cyclization yielding products (**312**) <59GEP1104964, 59GEP1106329, 61AG15, 72CPB391, 76JOC3781, 80EGP218620, 89IJC(B)346, 90JIC153>. Similarly, reaction with ureas yields pyrazolo[3,4-*d*]pyrimidines, perhaps via acyclic urea derivative <91PHA98>. The isomeric amines (**313**) behave similarly, yielding compounds (**314**) <91EGP2901657, 91JPR437>.



The reaction of isocyanates and isothiocyanates with 3(5)-aminopyrazole-4-carbonitrile affords aminopyrazolo[3,4-*d*]pyrimidines <90CCC728, 91TL6787>. Intermediate pyrazolyl thioureas were isolated in several cases and cyclized into aminopyrazolo[3,4-*d*]pyrimidines <91AJC1001>. The reaction of the amines (**315**) with formamide gives aminopyrazolo[3,4-*d*]pyrimidines <81OPP379>.

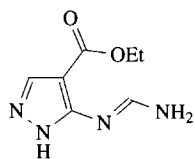
An unusual reaction leading to formation 1-substituted-4-thioxopyrazolo[3,4-*d*]pyrimidines (**317**) has been reported <B-70MI 712-01>. Thus reaction of the amines (**315**) with phenyl isothiocyanate in DMF saturated with hydrogen chloride gives derivatives (**317**) (Scheme 27). A proposed reaction sequence involves initial electrophilic addition of phenyl isothiocyanate to the protonated *o*-aminonitrile to give an *o*-aminothioamide. This is followed by condensation with DMF-HCl to yield this amide (**316**) which then cyclizes to the product (**317**) <B-70MI 712-01>.



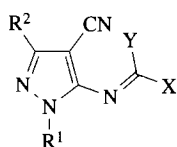
Scheme 27

The reaction of 5-aminopyrazole-4-carboxylates with amides affords pyrazolo[3,4-*d*]pyrimidines <79AP(312)703, 87MI 712-02>. The synthesis of allopurinol (**53**) by reaction of ethyl ethoxymethylenecyanoacetate, hydrazine, and formamide probably proceeds via intermediacy of ethyl 5-amino-1*H*-pyrazole-4-carboxylate which then condenses with formamide to yield intermediate (**318**) which readily cyclizes to allopurinol (**53**) <74NEP7507554>.

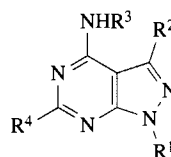
The reaction of the amines (**315**) with formamidine or with formamide gives compounds (**320**) via intermediacy of (**319a**) which could be isolated <58JOC191, 65CB3377, 70GEP1904894, 75JOC1822, 84KGS259, 86JHC1869>. Very similar to this is the reported cyclization of amines (**315**) on treatment with chloroformamidine <88S242>: intermediates (**319b**) are most likely formed.



(318)



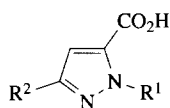
- (319a) X = H, Y = NH₂
 (319b) X = Y = NH₂
 (319c) X = H, Y = OEt
 (319d) X = H, Y = NHR³



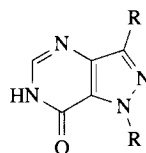
(320)

(ii) *Pyrazolo[4,3-d]pyrimidines*

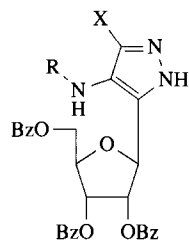
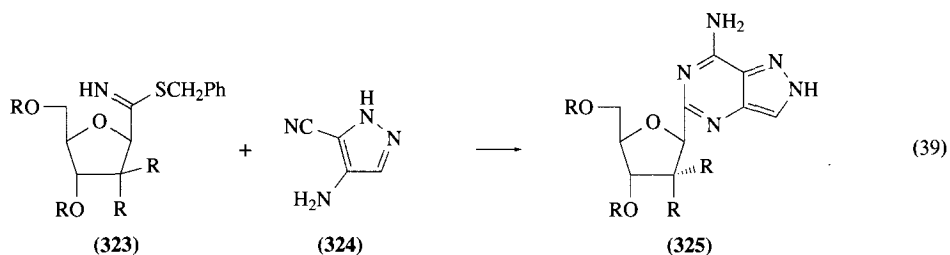
Ethyl 4-aminopyrazol-5-carboxylate, prepared from the acid (321) via nitration, esterification, and reduction <72CCC2786, 79BCJ208, 81USP482361>, is converted into the pyrazolo[4,3-*d*]pyrimidine (322) on reaction with formamide <80MI 712-02>. The reaction of the furanose (323) with compound (324) gives the β -glucoside (325) (Equation (39)) <83FES369>. Formycin A (54a) and formycin B (88b) are prepared by condensation of the 4-aminopyrazolo-3-carbonitrile (326a) and the ester (326b) with formidine <78CCC1431>.



(321)



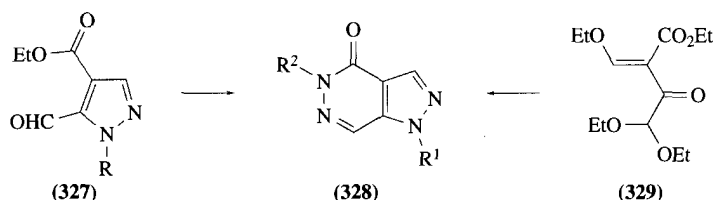
(322)



- (326a) X = CN
 (326b) X = CO₂Et

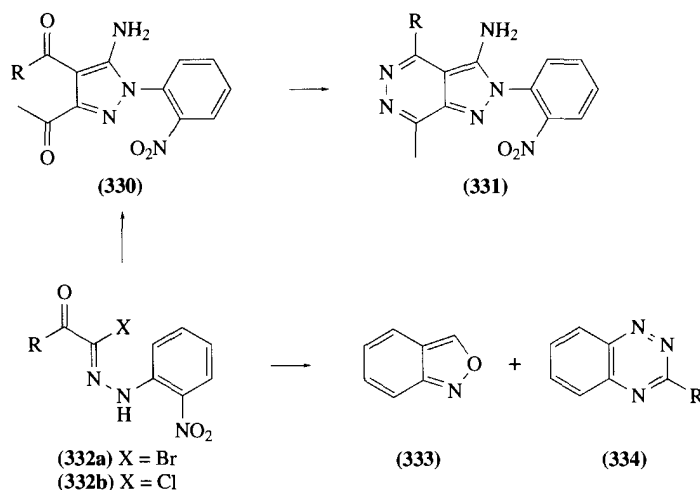
(iii) *Pyrazolo[3,4-d]pyridazines*

Pyrazoles with vicinal 3,4-dioxosubstituents react with hydrazines to yield pyrazolo[3,4-*d*]pyridazines <56JA159, 64G210, 67CCC3587, 69BSF2061, 69TL289, 70TL4611, 71BSF1336, 73T435, 73USP3716534, 73USP3758288, 75BSF1268, 75CJC3782, 77HCA2171, 77JHC375, 77OPP45, 78AP(311)480, 78JHC813, 82H(19)319, 84G261, 87MI 712-01, 88OPP521>. Literature up to 1989 has been surveyed by Elnagdi *et al.* <90AHC(48)223>. According to this review, the pyrazoles (327) give products (328) on reaction with hydrazines (Scheme 28). Compounds (328) were also prepared from the acyclic precursor (329) <75BSF1268, 90AHC(48)223>.



Scheme 28

It was reported that the diketones (330) react with hydrazine to yield the derivatives (331) (Scheme 29). Compounds (330) were prepared by reacting hydrazones (332a) with ethyl cyanoacetate <82H(19)319>. This is in contrast to the reported formation of a mixture of (333) and (334) upon treatment of hydrazones (332b) with ethyl cyanoacetate <83JHC511>.



Scheme 29

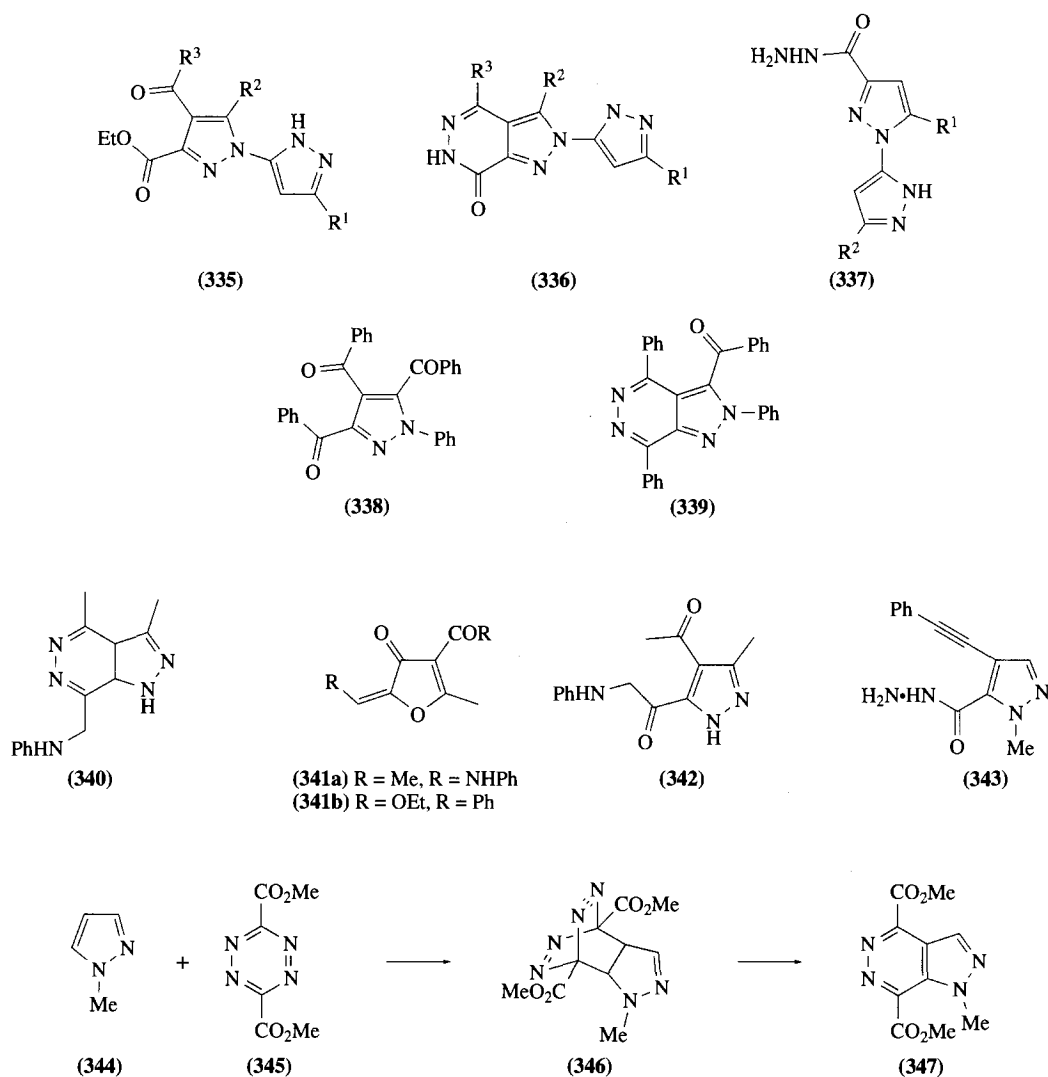
Treatment of the pyrazoles (335; $R^1 = \text{OC}_2\text{H}_5$, Ph) with hydrazines affords derivatives (336). However, reaction of the methyl derivative (335; $R^1 = \text{CH}_3$) with hydrazines is thought to yield only the hydrazides (337) <77HCA2171>. The reaction of compound (338) with hydrazine gives compound (339) <75CJC3782>.

Chantegrel *et al.* <77T45> reported synthesizing compound (340) by reaction of derivatives (341a) with excess hydrazine; the intermediate (342) was isolated. The reaction of (341b) with hydrazine directly gives (340) <77T45>. Treatment of (343) with cuprous chloride in DMF gives 1-methyl-4-benzylpyrazolo[3,4-*d*]pyrimidine-7-one <85IZV1367>.

The inverse [4 + 2] cycloaddition of 1-methylimidazole (344) to dimethyl tetrazine-1,4-dicarboxylate (345) gives the pyrazolopyridazine (347); intermediacy of the cycloadduct (346) is postulated (Scheme 30) <89CZ17>.

(iv) *Other rings*

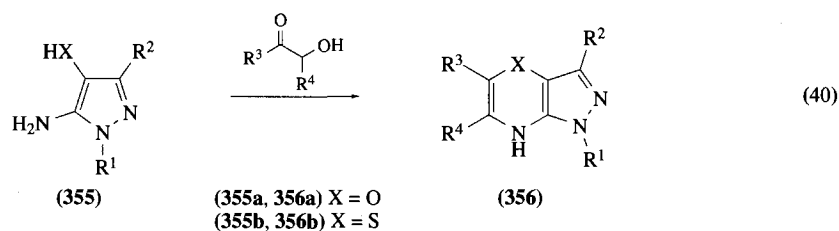
The reaction of the pyrazoles (348) with diethyl malonate gives derivatives (349) (Scheme 31) <73G1105, 78JOC4154>. Similarly condensation with benzyl cyanide in 2-hydroxydiethyl ether gives

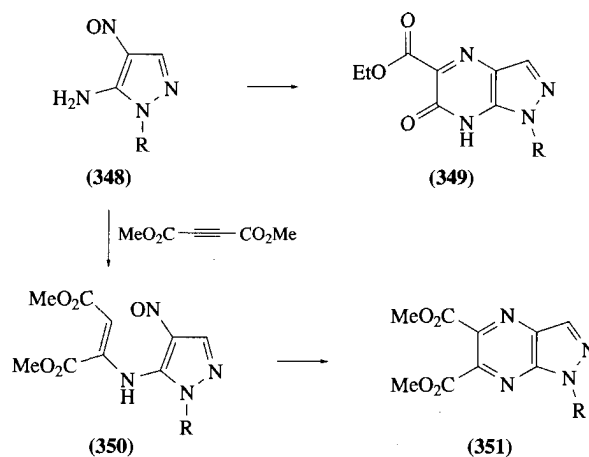


Scheme 30

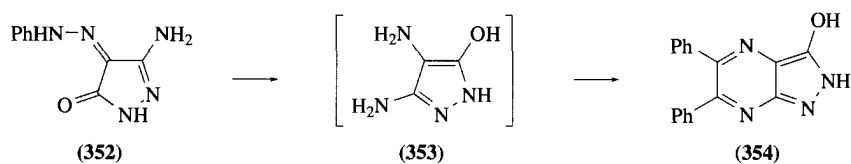
5-phenyl-6-aminopyrazolo[3,4-*d*]pyrazines <81USP4303658>. Derivatives of the amine (348) also add diethylalkyne dicarboxylate to yield the corresponding Michael adducts (350) that cyclize to form the diesters (351) <84S148>. Condensing ethyl 4-amino-2-methylthiolthiazole-5-carboxylate with formamide gives thiazolo[4,5-*d*]pyrimidines <89LA409>.

Cyclocondensation of vicinal diamino azoles with α -diketones produces azolopyrazines <09JPR1, 36G649, 58JA421, 58JA3752, 61AG15, 61LA(51)446, 68JCS(C)2159, 82FES116, 83FES24, 84JAP5962592, 89JHC949>. Since vicinal diaminoazoles are generally unstable they have been generated *in situ* in several cases. For example, reduction of compound (352) in the presence of benzyl yields the intermediate (353) that condenses *in situ* to yield compound (354) (Scheme 32) <58JA3752, 61AG15, 84JAP5962592>. Similar syntheses include the transformations (355a) and (355b $\rightarrow$ 356) (Equation (40)) <84GEP3246148, 84JHC945, 86EGP208352, 89KGS265>.



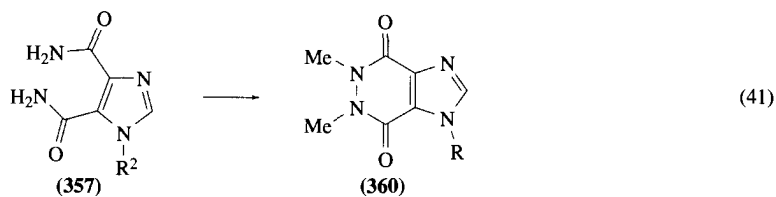


Scheme 31

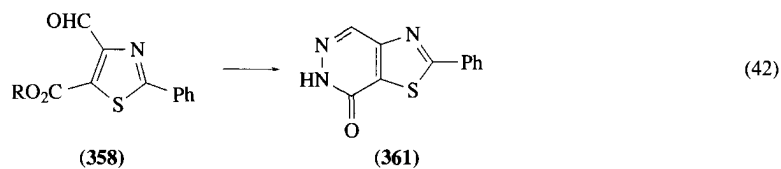


Scheme 32

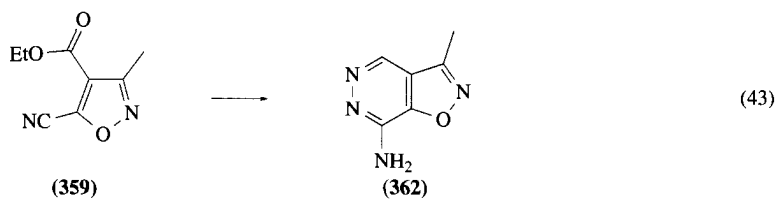
The reaction of azoles with vicinal dioxo substituents and hydrazines yields azolopyridazines. In this way, imidazopyridazines <68FRP6244, 71ZC175, 78JHC1451, 83ZOR416, 92JAP9235988>, thiazolopyridazines <66CR(C)1385, 74AC(R)477, 74LA477, 78AP(311)480, 83AP(316)1013>, thiazolo-1,2-oxazines <74MI 712-02>, and isoxazolopyridazines <65G1478, 67T681, 69FES885, 73MI 712-03, 91JCR(S)322> have been synthesized. For example, derivatives (357)–(359) condense with hydrazines to yield the bicyclic products (360)–(362) (Equations (41)–(43)) <83ZOR416, 85JHC1561>.



(41)

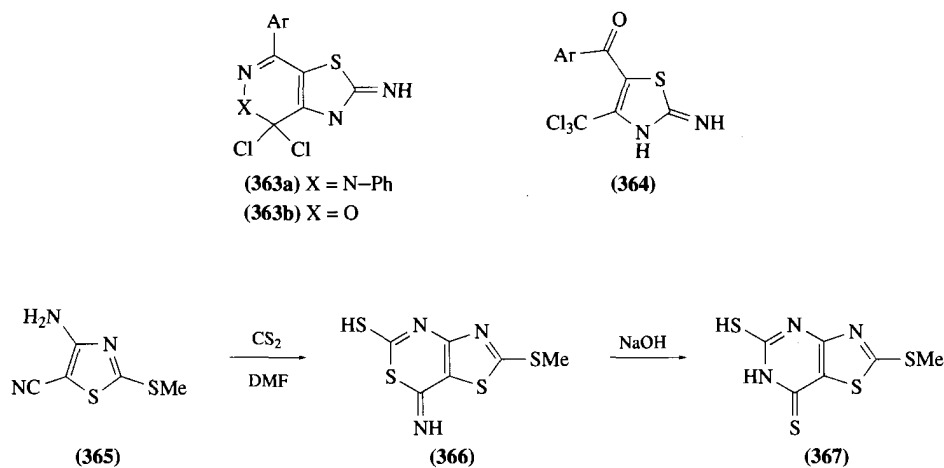


(42)



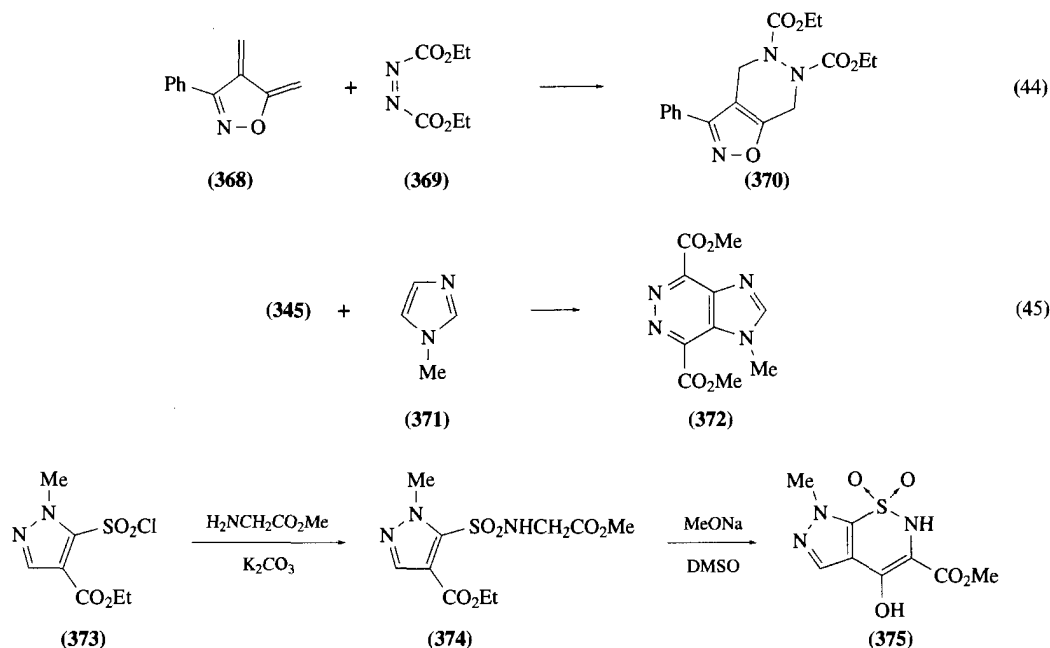
(43)

The thiazolopyridazine (363a) and the thiazolooxazine (363b) are obtained from the ketones (364) by reaction with phenylhydrazine and hydroxylamine respectively <87SUL155>. The 1,3-thiazolo[4,5-*d*]pyrimidine (367) was obtained by reacting compound (365) with carbon disulfide and subsequent treatment of the initial product (366) with sodium hydroxide (Scheme 33) <87EGP248595>. Although this reaction sequence seems to be an efficient synthetic route to azolopyrimidines, limited numbers of azolopyrimidines have been synthesized by this route <79KGS1687>.



Scheme 33

The [4 + 2] cycloaddition reaction between the diene (368) and DEAD (369) gives the cycloadduct (370) <91TL4603> and [3 + 2] 1,3-dipolar cycloaddition of nitrile oxides to electron-rich double bonds in uracils <92H(34)1423> and cytidine <92BMC941> affords isoxazolopyrimidines (Equation (44)). Reaction of 1-phenyl-3-methylpyrazolo[4,3-*c*]oxadiazine-6-one with enamines gives pyrazolo[3,4-*b*]pyrazine derivatives <93JOC6155>. The reaction of 1-methylimidazole (371) with the tetrazine (345) gives compound (372) (Equation (45)) <78AP(311)728>. The reaction of the sulfonyl chloride (373) with ethyl glycinate gives sulfonamide (374) which cyclizes with sodium methoxide to give compound (375) (Scheme 34) <84JHC1017>. The acylation of heterocyclic β -enamino acids usually affords azolooxazines <81S965, 86EGP240018, 86JHC1535, 90PHA282>.

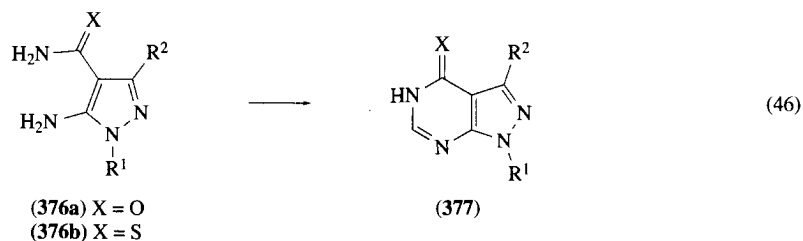


Scheme 34

7.12.9.1.3 From [5 + 1] atom fragments

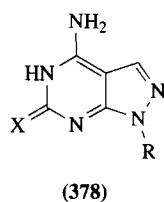
(i) *Pyrazolo[3,4-*d*]pyrimidines*

5-Aminopyrazole-4-carboxamides afford the corresponding acylaminoamides on acylation. These latter compounds are readily cyclized to give pyrazolo[3,4-*d*]pyrimidines <38G59, 56HCA986, 62JAP2785364, 72CPB391, 72USP3624205, 74GEP2343702, 74USP3833582, 76FRP2264015, 77CP1007229>. Similarly, the reaction of the amines (376a) with a mixture of acetic anhydride and formic acid gives the derivatives (377) (Equation (46)) <85MI 712-03>.

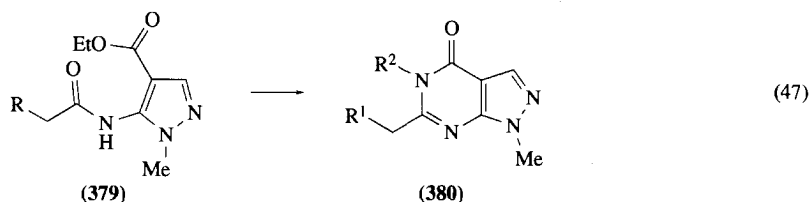


Pyrazolo[3,4-*d*]pyrimidine-5,7-diamines and 7-thioxopyrazolo[3,4-*d*]pyrimidine-5-ones are obtained on treatment of the amines (376a) and (376b) with urea and thiourea; intermediacy of pyrazolyl ureas is postulated <56JA784, 56JA2418, 56JOC1240, 58HCA1052, 58JOC852, 59JA2452, 65JOC199>. Similar to this is the reported cyclization of 1,3-dimethyl-4-aminopyrazolo-5-pyrimidine-5,7-dione on fusion with urea <87USP4663326>.

The reaction of 5-amino-1-phenylpyrazole-4-carboxamide with acyl or aroyl isothiocyanides gives pyrazolylureas or pyrazolylthioureas that cyclize readily into derivatives (378) upon treatment with sodium methoxide <91AJC1001>.



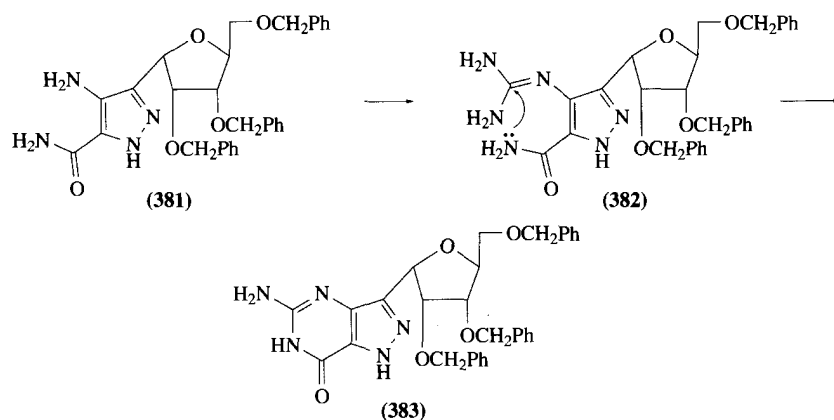
The reaction of the derivatives (319c) with ammonia or amines gives the corresponding amidines (319d) which cyclize to give the products (320) <86JHC1869>. 4-Iminopyrazolopyrimidines are first formed but rearrange on prolonged contact with base into the thermodynamically more stable products (320) <58JOC191, 68CB3377, 70GEP1904894, 75JOC1822>. The reaction of aminoethylpyrazole iminophosphoranes with isothiocyanate affords aminopyrazolo[3,4-*d*]pyrimidines <90S469>. The compounds (379) are converted into the derivatives (380) on treatment with aromatic amines (Equation (47)) <83CS171>.

(ii) *Pyrazolo[4,3-*d*]pyrimidines*

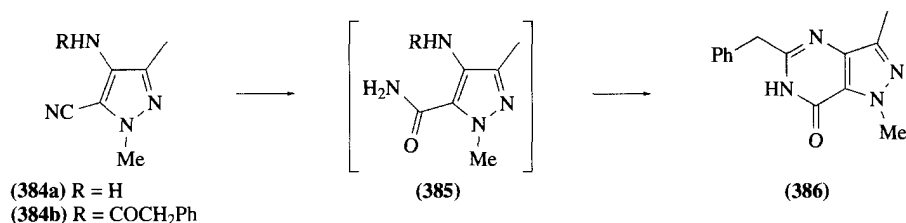
The 4-aminopyrazole-5-carboxamide (381) cyclizes to give compound (383) on heating with chloroformamide hydrochloride in DMSO; it is most likely that intermediate amidine (382) is first formed (Scheme 35) <78NJC357>.

The acylation of compound (384a) with phenylacetyl chloride gives the amide (384b) which is

transformed to the product (386) on treatment with sodium hydroxide (Scheme 36) <85JAP86236778>. The reaction proceeds via the intermediate (385) <85JAP86236778>.



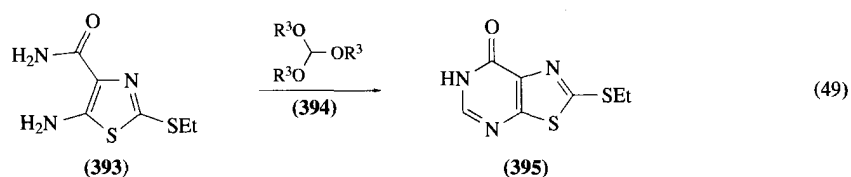
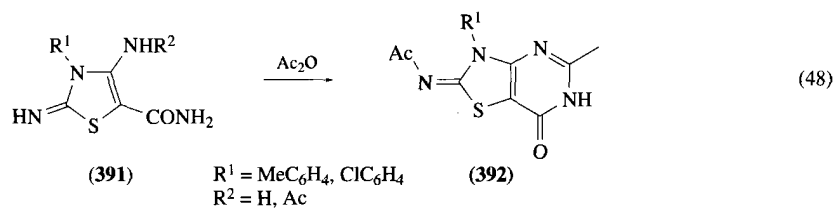
Scheme 35

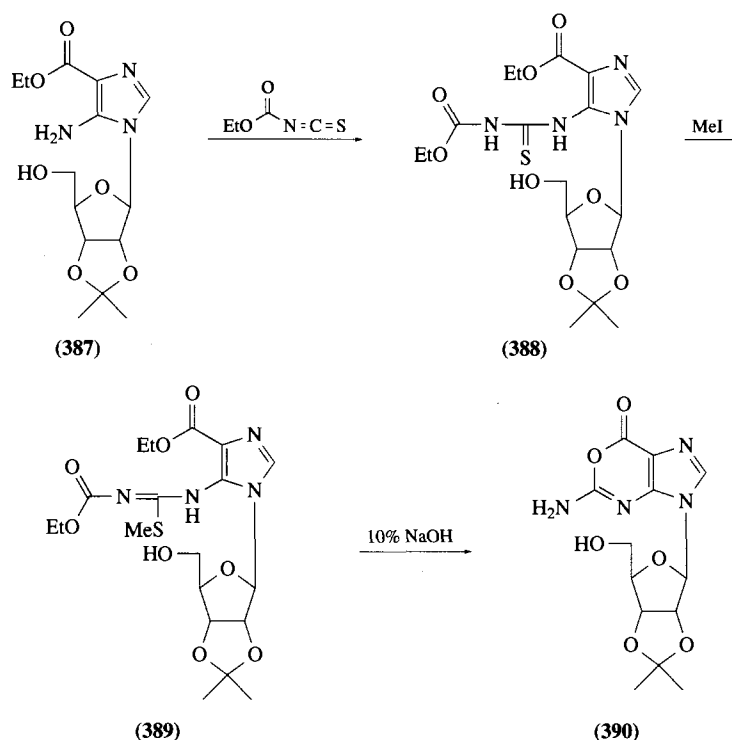


Scheme 36

(iii) Other rings

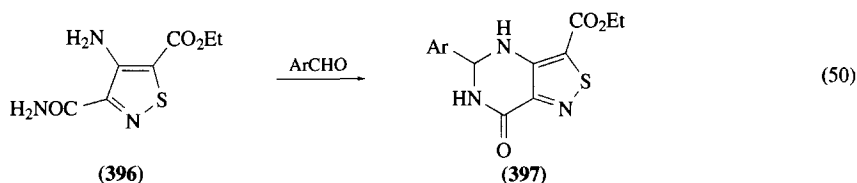
An interesting synthesis of imidazooxazines and pyrazolooxazines by reacting ethoxycarbonyl isothiocyanate with ethyl aminoimidazole carboxylates (387) and with ethyl aminopyrazole carboxylate has been reported. For example, compound (387) affords product (390) on treatment with ethoxycarbonyl isothiocyanate (Scheme 37); the esters (388)–(389) are intermediates <83TL931>. The cyclization of aminothiazole carboxamides with acetic anhydride gives cyclopyrimidines. For example, derivatives (391) give compounds (392) with formamidine (Equation (48)) <71IJC(B)651>. A similar cyclization of compound (393) using orthoformate (394) affords the thiazolopyrimidine (395) (Equation (49)) <65JCS7277>. Compound (395) is also formed from (393) and ethylchloroformate and DMF <88BCJ3794>. Similarly 3-aminoisothiazole-4-carboxamides condense with orthoformate yielding isothiazolo[4,3-*d*]pyrimidines <75ZC18>.



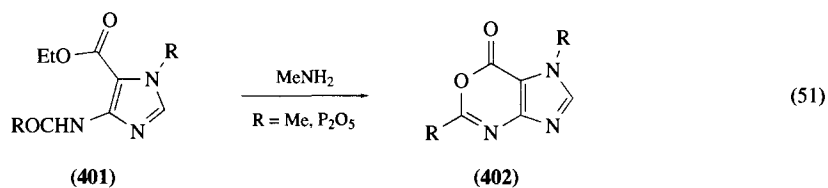


Scheme 37

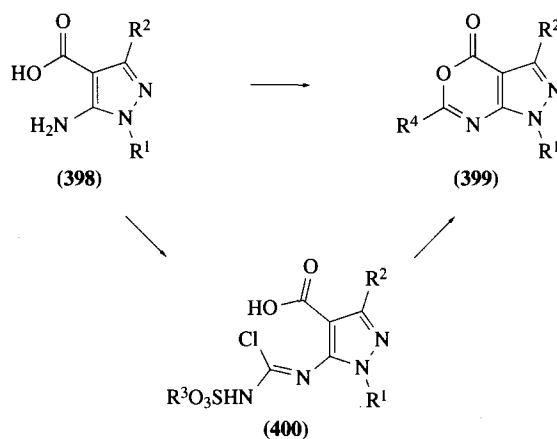
4,5-Dihydroisothiazolo[4,3-*d*]pyrimidines (397) are obtained by condensing the amines (396) with aromatic aldehydes (Equation (50)) <91MI 712-03>.



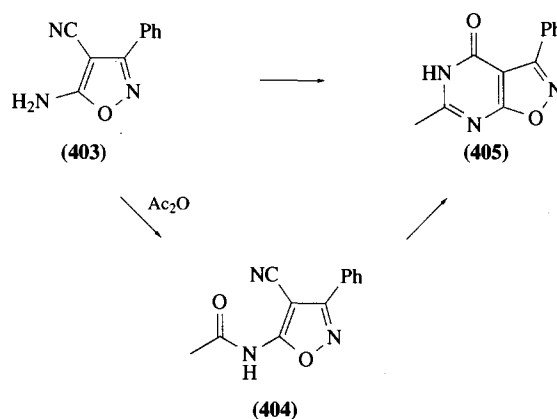
The acylation of heterocyclic β -enamino acids usually gives acylamino acids. These are cyclized using dehydrating agents giving azolo-1,3-oxazines <90PHA282, 91MI 712-04>. For example, the amino acids (398) give the products (399) on acylation and subsequent cyclization (Scheme 38). Very similar is the conversion of the amino acids (398) into the derivatives (400) and subsequent cyclization to yield the sulfonamides (399; $\text{R}^3 = \text{NHSO}_2\text{R}_2$) <81S965>. Unexpectedly, treatment of the amides (401) with methylamine and P_2O_5 at 150°C gives the imidazooxazines (402) (Equation (51)) <82T1439>.



5-Amino-3-phenylisoxazol-4-carbonitrile (403) cyclizes on treatment with acetic anhydride to give the isoxazolopyrimidine (405) (Scheme 39). It is most likely that compound (404) forms first and then cyclizes to give the final isolable product (405) <73AC(R)613>.



Scheme 38



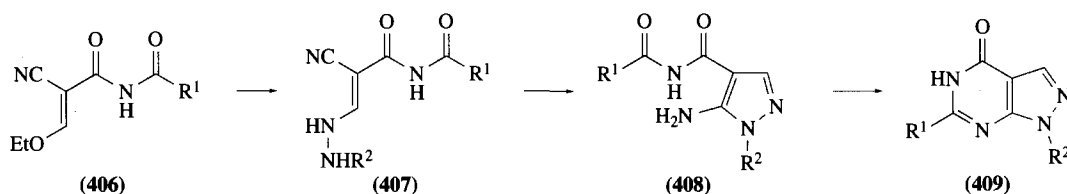
Scheme 39

7.12.9.2 Synthesis of Six-membered Rings by Formation of One Bond

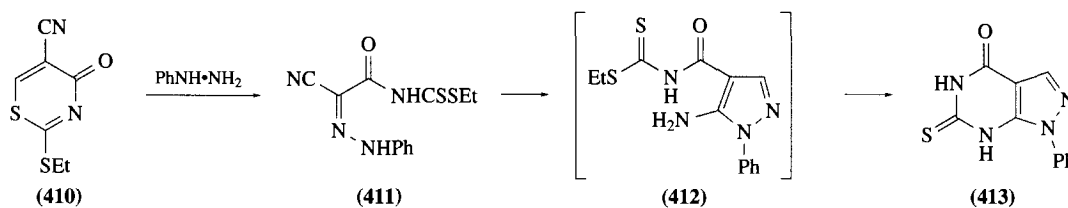
7.12.9.2.1 Bond formation α to a heteroatom

(i) Pyrazolo[3,4-*d*]pyrimidines

The cyclization of the derivatives (311b), (316), and (319a,b,d) to give pyrazolopyrimidines has been described earlier (Section 7.12.9.1.2(i)). The cyclization of derivatives (319b) with methylhydrazine affords 4-methylhydrazino-pyrazolo[3,4-*d*]pyrimidine-6-amines <88S242>. Treatment of pyrazolothiazines with base effects their rearrangement into pyrazolo[3,4-*d*]pyrimidines <76JOC3781>. The aminopyrazole (408), prepared from the acyclic precursors (406) via the intermediates (407), cyclizes to the derivatives (409) on heating <71JCS(C)1610> (Scheme 40). Similarly, compound (411) is formed by reaction of compound (410) with phenylhydrazine and cyclizes to compound (413), probably via the intermediate (412) (Scheme 41) <71JCS(C)1610>.

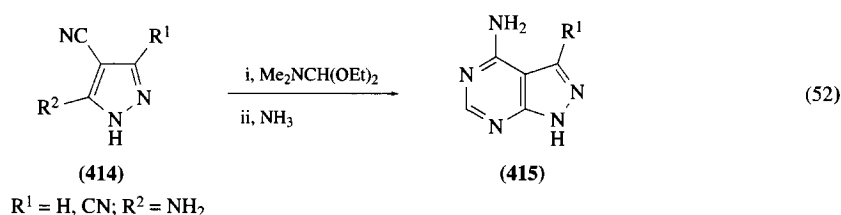


Scheme 40



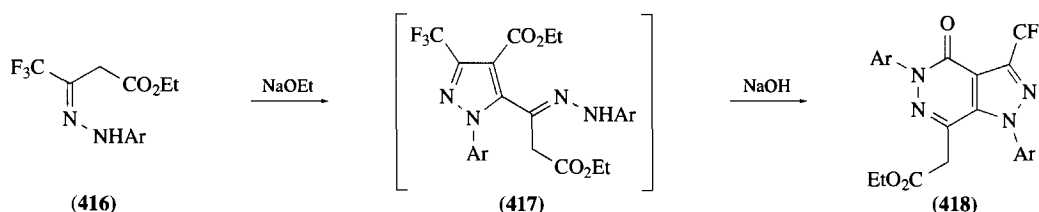
Scheme 41

Bulychev *et al.* <84KGS259> have reported the synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives (415) via the reaction of pyrazoles (414) with DMF diethylacetal (Equation (52)).



(ii) Pyrazolo[3,4-*d*]pyridazines

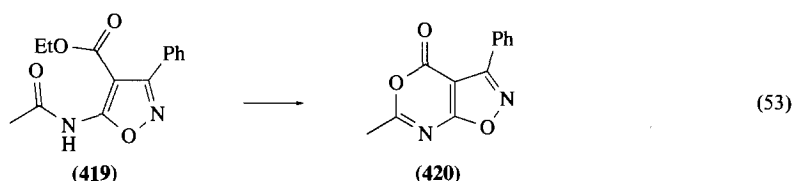
The pyrazolopyridazines (418) are formed on treatment of the hydrazones (416) with sodium ethoxide (Scheme 42); (417) are believed to be intermediates <88JHC139>.

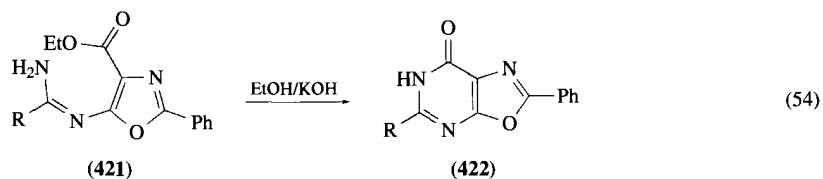


Scheme 42

(iii) Other ring systems

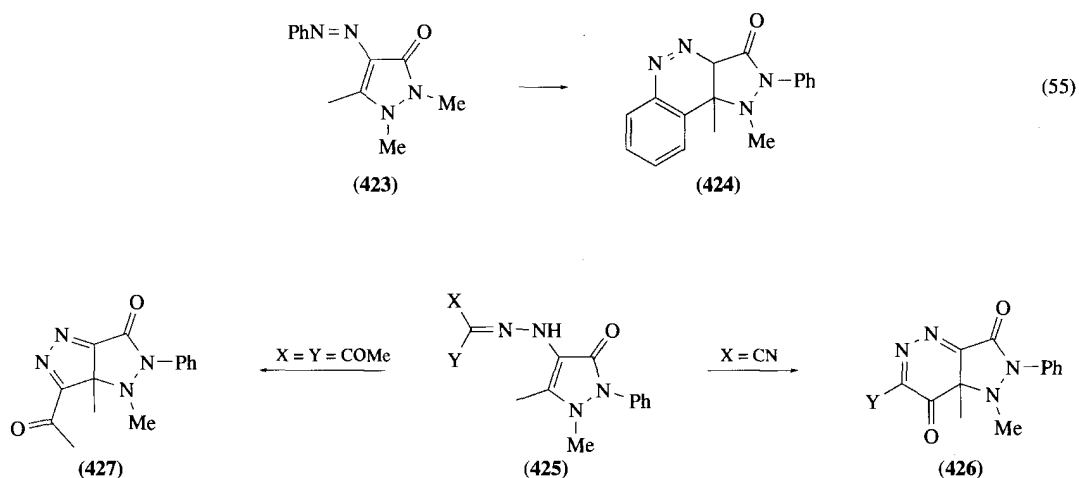
Ethyl 5-acylamino-3-phenylisoxazole-4-carboxylate (419) cyclizes on treatment with dibromotriphenylphosphine giving isoxazolo[4,5-*d*]-1,3-oxazin-4-one (420) (Equation (53)). This new cyclization provides an entry to azolooxazines <87CB1427>. Similar cyclizations of ethyl 1-bromo-5-acylaminoimidazole carboxylate with dichlorotriphenylphosphine give imidazo[4,5-*d*]oxazines. Thiazolo[4,5-*d*]oxazines were produced similarly <93S107>. Pyrazolothiazines are produced by cyclizing ethyl 1-substituted-3-thioureadopyrazol-4-carboxylates using concentrated sulfuric acid <91EGP2901657>. Treatment of the esters (421) with ethanolic KOH gives the oxazolodiazines (422) (79–96%) (Equation (54)) <83S837>.





7.12.9.2.2 Bond formation γ to a heteroatom

The only reported syntheses of this type of bond formation are the conversions of compound (423) into compound (424) (Equation (55)) and of compounds (425) into systems (426) or (427) (Scheme 43) $\langle 82\text{JCS(P1)989, } 87\text{AHC(41)319, } 89\text{ZN(B)951} \rangle$.



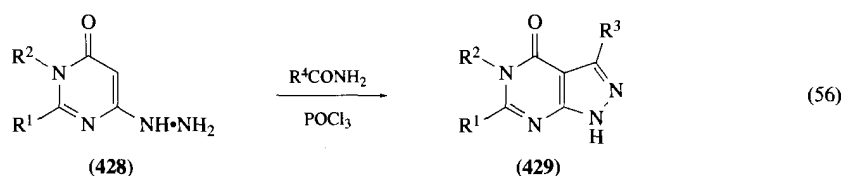
Scheme 43

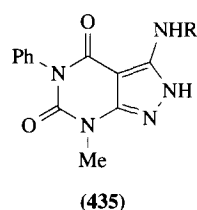
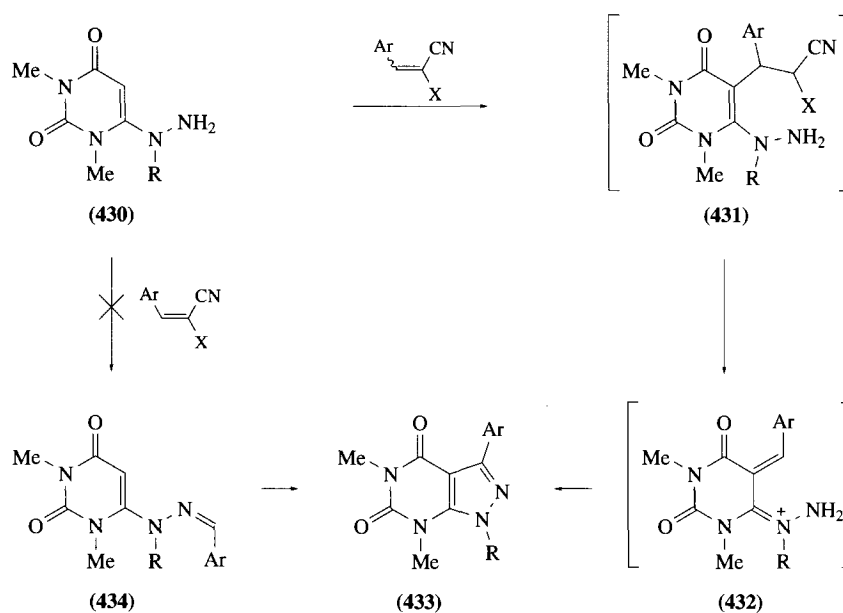
7.12.9.3 Synthesis of Five-membered Rings by Formation of Two Bonds

7.12.9.3.1 From [4 + 1] atom fragments

(i) *Pyrazolo[3,4-d]pyrimidines*

The reaction of the hydrazines (428) with primary amides in the presence of phosphorus oxychloride gives the derivatives (429) (Equation (56)) $\langle 65\text{GEP1186466, } 81\text{EUP63381} \rangle$. The reaction of arylidenemalononitrile and ethyl arylidenecyanoacetate with the hydrazines (430) affords compounds (433) (Scheme 44) $\langle 90\text{JOC568} \rangle$. The authors believe that this reaction proceeds via initial addition at C-5 of the uracil to yield the intermediate (431). This is followed by elimination of the active methylene group and cyclization (432 $\rightarrow$ 433). The alternative formation of a Schiff base (434) seems less likely as such an intermediate would cyclize only in the presence of NBS $\langle 84\text{JHC969} \rangle$. The reaction of the hydrazines (428) with aldehydes in DMF gives the hydrazones (434) and cyclocondensation with isothiocyanates gives the bicycles (435) $\langle 77\text{JCS(P1)765, } 78\text{JAP7831694} \rangle$. Compound (428) also condenses with DMF DMA to yield pyrazolo[4,3-*d*]pyrimidine $\langle 78\text{JHC359} \rangle$.

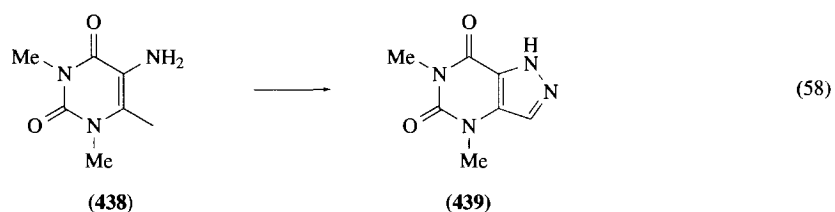
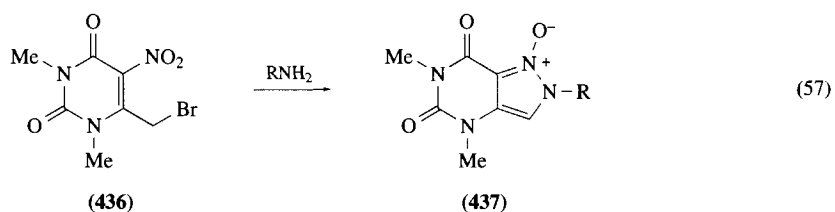




Pyrazolo[3,4-*d*]pyrimidines are also formed by reaction of the hydrazines (430) with isothiocyanates <87EUP237289, 87JAP6222717>. These compounds are probably formed via intermediacy of a thiosemicarbazide <77S176, 79CPB1328, 80JHC1305>.

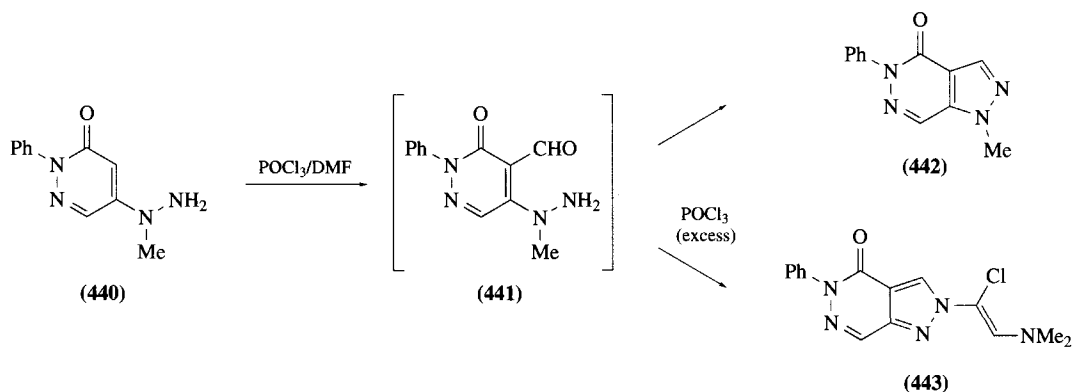
(ii) *Pyrazolo[4,3-*d*]pyrimidines*

Only two syntheses via this approach have been reported. Cyclocondensation of the nitrouracil (436) with amines gives the *N*-oxides (437) (Equation (57)) <82JCS(P1)277>. Alternatively diazotization of the amine (438) gives compound (439) (Equation (58)) <62ZOB1847, 70GEP1950075, 74CPB1269>.



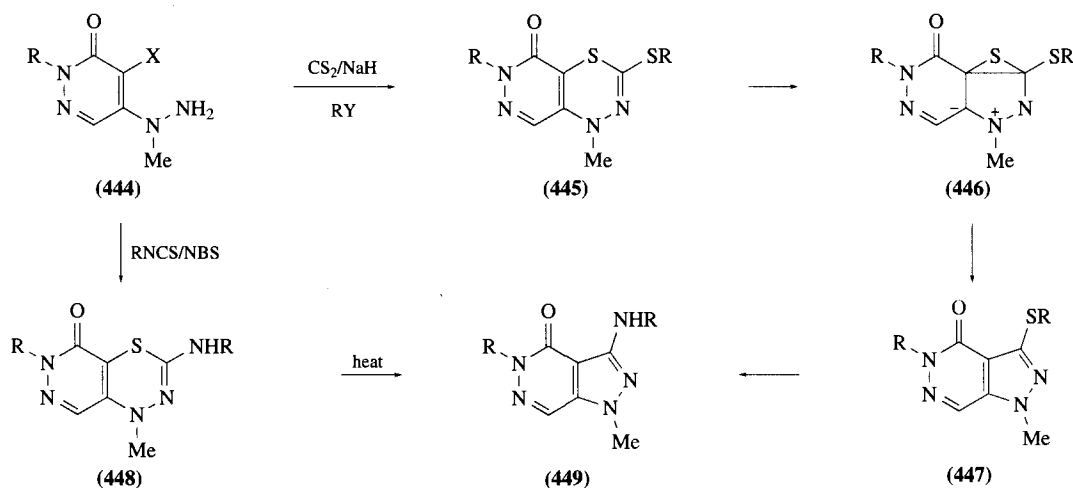
(iii) *Pyrazolo[3,4-d]pyridazines*

Pyrazolo[3,4-*d*]pyridazines are produced by reacting 5-unsubstituted-4-hydrazinopyridazines under Vilsmeier reaction conditions <82EUP63381, 85CPB982>. For example, compound **(440)** affords either **(442)** or **(443)** on treatment with phosphorus oxychloride in DMF (Scheme 45); depending on the reaction conditions, compound **(441)** is a common intermediate.



Scheme 45

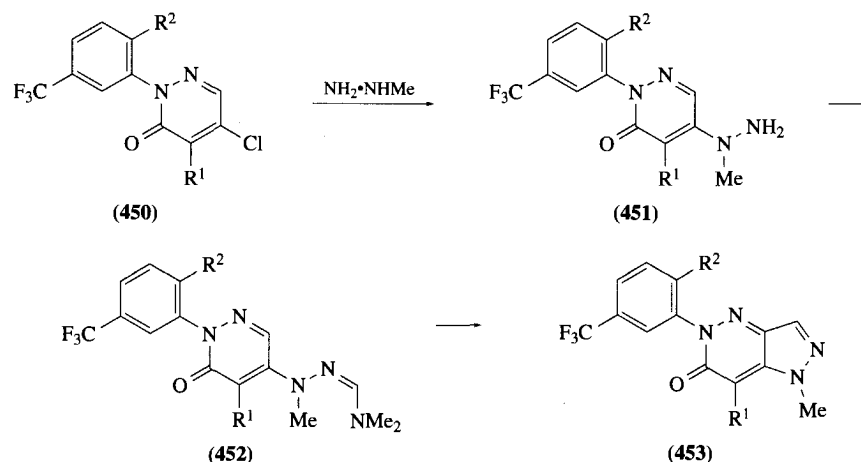
The reaction of the hydrazines **(444)** with carbon disulfide and sodium hydride followed by alkylation gives the thiadiazines **(445)** (Scheme 46). The latter gives the pyrazolo[3,4-*d*]pyridazines **(447)** on heating. It is suggested that this transformation (**445** → **447**) proceeds via an electrocyclization to yield the intermediate **(446)**. Similarly, the reaction of the hydrazines **(444)** with isothiocyanates and NBS gives thiadiazines **(448)** which are converted into the products **(449)** on heating <82EUP63881>. These products **(449)** are also prepared by reacting the sulfur analogues **(447)** with amines <85JHC161>.



Scheme 46

(iv) *Pyrazolo[4,3-c]pyridazines*

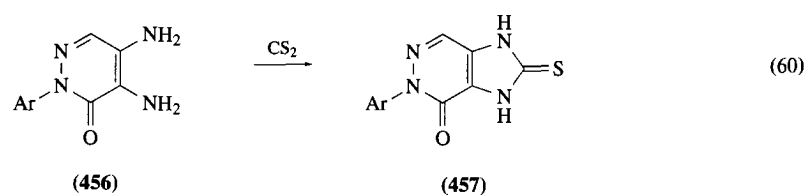
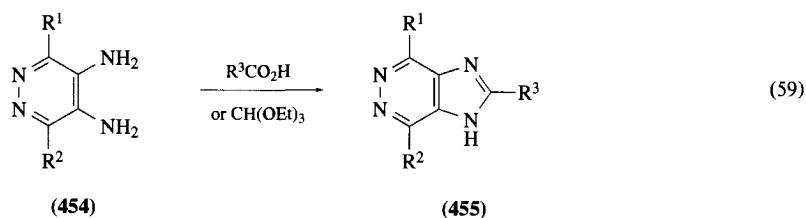
Only one synthesis of this ring system by this route has been reported <77GEP2632656>. Cyclizing derivatives **(452)**, prepared by treating **(450)** with hydrazine and subsequent treatment of the product **(451)** with DMF DMA, affords the pyrazolopyridazines **(453)** (Scheme 47).



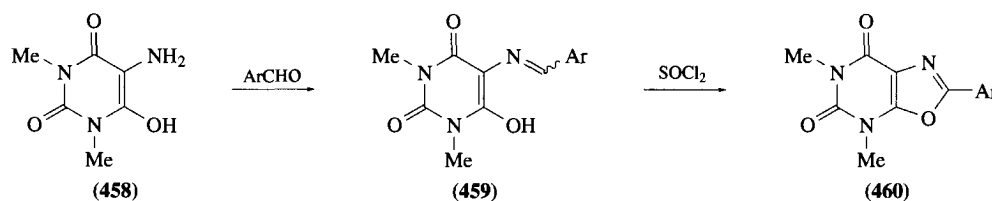
Scheme 47

(v) Other ring systems

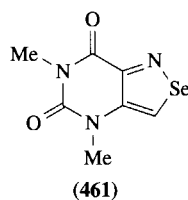
o-Diaminoazines cyclize on treatment with a variety of acylating agents to yield imidazoazines <75MI 712-01, 81JHC751, 85GEP3347290, 85JCS(P1)2573, 86GEP3445299>. For example, treatment of the diamines (454) with acids gives compounds (455) (Equation (59)). The derivatives (455; R¹ = H) are also produced by condensing the diamines (454) with triethyl orthoformate. Similarly the reaction of the diamines (456) with CS₂ gives the derivatives (457) (Equation (60)). Similar syntheses of imidazopyrazines from 2,3-diaminopyrazines have been reported <83GEP3217583, 84AJC1057, 85GEP3346640>.



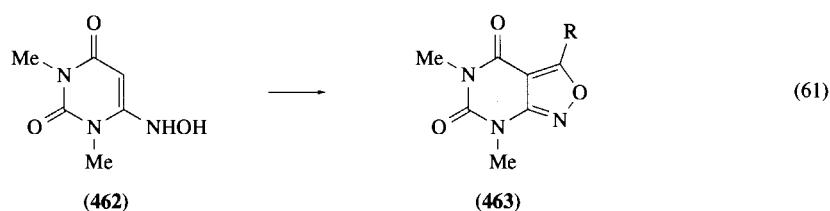
Condensation of the amine (458) with aromatic aldehydes gives the imines (459) which cyclize upon treatment with SOCl₂ to give the oxazolo[5,4-*d*]pyrimidines (460) (Scheme 48) <78CPB765>. *o*-Aminoazolols are also converted into oxazoloazines by the action of triethyl orthoformate <90TL1155>. Oxidative cyclocondensation of compound (458) with selenium dioxide gives the selenazolo[4,3-*d*]pyrimidine (461) <84JAP5920274, 87TL4579>.



Scheme 48

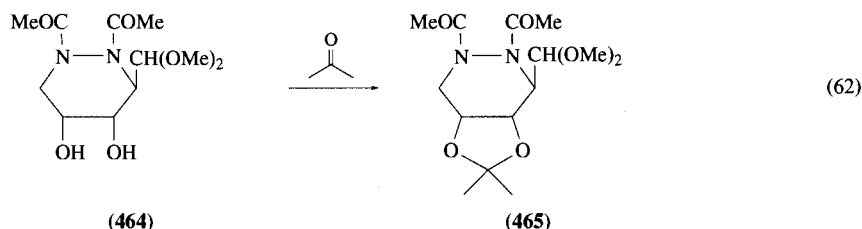


Isooxazoloazines are prepared by cyclizing azinyldihydroxylamines utilizing methods similar to those used to cyclize azinyldiazines <77JAP77139091, 78CPB2497, 79CL155, 81NKK721, 84H(22)1005, 84IJC(B)758>. For example, condensing compound (462) with aldehydes, imines, and α -chloroaldehyde amines in ethanol gives isoxazolopyrimidines (463) (Equation (61)) <84H(22)1005>. Similarly, reactions of compound (462) with acid anhydrides gives related derivatives <91AHC(55)129>.



Isothiazolo[5,4-*d*]pyrimidines are formed by the reaction of 5-acetyl-4-thiopyrimidines with sodium hypochlorite in a mixture of sodium hydroxide and ammonia <88SUL199>.

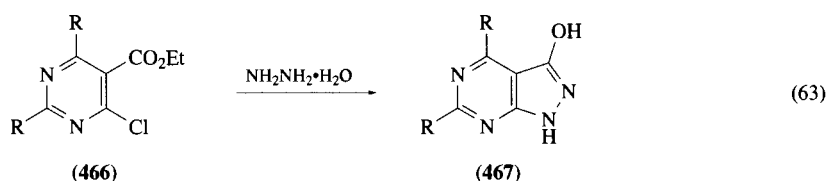
1,3-Dithiolo[4,5-*d*]pyridazines are prepared by reacting 4,5-dithiopyridazine-6-ones with aldehydes, and cyclic ketones afford spiro derivatives <64TL253, 65T1323>. Similarly, 1,3-dithiolo[4,5-*b*]pyrazines are obtained from reaction of pyrazine-2,3-dithiol with thionyl chloride <72JOC221>. Phenylcarbonylchloride also gives 1,3-dithiolo[4,5-*b*]pyrazines <70CPB147>. Similarly, the diols (464) give the dioxolanopyridazines (465) on treatment with acetone (Equation (62)) <81H(15)679, 90H(31)1>.

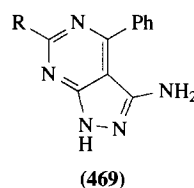
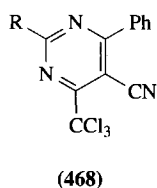


7.12.9.3.2 From [3 + 2] atom fragments

(i) Pyrazolo[3,4-*d*]pyrimidines

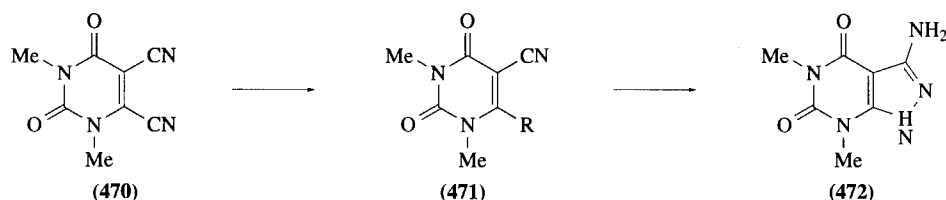
4-Halopyrimidine-5-carboxylic acids, 4-halo-5-pyrimidinals, 4-halopyrimidin-5-carbonitriles, and 4-chloro-5-pyrimidinals react with hydrazines to yield the corresponding pyrazolo[3,4-*d*]pyrimidines <58JOC191, 58LA(615)42, 61BRP884151, 62ZOB1847, 65CB346, 67CB2577, 85JAP85128285, 86EUP166054, 92EUP506628>. The transformation of the esters (466) into the derivatives (467) on treatment with hydrazine is a representative example of this approach (Equation (63)) <61JOC451, 62CB956>. Similarly, the nitriles (468) are converted into the derivatives (469) on reaction with hydrazines <79JHC1109>.





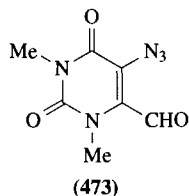
4-Chloro-5-pyrimidinyls react with hydrazine to yield the corresponding pyrazolo[3,4-*d*]pyrimidines <66MI611, 74GEP2343702>. Replacement of other functions at C-4 in pyrimidine-5-carbonitriles also affords pyrazolo[3,4-*d*]pyrimidines. Thus, 6-alkylthiouracil-5-carbonitriles, ethyl 6-methylmercaptouracil-5-carboxylate as well as 6-methylthiol-5-acyluracils react with hydrazines to yield pyrazolo[3,4-*d*]pyrimidines <91JHC1039>.

5,6-Dicyano-1,3-dimethyluracil (**470**) undergoes substitution reactions with amines or sodium methoxide to yield the derivatives (**471**; R = NHR, or OCH₃) (Scheme 49) which react with hydrazines to yield the pyrazolo[3,4-*d*]pyrimidine (**472**) <78CPB3208, 79CPB1328>.

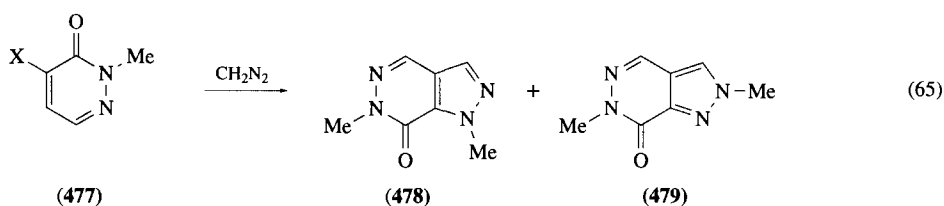
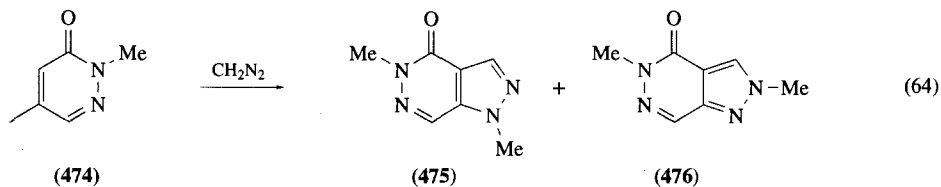


Scheme 49

5-Azido-6-formyl-1,3-dimethyluracil (**473**) is cyclized with hydrazines to form 1-substituted-5,7-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-diones <83CPB3959>.



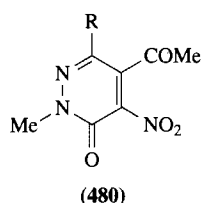
The pyridazinone (**474**) undergoes cycloaddition reactions with diazomethane to yield the isomers (**475**) and (**476**) (Equation (64)). On the other hand, the derivatives (**477**) give a mixture of (**478**) and (**479**) (Equation (65)) <82H(18)175>. Similar results have been reported for the 3-substituted-6-thioxo derivatives <91JHC417>.



5-Aminopyridazinyl-4-chlorophenyl ketone reacts with hydrazine hydrate to yield 3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyridazine <86JCS(P1)169>.

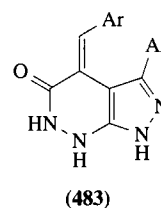
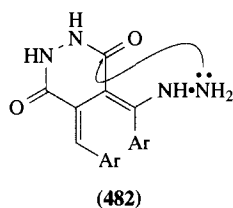
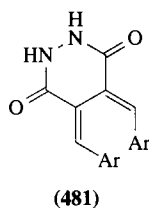
(ii) *Pyrazolo[3,4-*c*]pyridazines*

Substitution of halogen adjacent to a carbonitrile affords pyrazolopyridazine. This synthetic approach proved useful for the synthesis of both pyrazolo[3,4-*c*]pyridazines and pyrazolo[3,4-*d*]pyridazines. Thus the reaction of 3-chloropyridazin-4-carbonitriles with hydrazines gives 3-amino-pyrazolo[3,4-*c*]pyridazines <89MI 712-01>. The nitrofunction in 4-acetyl-5-nitropyridazinones (**480**) is replaced by hydrazine to yield pyrazolo[3,4-*c*]pyridazinones <89H(29)1595>. Acylpyridazinones and oxypyridazinone carboxylates condense also with hydrazine to yield pyrazolopyridazines <81JHC333, 86MI 712-01>. 3-Substituted-5-formyl-1-arylpyridazine-4(1*H*)-ones react with hydrazine hydrate to yield 3-substituted-5-arylpyrazolo[3,4-*d*]pyridazines <88IJC(B)1154>.



It has been reported that the reaction of 3,4-diphenyl-6-thioxopyridazine-5-carbonitrile with hydrazine hydrate affords 4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazin-3-amine <90JPR104>.

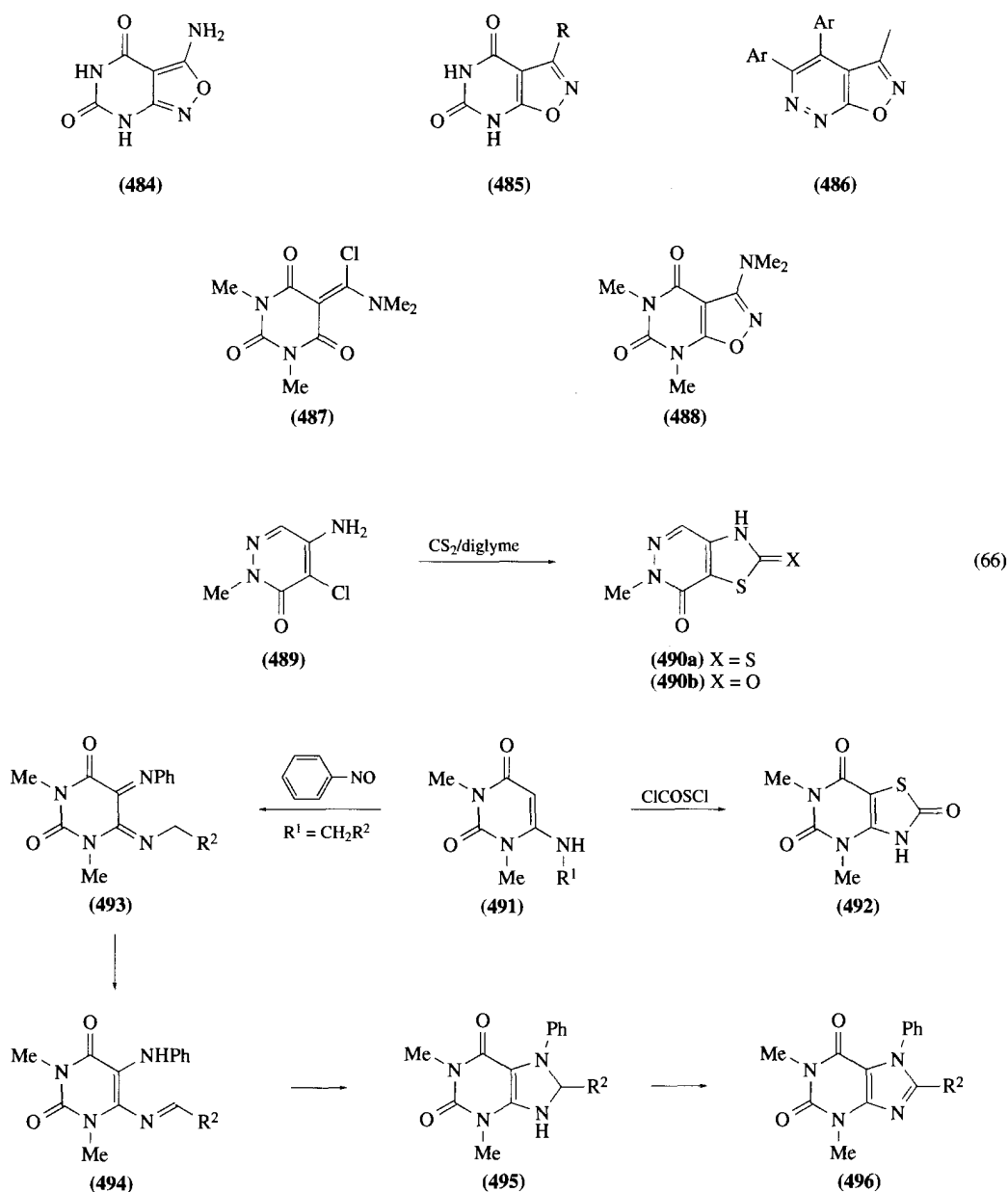
The reaction of the derivatives (**481**) with hydrazine hydrate gives the pyrazolo[3,4-*c*]pyridazines (**483**). This suggests that an intermediate Michael adduct (**482**) is first formed as pyridazinones do not normally react with hydrazines forming hydrazones. The aromaticity of the resulting ring system may be the driving force for this reaction <87JPR525>. The reaction of compounds (**481**) with substituted hydrazines, however, is claimed to give pyrazolopyridazinones resulting from initial attack at a carbonyl group <86JPR932>.

(iii) *Other ring systems*

Isoxazolo[3,4-*d*]pyrimidines (**484**) are also obtained via reaction of 6-methylthiouracil-5-carbonitrile with hydroxylamine <91JHC1039>. In contrast, 6-alkylthio-5-acylpyrimidines react with hydroxylamine to yield products (**485**), formed via initial condensation at the acyl function <89PHA489>. Similarly, the derivatives (**486**) are produced by the reaction of 3-chloro-5,6-diarylpyridazine derivatives with hydroxylamine <89JPR339>. The reaction of compound (**487**) with hydroxylamine gives the derivative (**488**) <80BSB651>.

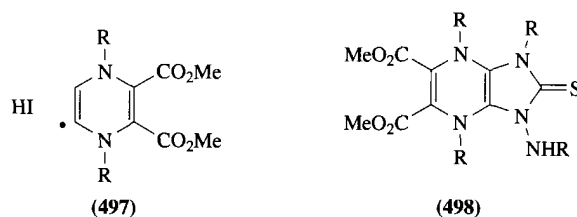
The reaction of 4-chloro-5-nitro-1,3-dimethyluracil with methylthioglycollate gives thiazolo[5,4-*d*]pyrimidines <82JHC77>. The acylation of *o*-chloroaminoazoles gives acyl amino derivatives that readily cyclize into oxazoloazines <75JOC3141>.

The reaction of compound (**489**) with carbon disulfide in diglyme gives compound (**490b**) (Equation (66)). It seems that desulfurization of the initial product (**490a**) takes place during treatment with alkali <79JAP79119490>. The reaction of 6-amino-1,3-dimethyluracil (**491**) with chlorosulfonyl chloride gives the thiazolopyrimidine derivative (**492**) (Scheme 50). The reaction of the uracil (**491**) with nitrosobenzene in the presence of acetic anhydride gives the derivatives (**496**) via the intermediates (**493-495**) <72JOC4464>.

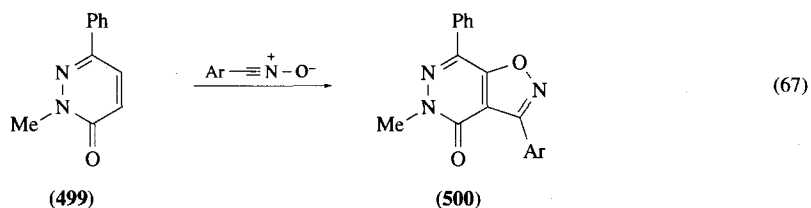


Scheme 50

Treatment of the diesters (497) with 1,4-disubstituted thiosemicarbazides gives the antiaromatic derivatives (498) <85KGS960>.



Nitrile oxides undergo regioselective 1,3-dipolar cycloaddition to the 4,5-double bond of the pyridazinone (499) to yield the isoxazolo[4,5-d]pyridazines (500) (Equation (67)) <89JHC553>.

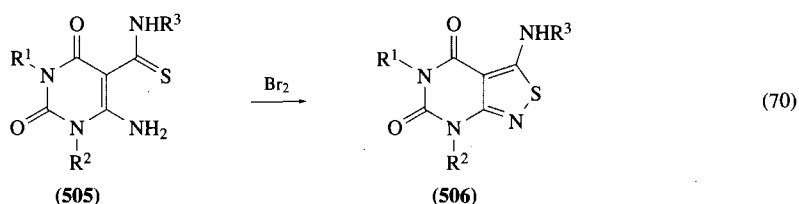
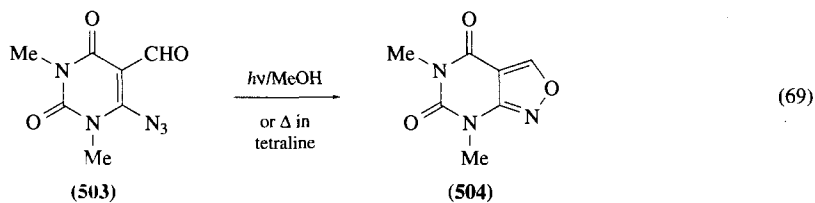
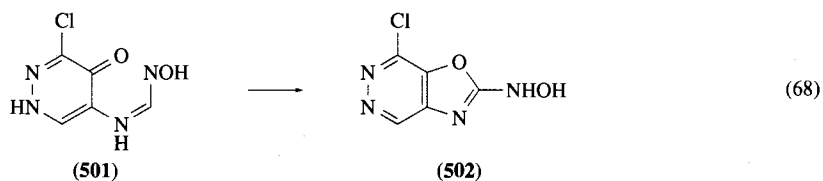


Pyrazolo[3,4-*d*][1,3]thiazin-4-ones and isoxazolo[5,4-*d*][1,3]thiazin-4-ones are produced by the reaction of 4-chloro-6-oxo-1,3-thiazin-5-yl with hydrazine and hydroxylamine <84KGS1328>.

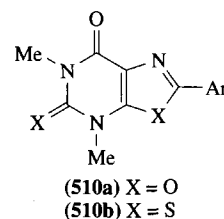
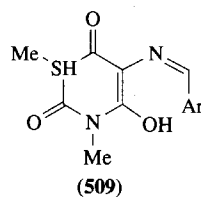
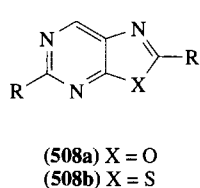
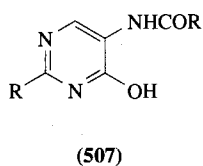
7.12.9.4 Synthesis of Five-membered Rings by Formation of One Bond

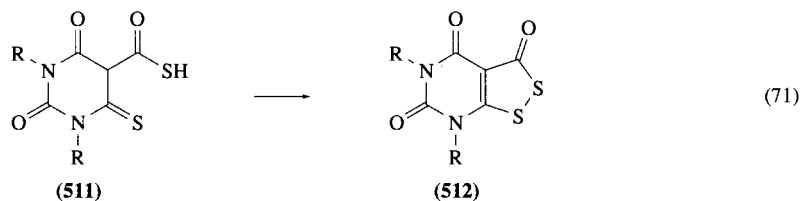
7.12.9.4.1 Bond formation α to a heteroatom

The cyclization of compound (501) gives compound (502) (Equation (68)) <85M1447>. 6-Azido-5-formyl-1,3-dimethyluracil (503) is cyclized on irradiation in methanol or by heating giving compound (504) (Equation (69)) <83CPB3959>. Another simple way to access 3-aminoisothiazolo[3,4-*d*]pyrimidines is by oxidative cyclization of 6-aminouracil-5-dithiocarboxylates <76CPB979, 79H(12)485> or 6-aminouracil-5-thiocarboxamide <74LA2019>. For example, cyclization of the derivatives (505) using bromine gives the thiazolo[3,4-*d*]pyrimidines (506) (Equation (70)) <76CPB979, 76JAP7691294, 79CPB1147, 92AHC(55)129>.



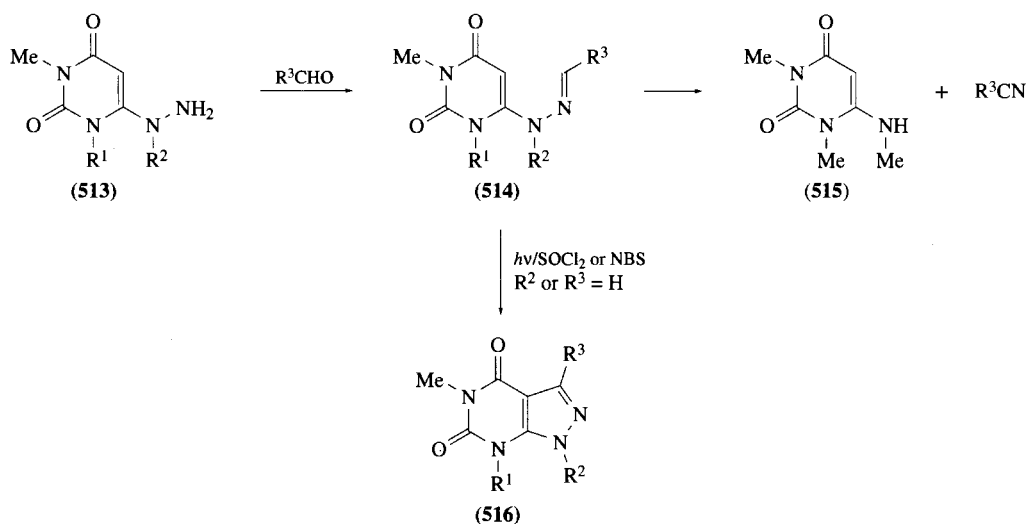
Acylaminopyrimidines (507) react with POCl_3 to give the oxazolopyrimidines (508a). The corresponding reaction with phosphorus pentasulfide gives compounds (508b) <91AJC129>. Treatment of the imines (509) with thionyl chloride or with NBS gives the derivatives (510a) which on treatment with phosphorus pentasulfide give the thio analogues (510b) <77H(6)1919, 78CPB765, 92AHC(55)129>. The monothiocarboxylic acids (511) are converted into the derivatives (512) on treatment with an oxidizing agent (Equation (71)) <76CPB2461, 90H(31)1>.





7.12.9.4.2 Bond formation β to a heteroatom

6-Benzylidenehydrazinouracils (**514**), derived from 6-hydrazinouracils (**513**) and aldehydes, are cyclized upon UV irradiation and treatment with thionyl chloride or NBS, to afford pyrazolo[3,4-*d*]pyrimidines (**516**), depending on the presence of protons at R^2 and/or R^3 (Scheme 51); fully methylated hydrazones are decomposed into 6-methylaminouracils (**515**) and nitriles $\langle 73S300, 74H(2)153, 75BCJ1484, 84JHC969, 92AHC(55)129 \rangle$.



Scheme 51

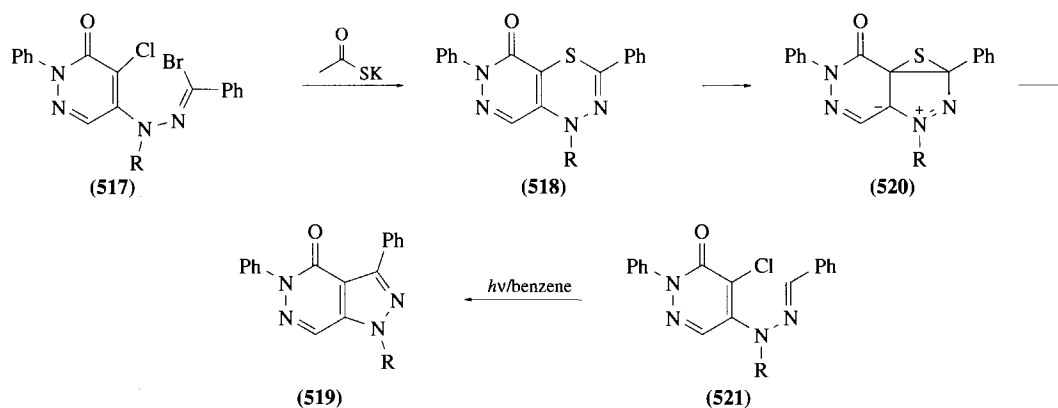
On the other hand, the hydrazones derived from the hydrazines (**513**) and ketones undergo facile Fischer-type cyclization to give pyrazolo[3,4-*d*]pyrimidines $\langle 72CL367, 74CPB1459, 74CPB2921, 74JCS(P1)1921 \rangle$. The photolysis of the 5-nitro derivatives of the hydrazones (**514**) leads to the formation of triazolo[4,5-*d*]pyrimidines along with the pyrazolopyrimidines (**516**) $\langle 71CC1442, 72TL1973, 74CPB1269 \rangle$. Furthermore, pyrazolo[3,4-*d*]pyrimidines are obtained by thermally induced cyclization of 6-alkylidenehydrazinouracil in the presence of aldehydes $\langle 58LA42, 74JA5607, 77JCS(P1)765 \rangle$.

The treatment of the derivatives (**517**) with potassium thioacetate affords the 1,3,4-thiadiazine derivatives (**518**) which when heated in alkali loses sulfur to give compounds (**519**) which are formed most likely via the intermediates (**520**) (Scheme 52) $\langle 84CPB4437, 84H(22)479 \rangle$. Compounds (**519**) are also formed by irradiation of the hydrazones (**521**) $\langle 84JHC1249, 85CPB982, 90AHC(48)223 \rangle$.

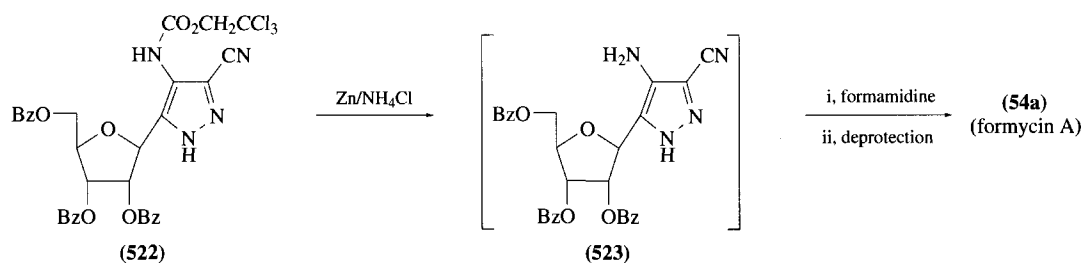
7.12.10 SYNTHESIS OF FORMYCINS, ALLOPURINOL, AND RELATED COMPOUNDS

Formycin A was initially isolated from rice mold $\langle 65JAN259 \rangle$ and identified $\langle 66JHC110, 66TL597 \rangle$ as 3-ribofuranosylpyrazolo[4,3-*d*]pyrimidine-7-amine (**54a**). The reported synthesis utilizes the pyrazole derivative (**522**) as starting material which is converted *in situ* on treatment with zinc dust in methanol in the presence of ammonium chloride into the amine (**523**) which is then reacted with formamidine to yield formycin A after deprotection (Scheme 53) $\langle 78CCCC1431 \rangle$.

A synthesis of formycin A employs the 1,4-dinitropyrazole (**524**) which is converted into the nitrile (**525**) on treatment with cyanide ion (Equation (72)). The latter is then reduced and treated with formamide or formamidine to give formycin A (**54a**) $\langle 80CJC2624, 81JCS(P1)2374, 91JCS(P1)1077 \rangle$.

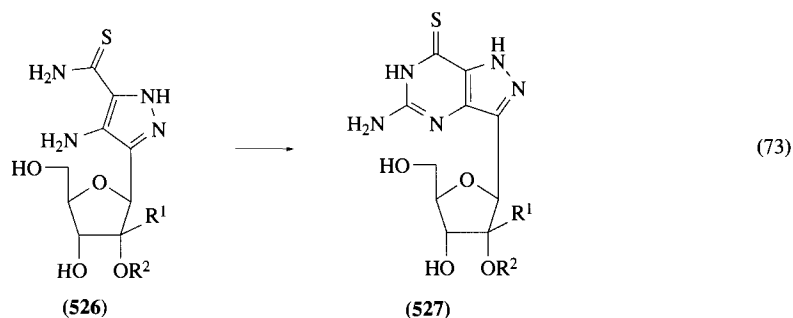
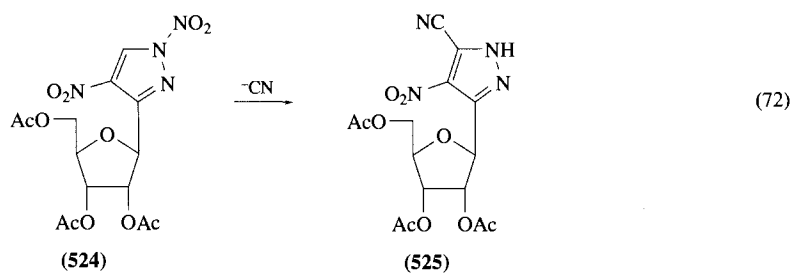


Scheme 52

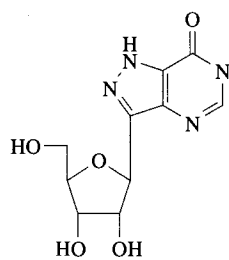


Scheme 53

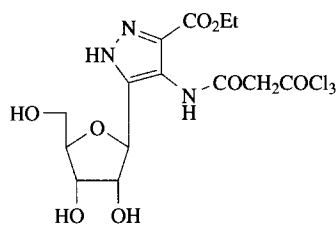
In a similar manner, the β -D-xylofuronoxyl analogue could be prepared $\langle 84\text{T}119, 86\text{JCS}(\text{P}1)1267 \rangle$. Several other derivatives of formycin have been prepared from C-glycosylaminopyrazole carboxylic acids $\langle 81\text{MI} 712-01 \rangle$.



Formycin B (528) is prepared from the pyrazole (529) by treatment similar to that reported for the synthesis of formycin A (54a) from (523) $\langle 72\text{CCC}2786 \rangle$.

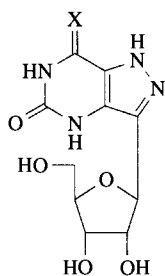
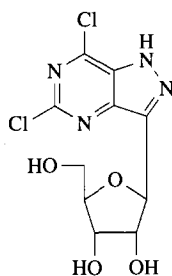


(528) formycin B

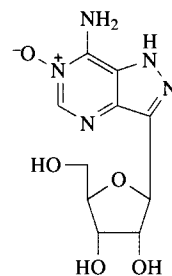


(529)

The dichloro formycin analogue (**531**) was prepared by the action of POCl_3 on compounds (**530**) <86BBR(137)76, 86MI 712-04>. Phosphorylation of compounds (**526**) and reaction with amino acids have also been reported, producing (**527**) (Equation (73)) <87S879>. The x-ray structure <78JA3957, 85MI 712-02>, luminescence spectra <82MI 712-02>, and quantum chemical studies <89MI 712-03> of the formycins have been reported (Section 7.12.3). The formycin *N*-oxide (**532**) has also been prepared <76JHC1359>.

(530a) X = O
(530b) X = S

(531)



(532)

Allopurinol, 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**53**), was first synthesized by Robins <56JA784> and by Schmidt <58HCA1052> from 5-aminopyrazole-4-carboxylic acid derivatives. Several syntheses starting from a simple acyclic intermediate have been reported. Thus, reacting ethyl alkoxymethylene cyanoacetate with hydrazine and formamide at 140–180°C gave allopurinol in high yield. An acid catalyst lowers the temperature required for cyclization of the intermediate 4-alkoxycarbonyl-3-aminopyrazole and raises the purity and the yield of allopurinol <69BRP1284084>.

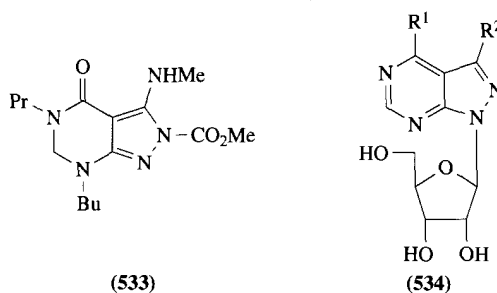
Allopurinol is obtained in 96.5% yield by alkaline hydrolysis of 4-chloropyrazolo[3,4-*d*]pyrimidine in the presence of 25–60 g l⁻¹ H₂O₂. It was obtained in similarly high yield by cyclizing 4,6-dichloro-5-formylpyrimidine with hydrazine hydrate and hydrolyzing the resulting 4-chloropyrazolo[3,4-*d*]pyrimidine *in situ* <69BRP1284084>. *N*¹, *N*⁵-Bis- α and β -D-glycopyranosides and *N*¹- α , *N*²- β -D-glycopyranosides of allopurinol have been prepared by glycosidation of allopurinol via the corresponding bis-trimethylsilyl intermediate and penta-*O*-acetyl- α -D-glucopyranose in the presence of tin tetrachloride <88IJC(B)390>.

7.12.11 IMPORTANT COMPOUNDS AND APPLICATIONS

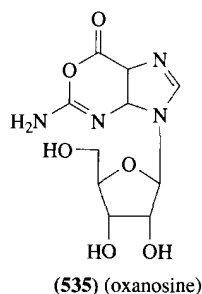
Azoloazines are purine analogues and as such are expected to exhibit diverse biological activities. The most important biologically active compounds of this class are the formycins and allopurinol. Formycin A has demonstrated antitumor, antibacterial, antifungal, and antiviral activity <B-70MI 712-02>. Formycin A acts as a substrate for many adenosine specific enzymes including adenosine kinase <65JAN259>. Additionally, formycin A is incorporated into RNA and DNA <69JBC(244)3243> and effectively replaces adenosine at the binding site of tRNA to ribosomes <68BBA(174)696>. Formycin A 5'-triphosphate is a competitive *in vitro* inhibitor of the nucleoside triphosphate reductase of *Lactobacillus leishmanni* and an effective substrate when the positive effector dGTP is present <78B2350>. Unfortunately, formycin A is also a good substrate for the adenosine catabolic enzyme, adenosine deaminase <67JAN317> and thus the activity of formycin A is diminished by ready conversion to the nearly inactive formycin B <80JA2817>.

Allopurinol is an effective drug for the therapy of both primary hyperuricemia (gout) and hematological disorders of antineoplastic therapy. This drug inhibits xanthine oxidase which is responsible for conversion of purines into uric acid <73B1196, 74MI 712-02>. Allopurinol also markedly enhances myocardial function and decreases tissue injury during myocardial reperfusion <86MI 712-03>. Administration of allopurinol increases arterial blood flow <79MI 712-04> and urinary excretion of the ammonium ion <76MI 712-02>.

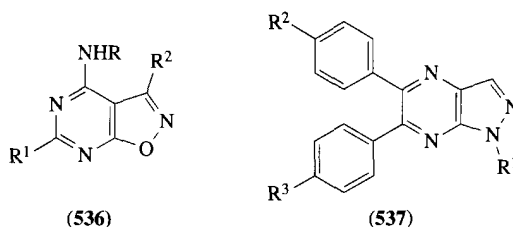
Pharmaceuticals, useful for the treatment of liver diseases, containing 3-aminopyrazolo[3,4-*d*]pyrimidines have been prepared. Thus compound (533) at 3.0 mg kg⁻¹ p.o. completely prevented lipopolysaccharide-induced liver failure in mice <85JAP86236778>. The pyrazolo[3,4-*d*]pyrimidine (534) proved effective against *Eimeritenella* <82JMC1040>. Compound (534; R¹ = NH₂; R² = CONH₂) has shown pronounced activity as a cytotoxin for the growth of fibroblasts <76B1005>. Activity against T-cells was reported for other pyrazolo[3,4-*d*]pyrimidines <89JMC1905>. Herbicidal activity <79MIP354186> was reported for some pyrazolo[3,4-*d*]pyrimidines.



Biological activities of other ring systems have also been reported. Most important is the reported antibacterial activity of oxanosine (535), produced by a number of *Streptomyces* genus, and active against Gram-negative bacteria: it also has anticancer and antiviral activities <82EUP53025, 90JAP0291077>.



The antibiotic activity of compound (535) is antagonized by guanine, guanosine, and guanulic acid. Oxanosine was confirmed to be a competitive inhibitor of GMP synthesis <82JAN755>. The isoxazolo[5,4-*d*]pyrimidines (536) are fungicides <78GEP2812367>. Compound (537) is reported to be a blood platelet aggregation inhibitor and antiinflammatory agent <90JAP2101078>.



ACKNOWLEDGEMENT

Mohamed H. Elnagdi is grateful to the University of Kuwait for partial financial support through Project SCO71.

7.13

Bicyclic 5-6 Systems: Five Heteroatoms 2 : 3 or 3 : 2

PHILIP KNOWLES

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7.13.1 INTRODUCTION

Fifty ring systems composed of a six-membered ring fused with a five-membered ring and having no heteroatoms at the ring junctions but with a 2:3 or 3:2 arrangement of the heteroatoms in the rings are described and characterized in the literature. These are shown in Structures (1) to (50) and may be divided into three classes: (i) systems that were described in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) on which further work has been carried out (Structures (1)–(14), Figure 1); (ii) systems that were not described in CHEC-I or have appeared in the literature since its publication (Structures (15)–(37), Figure 2); and (iii) systems that were described in CHEC-I on which no further work has been carried out (Structures (38)–(50), Figure 3). In order to give a consistent presentation, they are all depicted with the six-membered ring on the left-hand side and if possible a heteroatom at the top of the five-membered ring. The numbering of these systems, according to IUPAC rules, does not necessarily start from this position.

In many cases, the literature since CHEC-I of those systems in class (i) has been extensive, mainly because most are related to the purine nucleus by the inclusion of a further heteroatom for example “azapurine” derivatives which have shown pharmaceutical or physiological action. The methods of synthesis, except in a few cases, have not changed since the publication of CHEC-I and thus more emphasis has been placed on the physical properties, reactivity, and reactivity of substituents of compounds within these systems. In contrast, in most cases very little literature is available for systems of class (ii) and synthesis has assumed paramount importance. Only two reviews since the early 1980s are applicable to this chapter: the conversion of [1,2,5]oxadiazolo[3,4-*d*]pyrimidines (9) to pteridines (82MI 713-01) and the chemistry and physical properties of 1,2,3-triazolo[4,5-*d*]pyrimidines (7) (86AHC(39)117). The incidence of publications relating to the use of Structures (1)–(50) in such applications as pharmaceuticals, agrochemicals, and even explosives has increased since the publication of CHEC-I and these are discussed in Section 7.13.10.

7.13.2 THEORETICAL METHODS

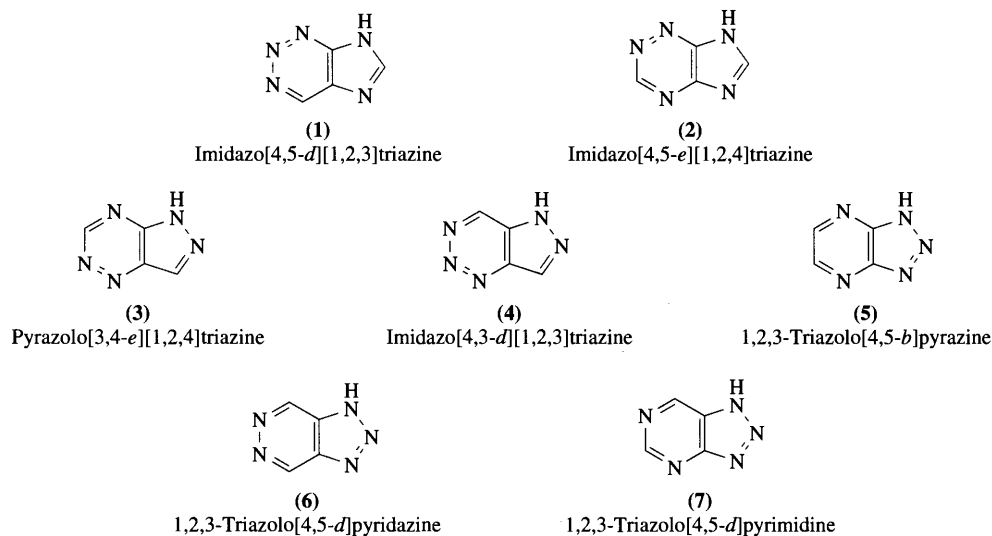
Ab initio molecular orbital calculations on these systems have been confined to the 1,2,3-triazolo[4,5-*d*]pyrimidines (7), the so-called “8-azapurines”, and references to this subject may be found in the previously mentioned review (86AHC(39)117). In 1989, quantum mechanical perturbation methods have been used to study the activity of 8-azapurine nucleoside antibiotics in transcription processes (89MI 713-01). The 1,2,3-thiadiazolo[5,4-*d*]pyrimidine derivative (51), a rearrangement product of 8-aza-6-thioinosine, has been used in a molecular modeling study of the antitumor activity of sugar derivatives of pyrimidopyrimidines (89PNA(86)8242).

7.13.3 EXPERIMENTAL STRUCTURAL METHODS

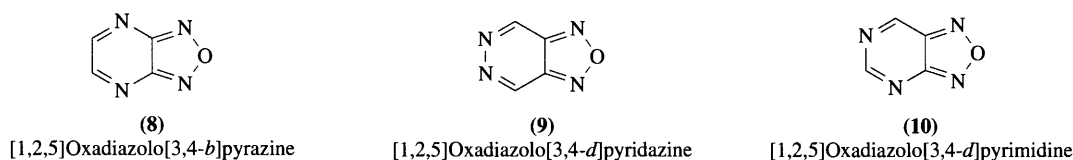
7.13.3.1 Nuclear Magnetic Resonance

Proton magnetic resonance, as a structure determining tool for these systems, is of very little use; in most cases most or all of the ring carbons are substituted. However, comprehensive data is

Azoloazines



Oxazoloazines



Azolothiazines and Thiazoloazines

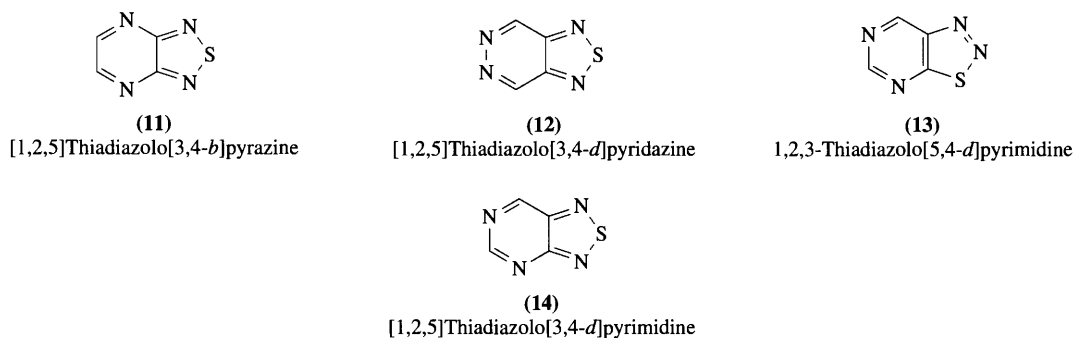


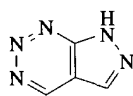
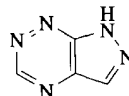
Figure 1 Systems mentioned in CHEC-I on which further research has been carried out.

available for the 1,2,3-triazolo[4,5-*d*]pyrimidine system <86AHC(39)117>. ^{13}C and ^{15}N NMR spectra provide more information but in only three systems, imidazo[4,5-*e*][1,2,4]triazines (2), [1,2,5]oxadiazolo[3,4-*d*]pyridazines (9), and 1,2,3-triazolo[4,5-*d*]pyrimidines (7), has any data been collected (see Tables 1 and 2).

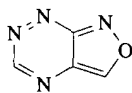
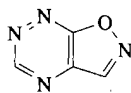
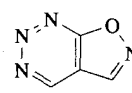
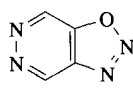
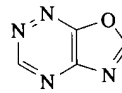
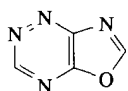
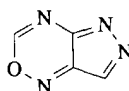
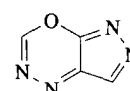
7.13.3.2 UV Spectroscopy

The UV data collected in CHEC-I and any further data has been compiled in Table 3. UV analysis is not a method of choice for structure determination; however, there is a tendency for those systems which exist in an “*o*-quinonoid” form to have their main absorption at a longer wavelength with a higher extinction coefficient.

Azoloazines

(15)
Pyrazolo[3,4-*d*][1,2,3]triazine(16)
Pyrazolo[4,3-*e*][1,2,4]triazine

Oxazoloazines and Azolooxazines

(17)
Isoxazolo[4,3-*e*][1,2,4]triazine(18)
Isoxazolo[4,5-*e*][1,2,4]triazine(19)
Isoxazolo[3,4-*d*][1,2,3]triazine(20)
1,2,3-Oxadiazolo[4,5-*d*]pyridazine(21)
Oxazolo[4,5-*e*][1,2,4]triazine(22)
Oxazolo[5,4-*e*][1,2,4]triazine(23)
Pyrazolo[4,3-*e*][1,2,5]oxadiazine(24)
Pyrazolo[4,3-*e*][1,3,4]oxadiazine

Thiazoloazines and Azolothiazines

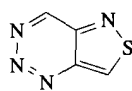
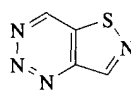
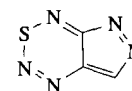
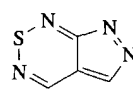
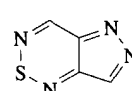
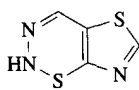
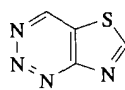
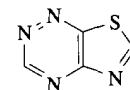
(25)
Isothiazolo[4,3-*d*][1,2,3]triazine(26)
Isothiazolo[4,5-*d*][1,2,3]triazine(27)
Pyrazolo[3,4-*c*][1,2,5]thiadiazine(28)
Pyrazolo[3,4-*c*][1,2,6]thiadiazine(29)
Pyrazolo[4,3-*c*][1,2,6]thiadiazine(30)
Thiazolo[5,4-*e*][1,2,3]thiadiazine(31)
Thiazolo[4,5-*d*][1,2,3]triazine(32)
Thiazolo[4,5-*e*][1,2,4]triazine

Figure 2 New systems or systems not mentioned in CHEC-I.

7.13.3.3 X-ray Crystallography

The crystalline nature of most of the compounds of these systems and the inadequacy of other methods has led to x-ray crystallography being the most popular method for determination of ring structure. Structure determination by this method has been used for imidazo[4,5-*e*][1,2,4]triazines

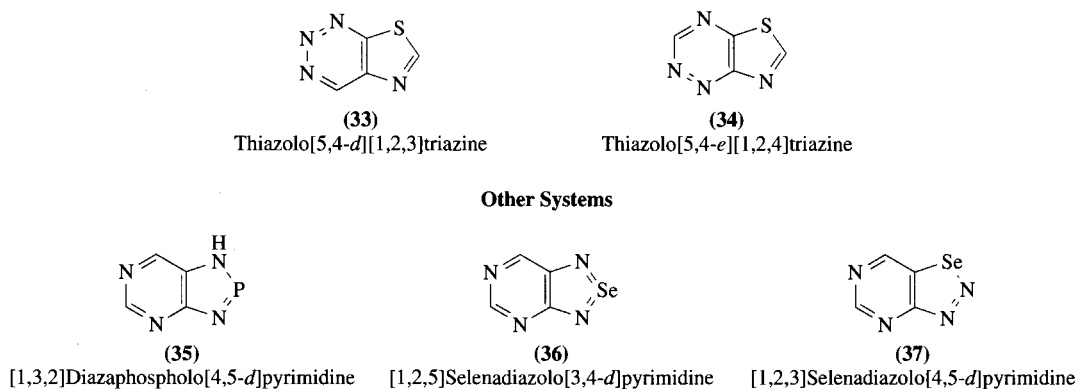


Figure 2 Continued.

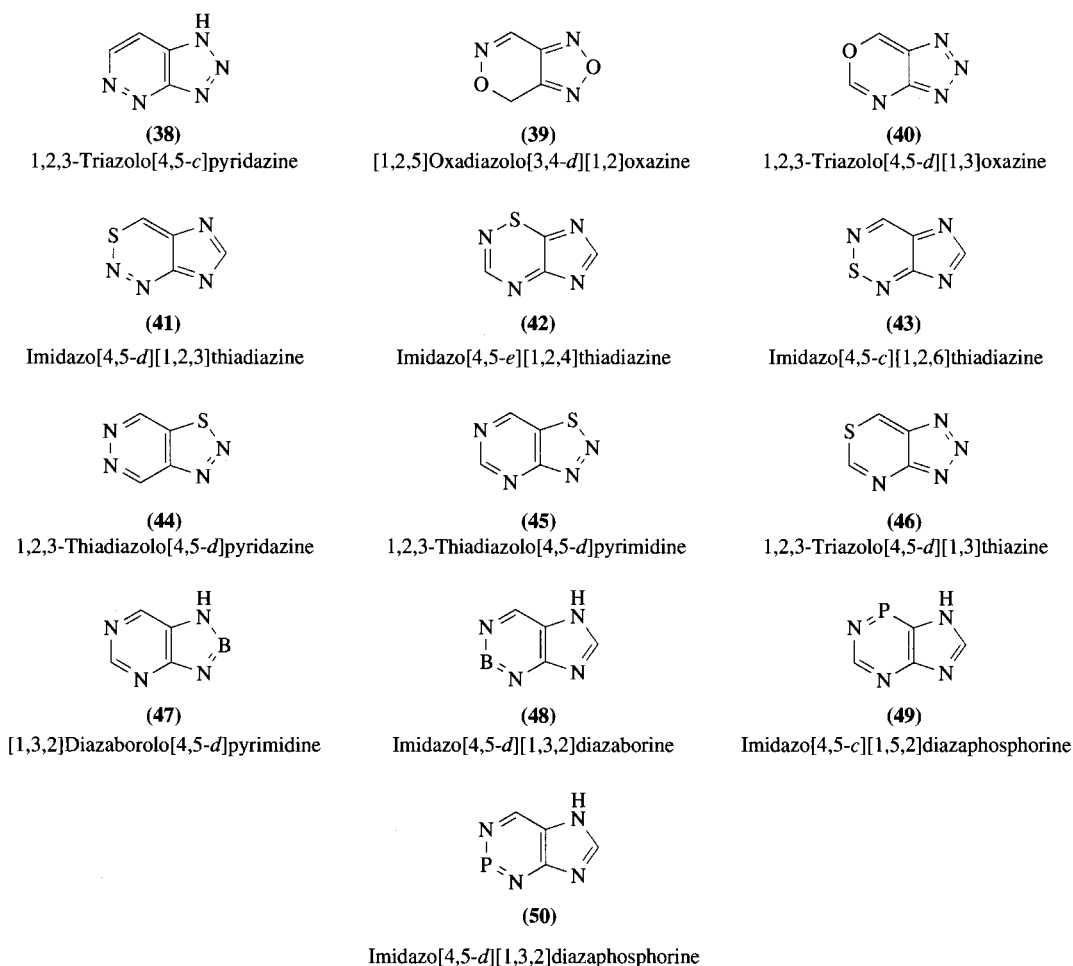
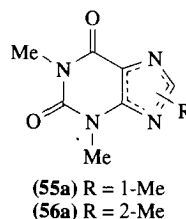
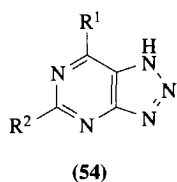
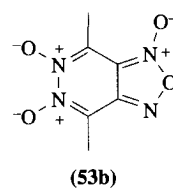
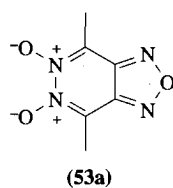
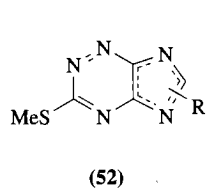
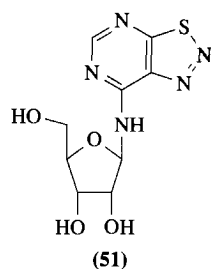


Figure 3 Systems mentioned in CHEC-I on which no further research has been carried out.

(2), [1,2,5]oxadiazolo[3,4-*b*]pyrazines (8), [1,2,5]oxadiazolo[3,4-*d*]pyridazines (9), pyrazolo[3,4-*c*]-[1,2,5]thiadiazines (27), pyrazolo[4,3-*e*][1,2,4]triazines (16), [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (14), 1,2,3-triazolo[4,5-*b*]pyrazines (5), 1,2,3-triazolo[4,5-*d*]pyrimidines (7), and 1,2,3-triazolo[4,5-*d*]-[1,3]thiazines (46). The bond lengths of selected derivatives of these systems and references are given in Table 4.

**Table 1** ^{13}C NMR spectral data (chemical shifts in ppm).

Compound	C-3	C-4	C-5	C-6	C-7	Others	Ref.
52a R = H	166.5			151.5		145.9(C-4a), 151.1(C-7a)	86JCS(P2)931
52b R = 5-Me	166.2			152.0		143.1(C-4a), 153.6(C-7a)	86JCS(P2)931
52c R = 7-Me	167.3			155.2		151.7(C-4a), 145.1(C-7a)	86JCS(P2)931
53a		113.6			113.6	141.1(C-3a, C-7a)	88LA1017
53b		113.8			116.4	144.5(C-3a), 105.9(C-7a)	88LA1017
54 R ¹ = NH ₂ , R ² = H ^a			155.8		158.9	154.2(C-3a), 124.0(C-7a)	74JOC3226
55a R = 1-Me			150.8		153.5	150.2(C-3a), 113.1(C-7a)	87BSB659
56a R = 2-Me			151.2		156.1	149.6(C-3a), 124.6(C-7a)	87BSB659

^aAs the anion.**Table 2** ^{15}N NMR spectral data (chemical shifts in ppm).

Compound	N-1	N-2	N-3	N-4	N-5	N-6	N-7	Ref.
52a R = H	4.8	-40.2		131.1				86JCS(P2)931
52c R = 5-Me	11.7	-41.1		-139.5	-234.4		-141.0	86JCS(P2)931
52c R = 7-Me	-12.5	-41.3		-117.6	-144.2		-235.3	86JCS(P2)931
53a	341.9		332.0		(316.2/317.4)			88LA1017
53b	389.3		389.3		326.0	326.0		88LA1017

7.13.4 THERMODYNAMIC ASPECTS

In the systems in this chapter, research has concentrated on the synthesis of the fully conjugated derivatives, most of which tend to be stable and crystalline. Only 1,2,3-triazolo[4,5-*d*]pyrimidine (**7**) has been compared with other common six-five heterocyclic systems using a theoretical "aromaticity" index $\langle 87\text{T4275} \rangle$ and was shown to be comparable to purine. With so many diverse structures, it is considered impossible to make useful comments about melting points, solubilities, etc. No record of any work on tautomerism has been found. The measurement of pK_a has been confined to a comprehensive list of derivatives of 1,2,3-triazolo[4,5-*d*]pyrimidine (**7**) $\langle 86\text{AHC}(39)117 \rangle$.

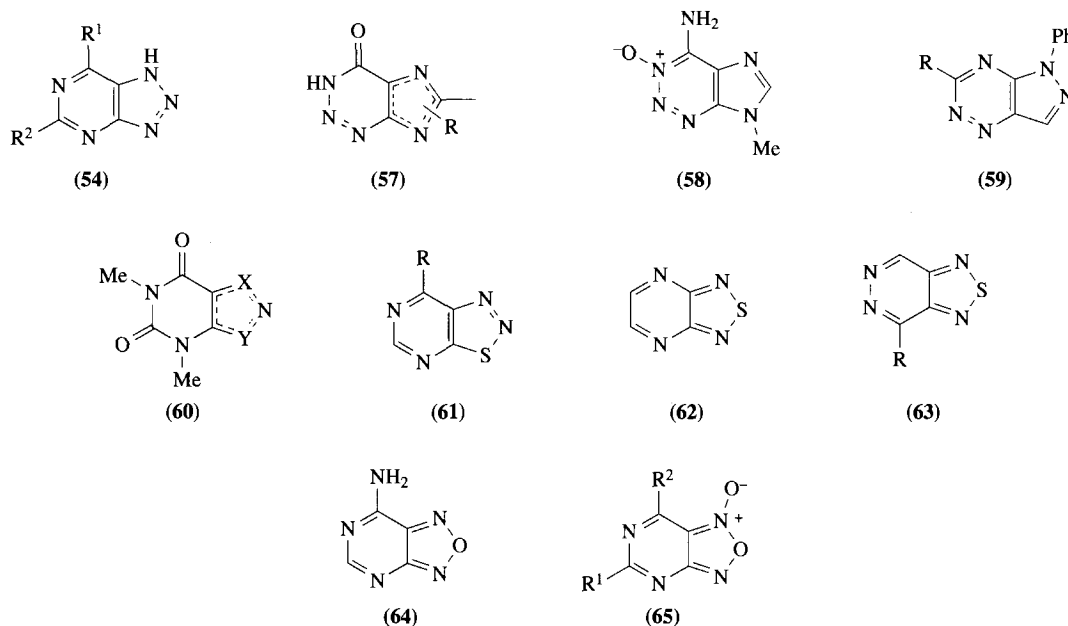


Table 3 UV spectral data.

Compound	Absorption (nm(ε))	Solvent	Ref.
54b R ¹ = R ² = H	268(7760)	H ₂ O(pH = 7)	86AHC(39)117
54c R ¹ = OH, R ² = H	259(9120)	H ₂ O(pH = 8)	86AHC(39)117
54d R ¹ = OH, R ² = OH	265(8510)	H ₂ O(pH = 7)	86AHC(39)117
57a R = 5-(β-ribofuranosyl)	255(1800), 280(1350)	H ₂ O	84JHC1221
57b R = 7-(β-ribofuranosyl)	245(5200), 293(5800)	H ₂ O	84JHC1221
58	222(25400), 242 ^a (17400), 270(4450), 345(5510)	H ₂ O(pH = 7)	90H(30)329
59a R = SEt	204(26000), 246(24400), 344(10700)	Ethanol	88JPR57
59b R = OH	205(32600), 218 ^a (24700), 242(15500), 322(6700)	Ethanol	88JPR57
59c R = NH ₂	204(28100), 224(26100), 242 ^a (21600), 332(11200)	Ethanol	88JPR57
60a X = S, Y = N	242(6455), 327(6165)	Ethanol	78JOC1677
60b X = N, Y = S	230 ^a (8710), 275(8320)	Ethanol	77CPB2790
61a R = OMe	234 ^a (5370), 260(6760), 280(5110)	Ethanol	64JOC2121
61b R = NH ₂	244(4900), 263 ^a (2885), 272 ^a (3225), 313(6165)	Ethanol	64JOC2121
62	304(13490), 311(18620), 317(20420), 324(18620)	CHCl ₃	75JHC451
63a R = OH	243(10715), 267 ^a (2455), 327(4570)	Ethanol	71JHC441
63b R = SH	204(13800), 210 ^a (13180), 324(5755)	Ethanol	71JHC441
63c R = SMe	218(9330), 238 ^a (6455), 260(3800), 301(1280)	Ethanol	71JHC441
64	210(15135), 253 ^a (1200), 340(6760)	Ethanol	71JOC3211
65a R ¹ = H, R ² = NH ₂	270(2820), 290(3800), 297(3715), 365(5495)	pH = 7	76JCS(P1)1327
65b R ¹ = H, R ² = OH	255 ^a (3160), 282(4365), 359(4170)	pH = 7	76JCS(P1)1327
65c R ¹ = Me, R ² = OMe	210(10715), 245(5625), 283(3467), 350(2820)	Methanol	76JCS(P1)1327

^aShoulder.

7.13.5 REACTIVITY OF FULLY CONJUGATED RINGS

References to reactivity of some of the systems mentioned in CHEC-I or other reviews are given in Table 5. New or improved reactions in these systems and reactions of other systems are given in the following sections.

7.13.5.1 Electrophilic Attack at Nitrogen

The interest in the sugar derivatives of some of these systems as isosteres of purine nucleosides has led to considerable research into their direct electrophilic coupling reactions with halo-sugars or other activated sugars. Generally however, electrophilic attack occurs at several positions as is evident with 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidine (**54a**), the so-called "8-azaadenine", giving rise

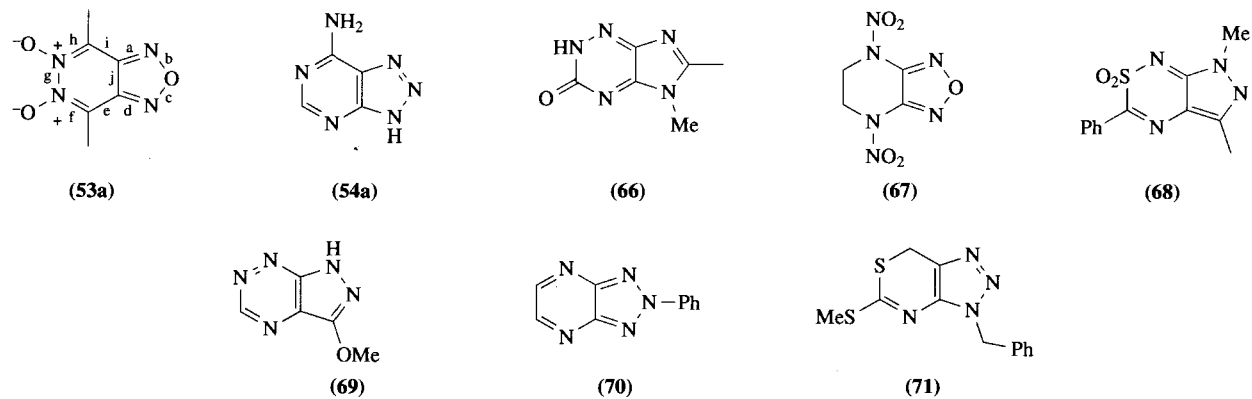


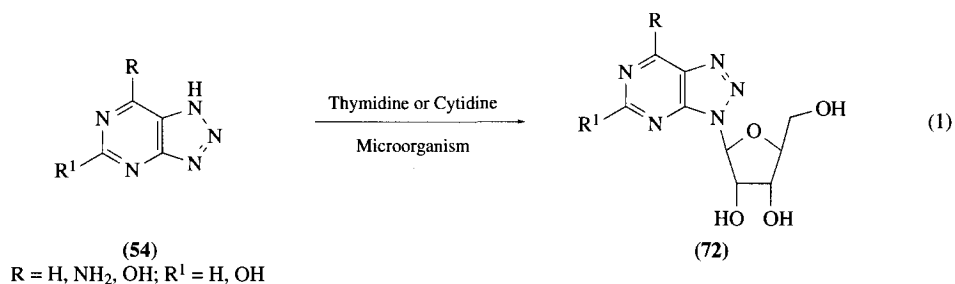
Table 4 Bond lengths determined using x-ray crystallography.

Compound	Bond lengths (Å)										Ref.
	a	b	c	d	e	f	g	h	i	j	
53a	1.259	1.451	1.404	1.185	1.386	1.371	1.617	1.319	1.365	1.498	88LA1017
54a	1.366	1.307	1.358	1.339	1.358	1.303	1.362	1.257	1.421	1.375	89AX(C)1586
66	1.395	1.310	1.386	1.356	1.301	1.393	1.394	1.349	1.298	1.424	87JCS(P2)1455
67	1.295	1.387	1.387	1.295	1.387	1.478	1.496	1.478	1.387	1.426	90AX(C)1853
68	1.339	1.369	1.339	1.376	1.369	1.278	1.805	1.583	1.356	1.403	89JHC797
69	1.355	1.394	1.302	1.434	1.344	1.341	1.341	1.356	1.357	1.388	72CB1949
70	1.338	1.343	1.330	1.351	1.350	1.327	1.409	1.316	1.356	1.393	90AX(C)1751
71	1.336	1.316	1.347	1.343	1.369	1.275	1.779	1.798	1.470	1.362	82AX(B)2299

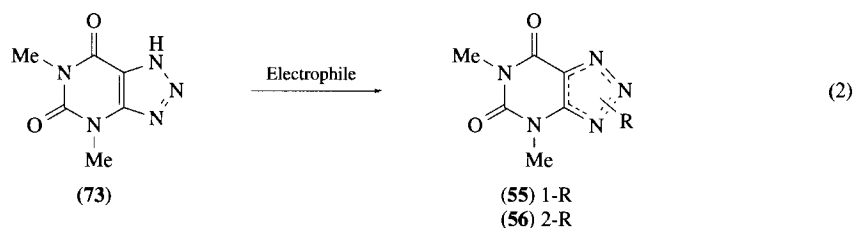
Table 5 References to reactivity of some of the systems mentioned in CHEC-I or other reviews.

Heterocyclic system	Ref.
Imidazo[4,5- <i>d</i>][1,2,3]triazines (1)	84CHEC-I(5)629
1,2,3-Triazolo[4,5- <i>b</i>]pyrazines (5)	84CHEC-I(5)878
1,2,3-Triazolo[4,5- <i>d</i>]pyrazines (6)	84CHEC-I(5)871
1,2,3-Triazolo[4,5- <i>d</i>]pyrimidines (7)	86AHC(39)117
[1,2,5]Oxadiazolo[3,4- <i>b</i>]pyrazines (8)	84CHEC-I(6)729
[1,2,5]Oxadiazolo[3,4- <i>d</i>]pyrimidines (10)	84CHEC-I(6)719
[1,2,5]Thiadiazolo[3,4- <i>b</i>]pyrazines (11)	84CHEC-I(6)732
[1,2,5]Thiadiazolo[3,4- <i>d</i>]pyridazines (12)	84CHEC-I(6)732
1,2,3-Thiadiazolo[5,4- <i>d</i>]pyrimidines (13)	84CHEC-I(6)732
[1,2,5]Thiadiazolo[3,4- <i>d</i>]pyrimidines (14)	84CHEC-I(6)732

to substitution at the 2, 3, and 4 positions <89HCA1527>. Until the early 1990s the preferred method of synthesis of such molecules was by formation of the triazole or imidazole ring with the sugar already attached. However, it has been shown that incubation of "8-azapurines" (54) with cytidine or thymidine in the presence of certain microorganisms transfers the sugar moiety to the isosterically correct position, giving compounds (72) without forming other isomers (Equation (1)) <90BRP2228479, 90GEP3840160>.



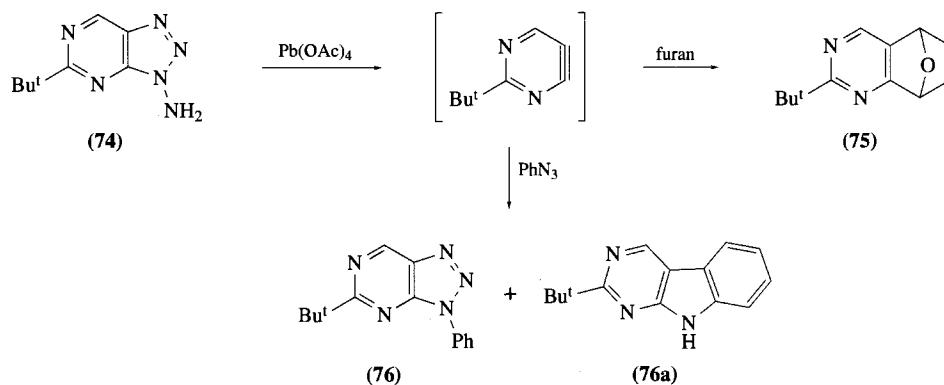
Electrophilic attack on nitrogen in derivatives of the general system (7) has been reviewed <86AHC(39)117>. Other research has shown that as expected, *N*-amination of 5-*t*-butyl-1,2,3-triazolo[4,5-*d*]pyrimidine gives a mixture of the 1, 2, and 3 isomers, the *t*-butyl group protecting the 4 and 6 nitrogens from attack <87JHC705>. The results of electrophilic reactions on 4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidine (73) (Equation (2)) are shown in Table 6.

**Table 6** Electrophilic reactions of 4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidine.

Reagent	R	Products	Ref.
MeI, K ₂ CO ₃ , DMF	Me	(55a) 40%, (56a) 60%	87BSB659
ClCH ₂ CO ₂ Et, K ₂ CO ₃ , DMF	CH ₂ CO ₂ Et	(56b)	87BSB659
Piperidine, CH ₂ O	CH ₂ NC ₅ H ₁₀	(56c)	87BSB659
Ac ₂ O	COMe	(56d)	87BSB659
PhCOCl/C ₅ H ₅ N	COPh	(56e)	87BSB659
ClCO ₂ Et/C ₅ H ₅ N	CO ₂ Et	(56f)	87BSB659

Lead tetraacetate oxidation of 3-amino-5-*t*-butyl-1,2,3-triazolo[4,5-*d*]pyrimidine (74), as in the case of 1-aminobenzotriazole, leads to a "pyrimidyne" intermediate which may be trapped using a

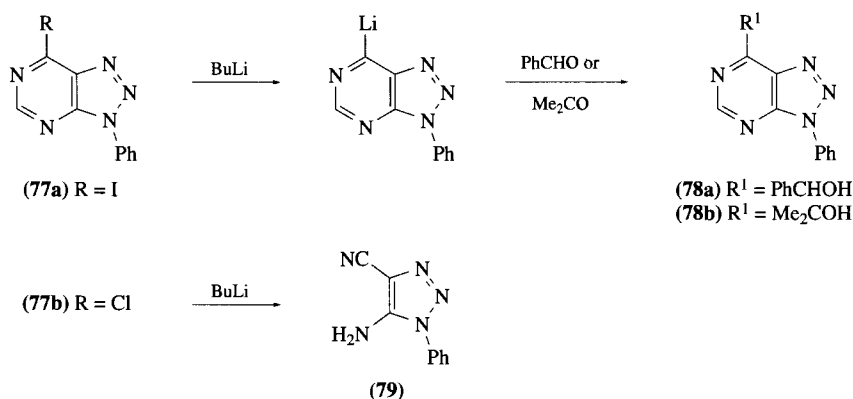
large excess of furan to give the adduct (**75**) (50%). With phenyl azide not only the expected triazole (**76**) (43%) is formed but also the loss of nitrogen followed by rearrangement forms the pyrazoloindole (**76a**) (19%) (Scheme 1) <92T10575>.



Scheme 1

7.13.5.2 Electrophilic Attack at Carbon

As in the previous section, electrophilic attack at carbon has only been mentioned in connection with the “8-azapurine” system. The iodo-compound (**77a**) is lithiated by butyllithium and the subsequent metalated derivative undergoes normal reactions with electrophiles to give compounds (**78a** and **b**) (Scheme 2). Under the same conditions of lithiation, the chloro compound (**77b**) is degraded to 5-amino-4-cyano-1-phenyltriazole (**79**) <91CPB2793>.



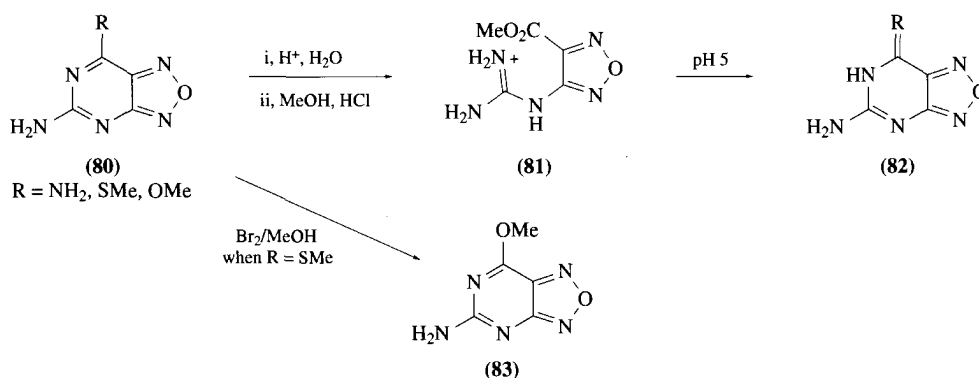
Scheme 2

7.13.5.3 Nucleophilic Attack at Carbon

In those systems where the five-membered ring contains three heteroatoms and is stable, the adjacent carbon atoms on the six-membered ring are subject to nucleophilic attack because of the reduction of electron density at these points. These reactions for 1,2,3-triazolo[4,5-*d*]pyrimidines (**7**), for [1,2,5]oxadiazolo[3,4-*d*]pyrimidines (**10**), and for [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (**14**) have been reviewed (see Table 5 for references). New reactions and reactions of other systems are discussed in the following sections.

7.13.5.3.1 [1,2,5]Oxadiazolo[3,4-d]pyrimidines (10)

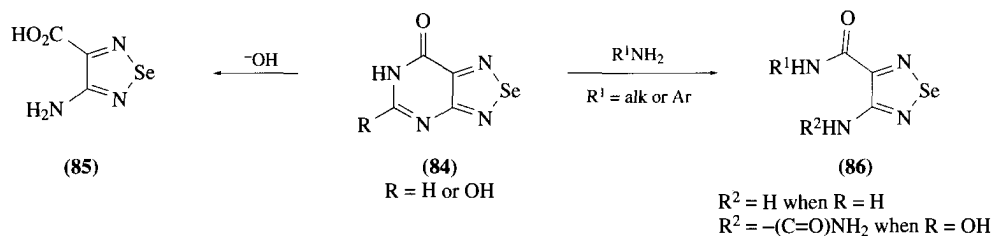
In Scheme 3 the relative ease of attack at the 7-position is demonstrated by the opening of the pyrimidine ring of the 5-amino derivatives (**80**) by aqueous acid under mild conditions, possibly assisted by the protonation of the resulting guanidine derivative. Methylation gives the ester (**81**) which recyclizes to the 7-one derivative (**82**) at pH 5 <84T879>. With derivative (**80**; R = SMe) nucleophilic displacement can take place with the weak nucleophile methanol by *in situ* oxidative activation of the leaving group to give compound (**83**) (80%) <85JOC5127>.



Scheme 3

7.13.5.3.2 [1,2,5]Selenadiazolo[3,4-d]pyrimidines (36)

As would be expected, nucleophilic attack on the derivatives (**84**) leads to ring-opening reactions with alcoholic sodium hydroxide to give the selenadiazole (**85**) and with amines to give compounds (**86**) <66BP1610>. There appears to be no tendency to recyclize, as in the case of the corresponding oxygen and sulfur heterocycles (Scheme 4).



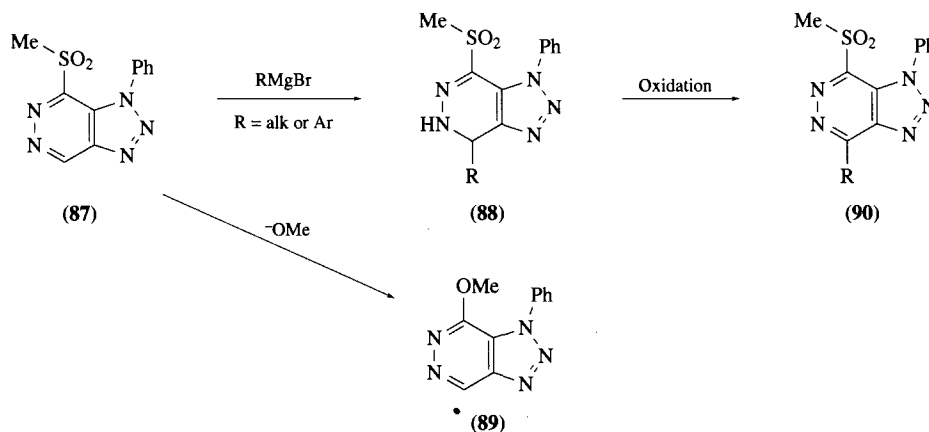
Scheme 4

7.13.5.3.3 1,2,3-Triazolo[4,5-d]pyridazines (6)

Although the methanesulfonyl derivative (**87**) undergoes normal nucleophilic displacement with methoxide ion to give compound (**89**) (77%), with a variety of Grignard reagents attack occurs at the 4-position to give the 4,5-dihydrotriazolopyridazines (**88**) in poor to moderate yields. These compounds (**88**) can be oxidized under mild conditions by potassium ferricyanide to give the fully conjugated derivatives (**90**) (Scheme 5) <87CPB514>.

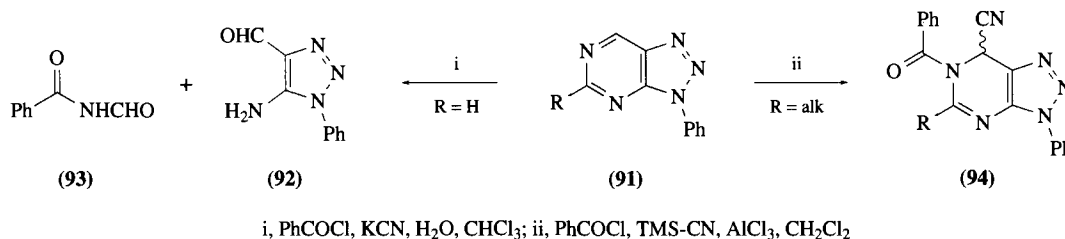
7.13.5.3.4 1,2,3-Triazolo[4,5-d]pyrimidines (7)

Using the original conditions for the formation of Reissert compounds the triazolopyrimidine (**91**; R = H) undergoes ring fission producing the triazole (**92**) and the amide (**93**) (Scheme 6). Under



Scheme 5

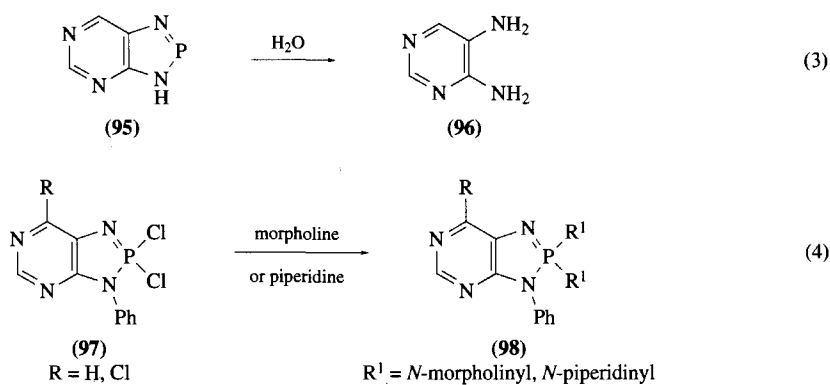
anhydrous conditions, in the presence of TMS-CN and aluminum chloride, the Reissert compounds (94) (40–96%) are formed <87CPB4803>.



Scheme 6

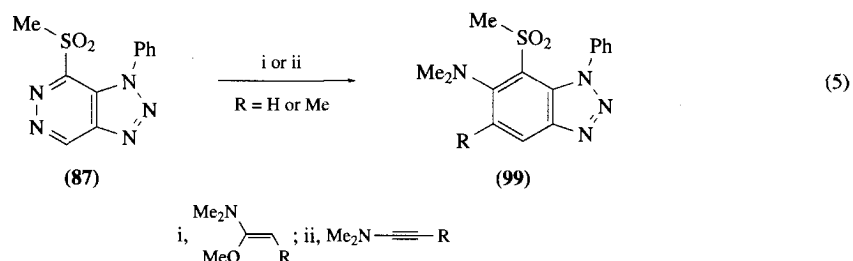
7.13.5.4 Nucleophilic Attack at Phosphorus

The presence of phosphorus in these heterocycles leads to the possibility of a nucleophilic attack at this heteroatom. In the trivalent state, as in [1,3,2]diazaphospholo[4,5-*d*]pyrimidine (95), facile hydrolysis occurs with water eliminating the phosphorus and producing the diaminopyrimidine (96) (Equation (3)) <79MI 713-01>. In the pentavalent state, as in compound (97), halogen substituents on the phosphorus atom can easily be substituted by amines without ring rupture (Equation (4)). However, the resulting compound (98) can be opened in aqueous potassium carbonate <70KGS710>.



7.13.5.5 Cycloaddition Reactions

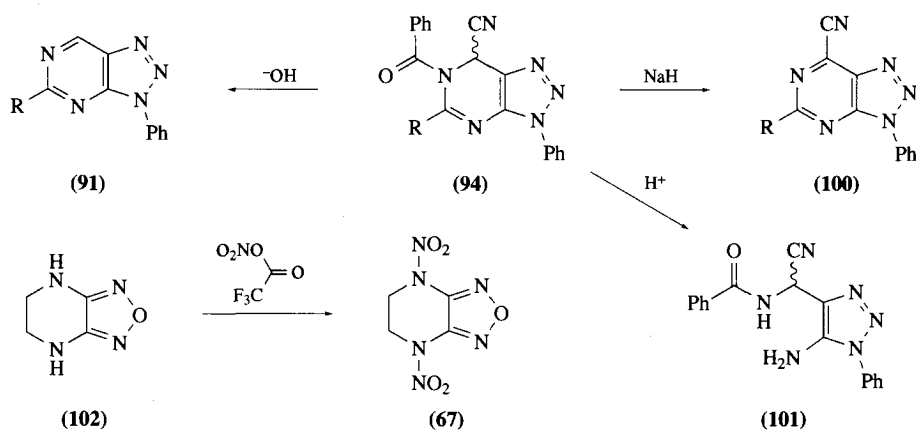
The electron-withdrawing methanesulfonyl group together with the effect of the triazole ring and the pyridazine nitrogens allows the triazolopyridazine (**87**) to act like an electron-deficient diene and to react with electron rich mono-enes with elimination of nitrogen to give the benzotriazoles (**99**) (20–50%) (Equation (5)) <87CPB2686>.



7.13.6 REACTIVITY OF NONCONJUGATED RINGS

Very little research on the reactivity of nonconjugated rings has occurred since the publication of CHEC-I and mainly concerns the conversion to a conjugated system. An example has already been given in Section 7.13.5.3.3 with the oxidation of compounds (**88**) to (**90**) (Scheme 5).

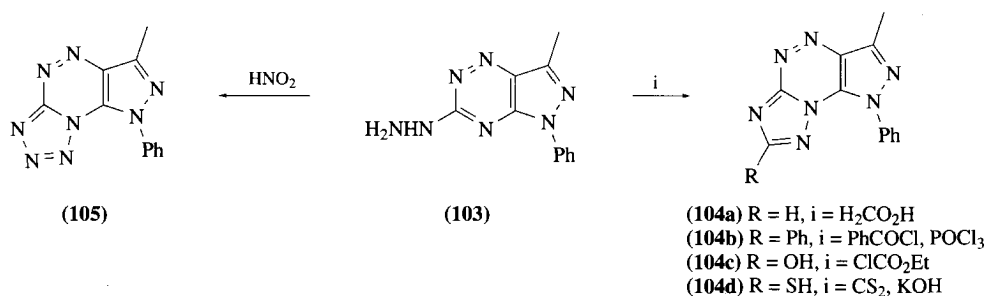
The previously described Reissert compounds (**94**) can be converted back to the original heterocycles (**91**) by sodium hydroxide or, more usefully, by sodium hydride to the nitrile substituted heterocycles (**100**) <92CPB5137>. Under acidic conditions fission of the dihydropyrimidine ring occurs to give the triazole (**101**). *N*-Nitration of the tetrahydro[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**102**) gives the explosive dinitro compound (**67**) (Scheme 7) <85JOC5123>.



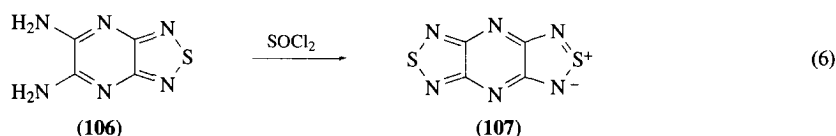
Scheme 7

7.13.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

In Scheme 8, the 3-hydrazinopyrazolo[3,4-*e*][1,2,4]triazine (**103**) has been used as a template for the build up of the pyrazolotetrazolotriazine (**105**) and a series of pyrazolotriazolotriazines (**104a–d**) <84JHC1565>. The hydrazine derivative is produced by nucleophilic displacement of the thiol (see Section 7.13.9). The 5,6-diamino[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**106**) reacts with thionyl chloride to produce the tricyclic conjugated mesomeric betaine (**107**) (Equation (6)).

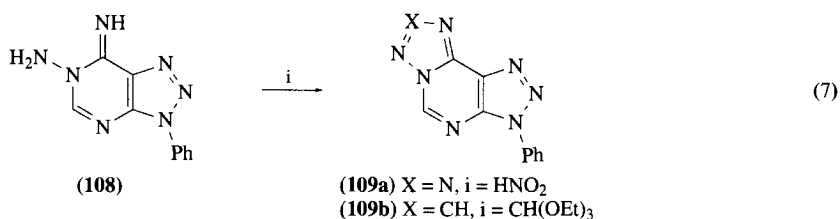


Scheme 8



7.13.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

As in the previous section a hydrazine compound has been used to build other polynitrogen heterocycles (**109a–b**). In this case, the hydrazine is incorporated into a ring as *N*-amino-1,2,3-triazolo[4,5-*d*]pyrimidine (**108**) (Equation (7)) <90CZ246>.



7.13.9 SYNTHESIS

References to the synthesis of those systems mentioned in CHEC-I are shown in Table 7. In the following subsections new routes to the above systems are described and also the methods of synthesis of new systems and systems not previously mentioned.

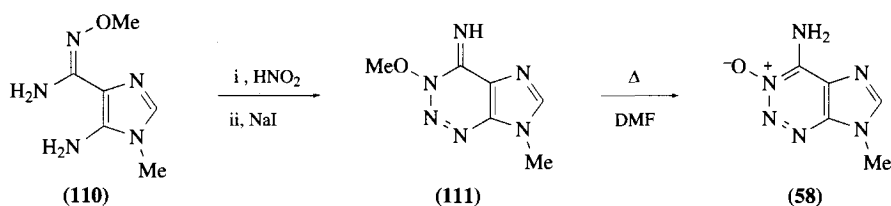
Table 7 References to the synthesis of systems mentioned in CHEC-I.

Heterocyclic system	Ref.
Imidazo[4,5- <i>d</i>][1,2,3]triazines (1)	84CHEC-I(5)644
Imidazo[4,5- <i>e</i>][1,2,4]triazines (2)	84CHEC-I(5)655
Pyrazolo[3,4- <i>e</i>][1,2,4]triazine (3)	70JCS(C)1313, 77ZN(B)430
Pyrazolo[4,3- <i>d</i>][1,2,3]triazines (4)	81JCS(P1)2387
1,2,3-Triazolo[4,5- <i>b</i>]pyrazines (5)	84CHEC-I(5)897
1,2,3-Triazolo[4,5- <i>d</i>]pyridazines (6)	84CHEC-I(5)890
1,2,3-Triazolo[4,5- <i>d</i>]pyrimidines (7)	86AHC(39)117
[1,2,5]Oxadiazolo[3,4- <i>b</i>]pyrazines (8)	84CHEC-I(6)729
[1,2,5]Oxadiazolo[3,4- <i>d</i>]pyridazines (9)	84CHEC-I(6)730
[1,2,5]Oxadiazolo[3,4- <i>d</i>]pyrimidines (10)	84CHEC-I(6)729
[1,2,5]Thiadiazolo[3,4- <i>b</i>]pyrazines (11)	84CHEC-I(6)747
[1,2,5]Thiadiazolo[3,4- <i>d</i>]pyridazines (12)	84CHEC-I(6)748
1,2,3-Thiadiazolo[5,4- <i>d</i>]pyrimidines (13)	84CHEC-I(6)746
[1,2,5]Thiadiazolo[3,4- <i>d</i>]pyrimidines (14)	84CHEC-I(6)747

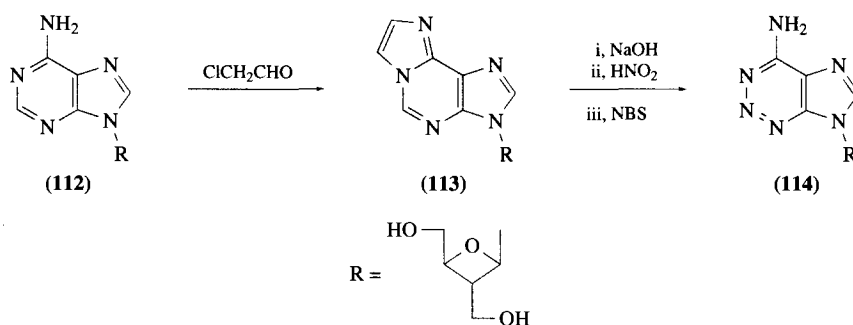
7.13.9.1 Synthesis of Azoloazines

7.13.9.1.1 Imidazo[4,5-d][1,2,3]triazines (1)

Previous syntheses of this system have been carried out exclusively by the nitrous acid cyclization of 5-aminoimidazole-4-carboxamides. An interesting variation on this theme is seen in Scheme 9 where the *O*-methyloxime (110) forms the 3-*N*-oxide (58) (50%) via the salt (111) <90H(30)329>. The 4-amino derivatives (114) are also formed from the corresponding purine derivative (112) by initially forming the tricyclic compounds (113) (see Scheme 10). The pyrimidine nucleus is now susceptible to hydrolysis, the triazine ring is formed and the additional ring is removed <91EUP416605>. This method has previously been applied to the synthesis of pyrazolo[3,4-*e*]-[1,2,4]triazines <81JCS(P1)2387>.



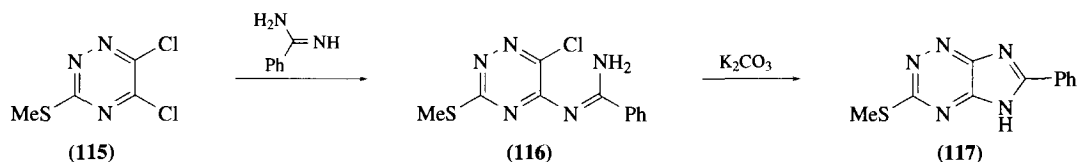
Scheme 9



Scheme 10

7.13.9.1.2 Imidazo[4,5-*e*][1,2,4]triazines (2)

The usual synthetic method for the production of this system is the reaction of a 5,6-diamino-triazine with an organic acid equivalent. In Scheme 11 the activated nitrile (115) is displaced by benzamidine to give the intermediate (116) which is cyclized by base forming the imidazotriazine (117) <85JOC2293>.

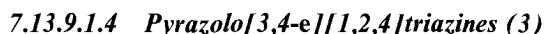


Scheme 11

7.13.9.1.3 Pyrazolo[3,4-*d*][1,2,3]triazines (15) and pyrazolo[4,3-*d*][1,2,3]triazines (4)

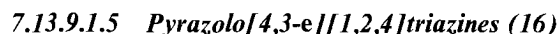
The methods of synthesis of both these systems are very similar and are almost exclusively by the treatment of the corresponding aminopyrazole carboxamide with nitrous acid (Equation (8)).

(118) $X = \text{CMe}, Y = \text{N}, R = \text{H or alkyl}, R^1 = \text{sugar}$ **(119)**
(120) $X = \text{N}, Y = \text{CMe}, R = \text{H or alkyl}, R^1 = \text{sugar}$ **(121)**

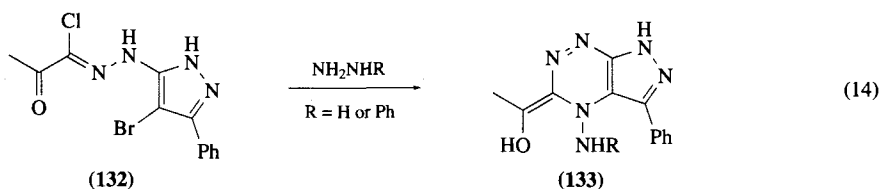
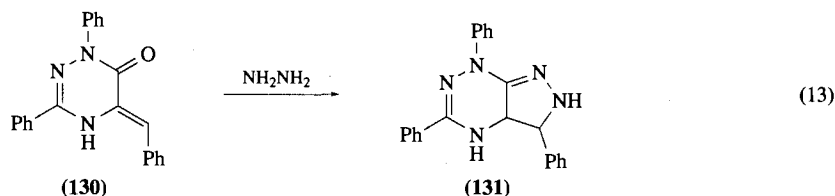
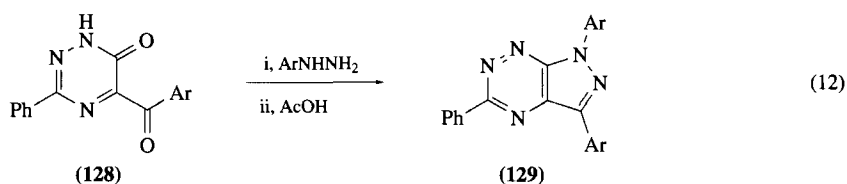


(124) $\xrightarrow{\text{i, ii}}$ (125)

i, $\text{NH}_2\text{N}=\text{C}(\text{Y})\text{NH}_2$, $\text{Y} = \text{SH}, \text{S(4)Et}, \text{N(Me)}_2$; ii, aq. K_2CO_3 or Δ

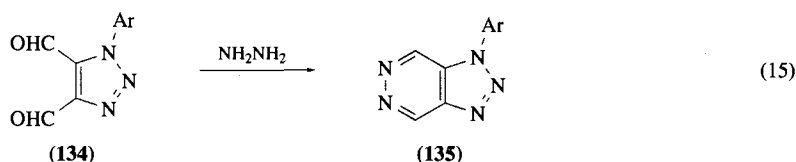


In contrast to the previous system, the azine approach is favored to produce both the fully conjugated and the tetrahydro derivatives. Acyl triazinones (**128**) condense with hydrazines (Equation (12)) to produce the fully conjugated pyrazolotriazines (**129**) <85MI 713-01>. The benzilidene triazinones (**130**) give the tetrahydro derivatives (**131**) (Equation (13)) <82JHC(B)115>. The alternative azole approach (Equation (14)) leads to the unusually substituted derivatives (**133**) (65%) <80JHC209>.



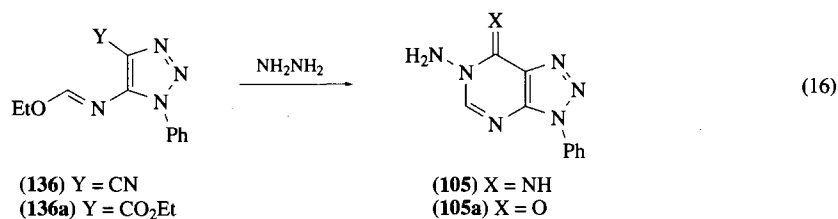
7.13.9.1.6 1,2,3-Triazolo[4,5-d]pyridazines (6)

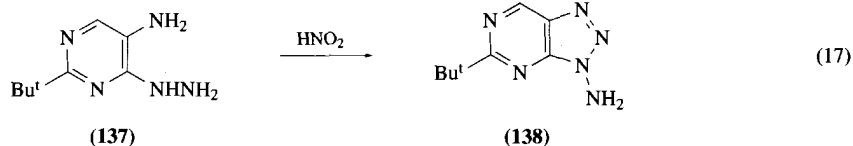
The previous approaches to this system have been by diazotization of 4,5-diaminopyridazines. The synthesis of the triazole dialdehyde (134) has made the condensation with hydrazine a feasible route to compounds of type (135) in good yields (Equation (15)) <88ZC211>.



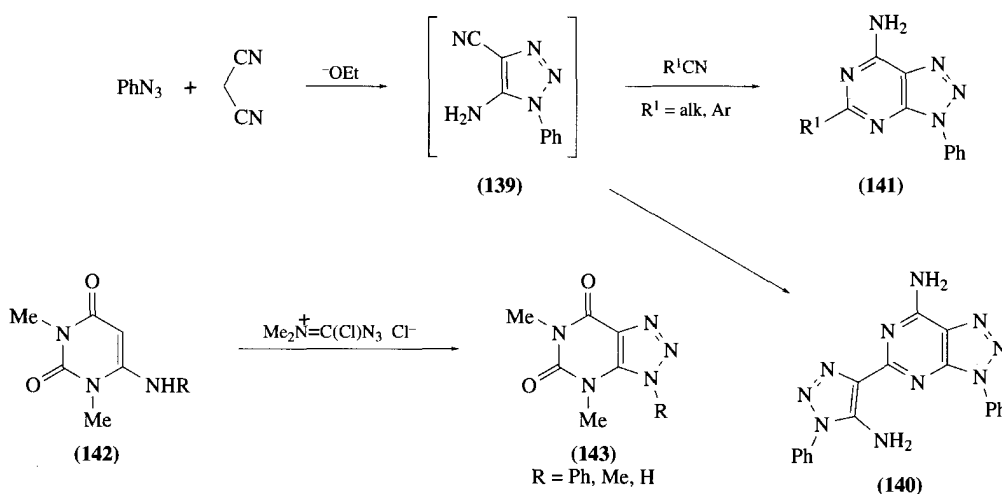
7.13.9.1.7 1,2,3-Triazolo[4,5-d]pyrimidines (7)

The many routes used to synthesize this system have been reviewed <86AHC(39)117>. Since the late 1980s, emphasis has been placed on the synthesis of *N*-amino derivatives both for the production of the reactive species "pyrimidyne" and polynitrogen heterocycles. Hydrazine insertion into the triazoles (136) (Equation (16)) produces the 6-amino derivatives (105) <88LA1107> whilst diazotization of the aminohydrazino pyrimidine (137) (Equation (17)) forms the 3-amino derivative (138) <87JHC705>.





Another field of research is concerned with the “one-pot” synthesis of this system from readily available starting materials. In Scheme 12, reaction of phenyl azide and malononitrile in the presence of sodium ethoxide leads, via the intermediate triazole (139), to the self-condensation product (140), itself a triazolopyrimidine. In the presence of other nitriles the preferred formation of the more useful compounds (141) occurs in low to moderate yields with small amounts of dimer <87JHC997>. Direct synthesis of the 5,7-dione derivatives (143) (60–90%) is achieved by the reaction of the readily available aminopyrimidinedione (142) with an azide iminium salt in dichloromethane at moderately high dilution <87JHC1493>.

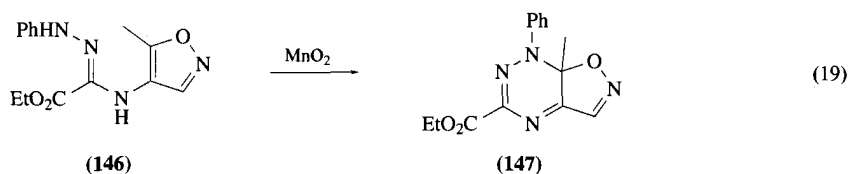
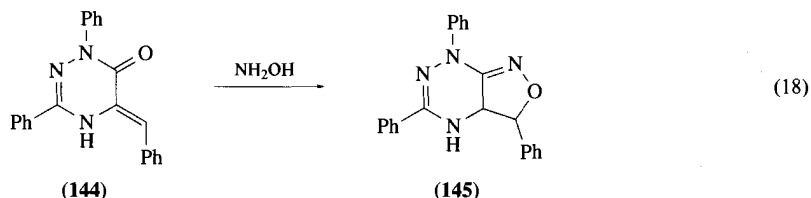


Scheme 12

7.13.9.2 Oxazoloazines and Azolooxazines

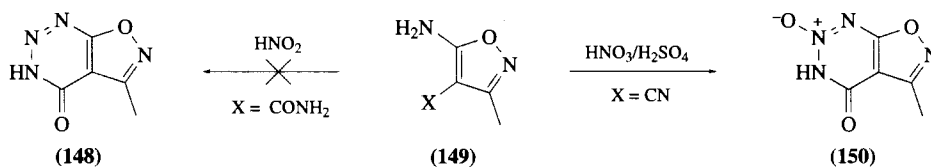
7.13.9.2.1 Isoxazolo[4,3-e][1,2,4]triazines (17) and isoxazolo[4,5-e][1,2,4]triazines (18)

Neither of these systems has been prepared in the fully conjugated state. The tetrahydroisoxazolo[4,3-e][1,2,4]triazine (145) is prepared by cyclization of the benzylidene triazinone (144) with hydroxylamine (Equation (18)) <82JCB115>. Manganese dioxide oxidation of the isoxazole (146) forms the isoxazolo[4,5-e]triazine derivative (147) (Equation (19)) <86JHC1795>.



7.13.9.2.2 Isoxazolo[5,4-d][1,2,3]triazines (19)

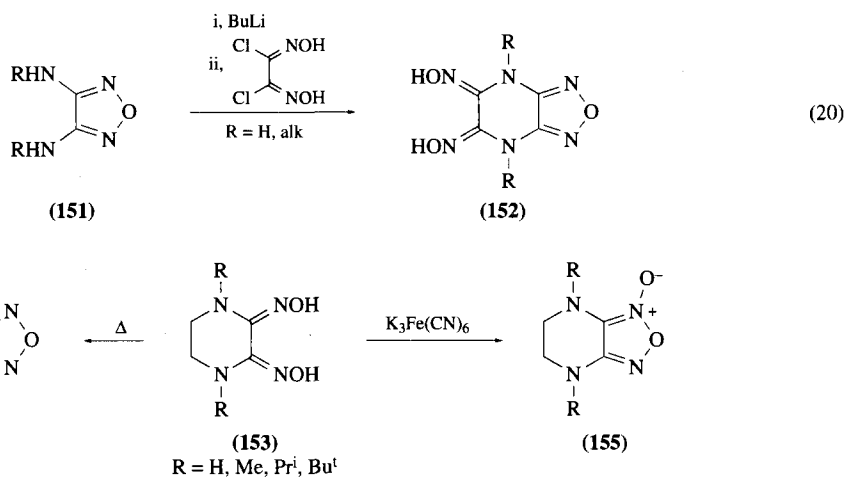
The most obvious synthesis of this system by the diazotization of the isoxazole (**149**; X = CONH₂) fails (Scheme 13). However, the use of mild nitrating conditions on compound (**149**; X = CN) produces the *N*-oxide (**150**) (16%) <88JCS(P1)1509>.



Scheme 13

7.13.9.2.3 [1,2,5]Oxadiazolo[3,4-b]pyrazines (8)

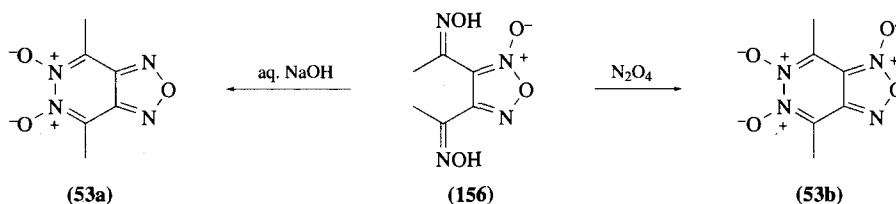
The usual method of synthesis of this system is by condensation of a diketone with 3,4-diamino-oxadiazoles (**151**). The alternative use of butyllithium followed by a bis-chlorooxime leads to the formation of the derivative (**152**) <91JHC1677> which can be cyclized to a bis(oxadiazolo)pyrazine (Equation (20)). Tetrahydro derivatives are formed from the bis-oximes (**153**) which give either the furoxan derivatives (**155**) (70–98%) by oxidation with potassium ferricyanide or the oxadiazoles (**154**) (55–70%) on heating (Scheme 14) <85JOC5123>.



Scheme 14

7.13.9.2.4 [1,2,5]Oxadiazolo[3,4-d]pyridazines (9)

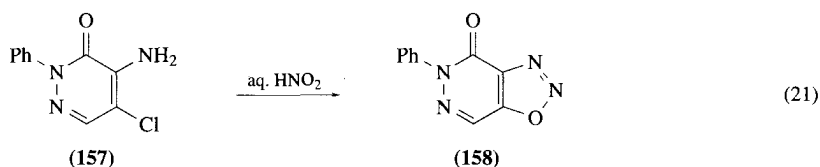
The so-called “Tryller’s” compound, shown to be the furoxan (**156**), is cyclized to the bis-*N*-oxide (**53a**) with aqueous sodium hydroxide (Scheme 15). Treatment of compound (**156**) with dinitrogen tetroxide results in the formation of the tris-*N*-oxide (**53b**) <88LA1017>.



Scheme 15

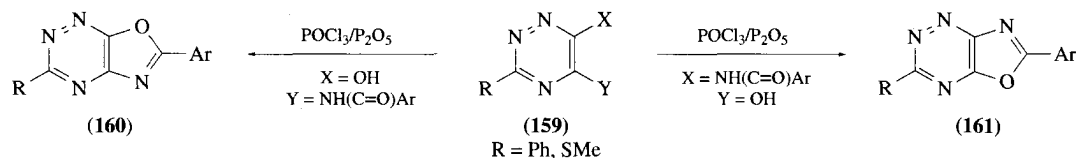
7.13.9.2.5 [1,2,3]Oxadiazolo[4,5-d]pyridazines (20)

The diazotization of the aminochloropyridazinone (**157**) induces internal nucleophilic displacement of the flanking chlorine atom in the aqueous solution. Subsequent cyclization produces the oxadiazolopyridazine (**158**) (Equation (21)) <78BEP877937>.



7.13.9.2.6 Oxazolo[4,5-e][1,2,4]triazines (21) and oxazolo[5,4-e][1,2,4]triazines (22)

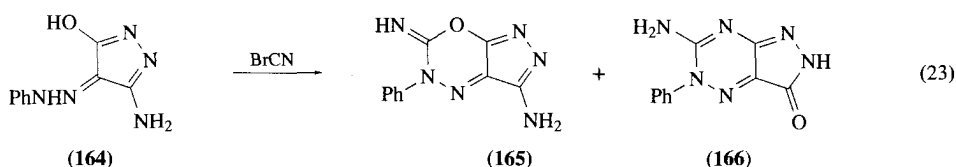
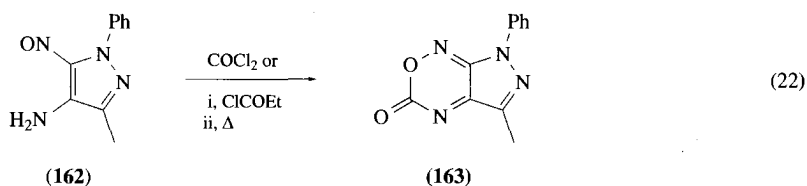
Dehydration with phosphorus oxychloride and phosphorus pentoxide of the appropriate hydroxy- and arylcarboxamido-substituted triazines (**159**) (Scheme 16) results in the formation of the oxazolo[4,5-e][1,2,4]triazines (**160**) (20–68%) or the oxazolo[5,4-e][1,2,4]triazines (**161**) (20–87%) <87AJC977>.



Scheme 16

7.13.9.2.7 Pyrazolo[4,3-e][1,2,5]oxadiazines (23) and pyrazolo[4,3-e][1,3,4]oxadiazines (24)

The pyrazolo[4,3-e][1,2,5]oxadiazin-3-ones (**163**) are formed by the action of phosgene or ethyl chloroformate on the aminonitrosopyrazoles (**162**) (Equation (22)). They have been used as intermediates in peptide synthesis <76FES70>. A pyrazolo[4,3-e][1,3,4]oxadiazine (**165**) is formed together with a pyrazolotriazine (**166**) (Equation (23)) by the reaction of the phenylhydrazone of a pyrazolone (**164**) with cyanogen bromide <85JCS(P1)1499>.

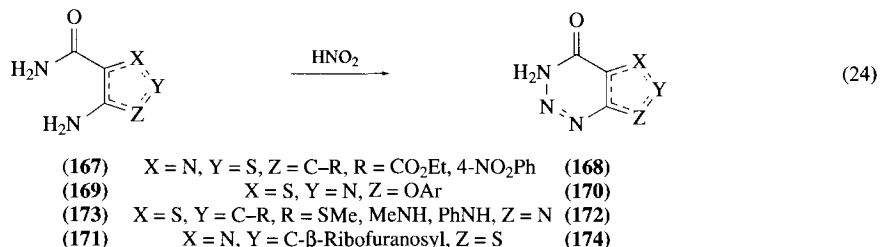


7.13.9.3 Thiazoloazines and Azolothiazines

7.13.9.3.1 Isothiazolo[4,3-d][1,2,3]triazines (25), isothiazolo[4,5-d]triazines (26), thiazolo[4,5-d][1,2,3]triazines (31), and thiazolo[5,4-d][1,2,3]triazines (33)

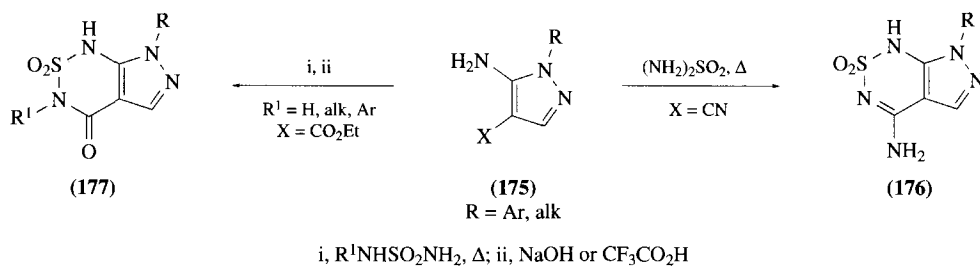
The diazotization of the appropriate aminoisothiazole or aminothiazole carboxamides (**167**), (**169**), (**171**), (**173**) (Equation (24)) leads to the formation of isothiazolo[4,3-d][1,2,3]triazine-4-ones

(168) <75ZC18, 79LA1534>, isothiazolo[4,5-*d*][1,2,3]triazine-4-ones (170) <86EUP274654>, thiazolo[4,5-*d*]-[1,2,3]triazine-4-ones (172) <84LA1994>, and thiazolo[5,4-*d*][1,2,3]triazine-4-ones (174) <85JOC1741> in good to very good yields.

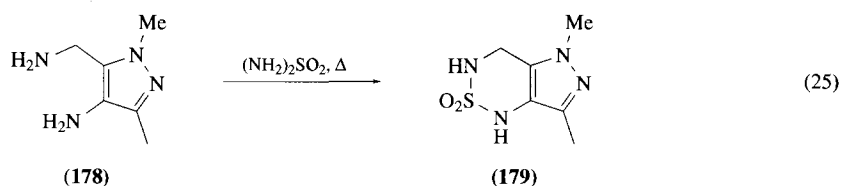


7.13.9.3.2 Pyrazolo[3,4-*c*][1,2,6]thiadiazines (28) and pyrazolo[4,3-*c*][1,2,6]thiadiazines (29)

All the recorded derivatives of these systems have the sulfur atom in the fully oxidized state, the N—SO₂—N grouping being introduced by the use of sulfamide or a substituted derivative. The 3-unsubstituted 2,2-dioxypyrazolo[3,4-*c*][1,2,6]triazines (176) and (177; R = H) are formed by heating with sulfamide. With the substituted sulfamides, cyclization of the intermediate is achieved with either alcoholic sodium hydroxide or trifluoroacetic acid in moderate yields (Scheme 17) <85S190>. In a similar synthesis (Equation (25)) the tetrahydro-2,2-dioxypyrazolo[4,3-*c*][1,2,6]thiadiazine (179) is formed from the aminopyrazole (178) <76IJC(B)766>.

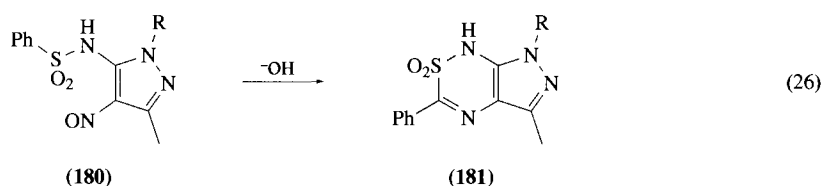


Scheme 17



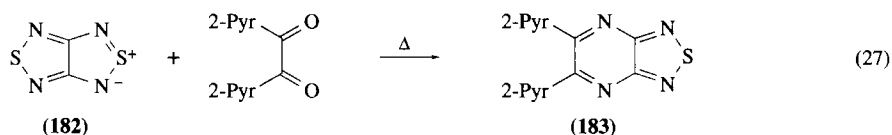
7.13.9.3.3 Pyrazolo[3,4-*c*][1,2,5]thiadiazines (27)

The activation of the benzyl CH₂ by the flanking sulfamoyl group in the pyrazole (180) induces cyclization on to the nitroso group in the presence of base to give the 2,2-dioxypyrazolo[3,4-*c*][1,2,6]triazines (181) (60–70%) (Equation (26)) <89JHC797>.



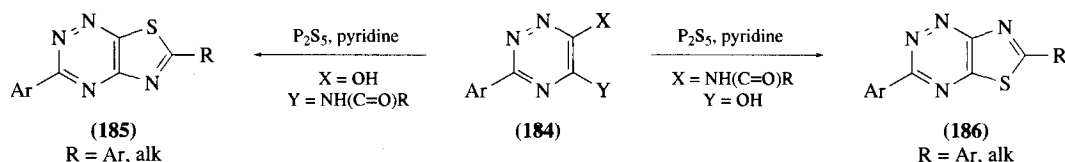
7.13.9.3.4 [1,2,5]Thiadiazolo[3,4-b]pyrazines (11)

The standard synthetic method for the synthesis of this system is the condensation of diaminothiadiazoles with 1,2-diketones. A variation on this method, as shown in Equation (27), is the use of the thiadiazolothiadiazole (182) <84BRP2122492>.



7.13.9.3.5 Thiazolo[4,5-e][1,2,4]triazines (32) and thiazolo[5,4-e][1,2,4]triazines (34)

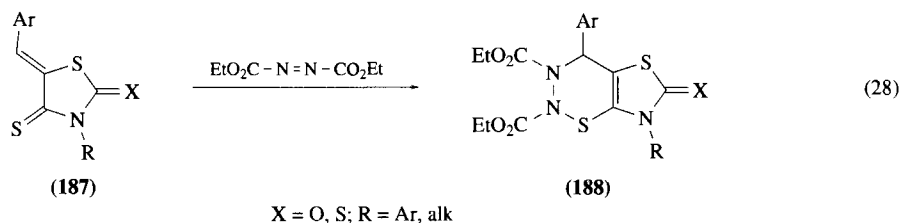
Cyclization of the appropriate hydroxycarboxamidotriazine (184) with phosphorus pentasulfide and pyridine (Scheme 18) produces the thiazolo[4,5-e][1,2,4]triazines (185) (37–97%) <87AJC693> or the thiazolo[5,4-e][1,2,4]triazines (186) (20–97%) <87AJC491>.



Scheme 18

7.13.9.3.6 Thiazolo[5,4-e][1,2,3]thiadiazines (30)

The Diels–Alder addition of diethyl azodicarboxylate to the thiazole (187) leads to the formation of the tetrahydro derivative (188) (Equation (28)) <89SUL23>.



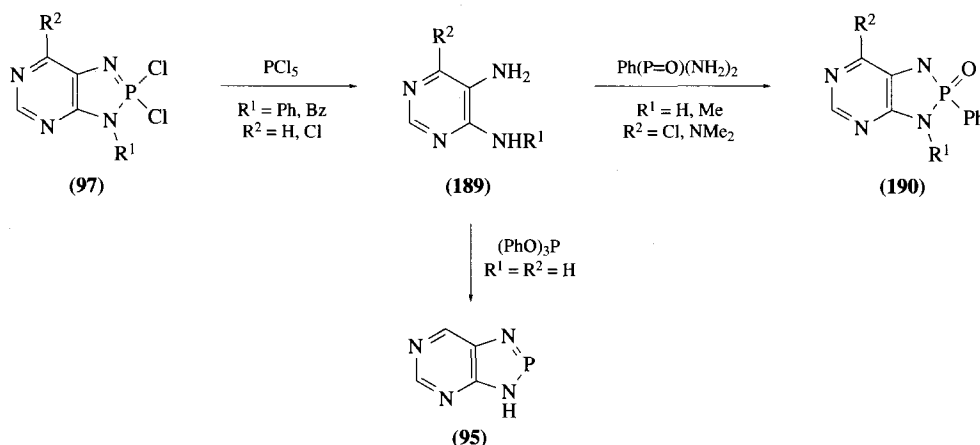
7.13.9.4 Synthesis of Other Systems

7.13.9.4.1 [1,3,2]Diazaphospholo[4,5-d]pyrimidines (35)

Phosphorus in both the 3 and 5 coordination states can be introduced into this class of heterocycle (Scheme 19). The diaminopyrimidine (189; R¹ = R² = H) reacts with triphenyl phosphite to give the phosphorus(III) derivative (95) <79MI 713-01>. By the use of phosphorus pentachloride the dichloro compounds (97) are formed <70KGS710>, whilst phenyl phosphonamide produces the derivatives (190) <63CI(L)819>.

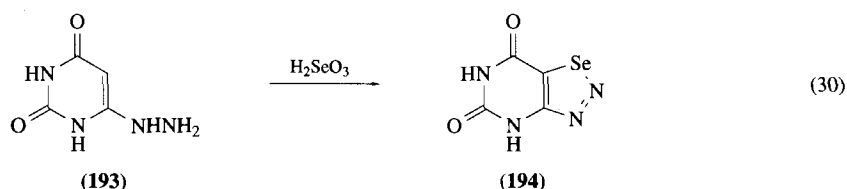
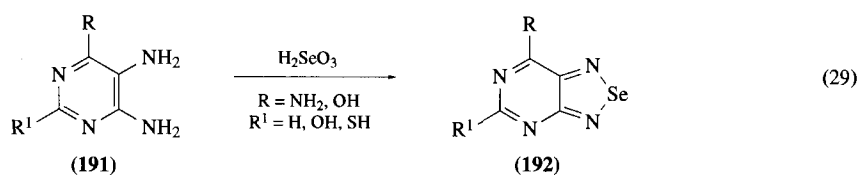
7.13.9.4.2 [1,2,5]Selenadiazolo[3,4-d]pyrimidines (36) and 1,2,3-selenadiazolo[4,5-d]pyrimidines (37)

In both these systems selenium is introduced into the ring using an aqueous solution of selenous acid. Thus, the diaminopyrimidines (191) produce the [1,2,5]selenadiazolo[3,4-d]pyrimidine



Scheme 19

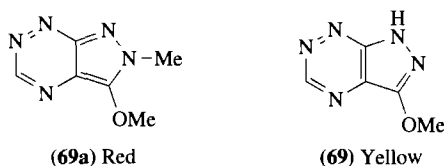
derivatives **(192)** (50–65%) (Equation (29)) <08CB3957, 58JOC1940, 67JHC96>. The hydrazino-pyrimidine dione **(193)** forms the 1,2,3-selenadiazolo[4,5-*d*] pyrimidine-5,7-dione **(194)** (Equation (30)) <86KGS1138>.



7.13.10 IMPORTANT COMPOUNDS AND APPLICATIONS

7.13.10.1 Natural Products

Surprisingly, in the systems considered in this chapter, which are related to the purines by inclusion of one more heteroatom, no natural products have been found. Only two natural products which fall within the scope of this chapter, the pyrazolo[4,3-*e*][1,2,4]triazines **(69)** and **(69a)**, have been isolated <72CB1949>. These compounds are the fluorescent principle in the monocellular organism, *Pseudomonas fluorescens*. The yellow pigment is a precursor of the red pigment and the shift in the spectrum is due to the formation of an “*o*-quinonoid” structure on methylation.



7.13.10.2 Pharmaceutical Applications

Since the publication of CHEC-I, the main interest in these systems as pharmaceuticals, as indicated by the patent literature, is as antiviral agents. Work has concentrated mostly on the derivatives of "8-azapurines", the 1,2,3-triazolo[4,5-*d*]pyrimidines of type (72) <86EUP334361, 90BRP2228479, 92JMC3991> or of type (72) where the furanose sugar is replaced by a simulation of this group <89EUP298467, 91EUP410660>. Such systems mimic the purine nucleosides and are incorporated into viral DNA. The "2-azapurines", imidazo[4,5-*d*][1,2,3]triazine derivatives of type (114), have also been utilized <91EUP416605>.

Other claims are: the isothiazolo[4,5-*d*][1,2,3]triazine-4-ones (170) for the treatment of gout and eschemia <86EUP274654>, the 3-aryl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-7-ones as antiallergics <90EUP349239>, 3-dialkylaminoethyl-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-diones as bronchodilators <88EUP272226>, and the 5-aryl-1,2,3-triazolo[4,5-*d*]pyrimidines as antihypertensives <88USP4923874>.

7.13.10.3 Agrochemical Applications

In all the reported agrochemical applications a sulfur heterocycle is used. The 2,2-dioxo-pyrazolo[3,4-*c*][1,2,5]thiadiazines <90MI 713-01> and the 5,6-dipyridyl[1,2,5]thiadiazolo[3,4-*b*]pyrazine (183) <84BRP2122492> are fungicidal. The 2,2-dioxopyrazolo[3,4-*c*][1,2,6]thiadiazines are herbicides <80USP4182623>.

7.13.10.4 Miscellaneous Applications

The 4,7-dinitro-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-*b*]pyrazine (67) has been tested as an explosive <85USP4539405>. The "o-quinonoid" nature of the [1,2,5]thiadiazolo[3,4-*d*]pyridazines results in their 4,7-diaryl derivatives being used as fluorescent yellow-red dyes for organic polymers <89JAP(K)02263868>.

7.14

Bicyclic 5-6 Systems: Six and Seven Heteroatoms

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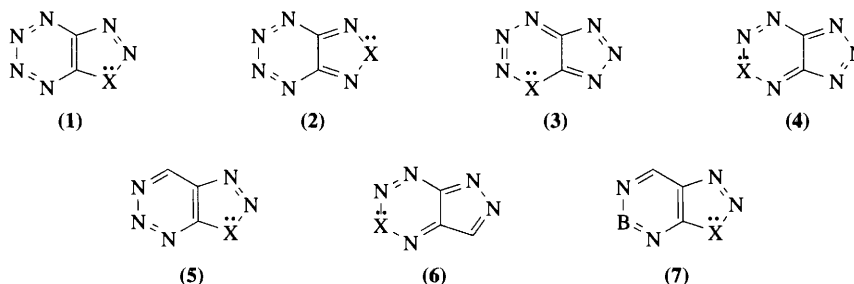
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7.14.1 INTRODUCTION

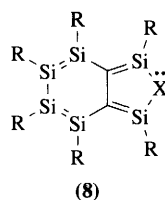
This chapter reviews the chemistry of those bicyclic 5-6 heterosystems which have a total of six or seven ring heteroatoms but do not have ring junction heteroatoms. The study of this area of chemistry is in its infancy.

The subject has not previously been reviewed, and all literature up to June 1994 has been included.

The general structures (1)–(4) show the possible fully conjugated 10 π -electron systems with seven heteroatoms. If the heteroatom X is restricted to O, S, or NR then 12 systems are possible but a derivative of only one has been reported. Possible six heteroatom systems (2:4 or 3:3) can be derived from the structures (1)–(4) by systematically replacing each nitrogen atom in turn by carbon. Inspection of structures (1)–(4) reveals that there are 21 discrete pyridine-type nitrogen atoms: the total number of possible six heteroatom systems, with X restricted to O, S or NR, is therefore 63 (21×3). Representatives of only two of these possible systems have been reported and these belong to the subgroups having the general structures (5) and (6). In addition, one example of a boraza heterocycle of the general type (7) has been reported.



If the heteroatoms in the ring are silicon rather than nitrogen, then a family of sila derivatives, e.g. (8) is defined, of which two examples are known. The combination of both silicon and nitrogen extends the scope, and one example of this type has been reported.



Extension of the analysis to parent heterocycles having 12 π -electrons again leads to a large number of possible systems of which only three examples are known. These are compounds with the general structure (9; X = O, S, NR), and they are derivatives of the generalized 12 π -electron system (10).

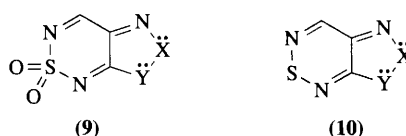
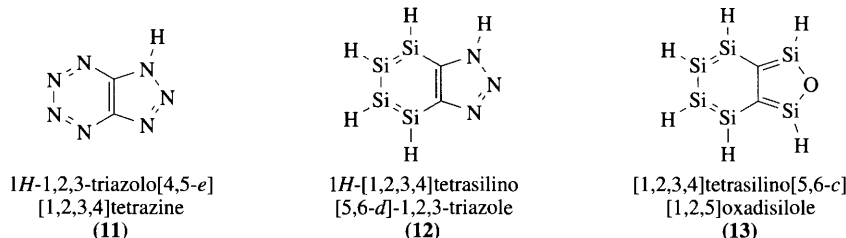
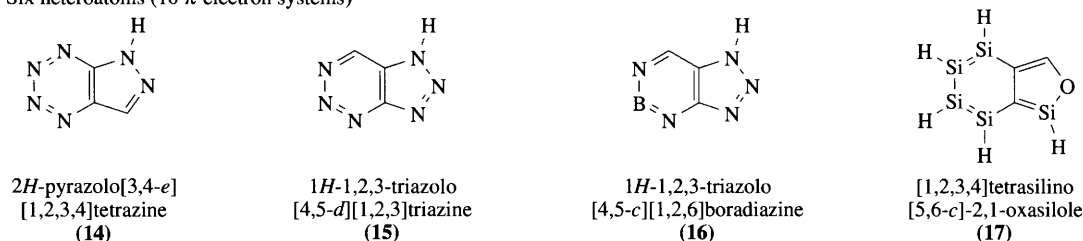


Figure 1 shows the structures of the parent heterocyclic systems of the known compounds which are discussed in this review together with their systematic names. All compounds are named as derivatives of these parent structures (11)–(20). Limited reference was made to the chemistry of derivatives of the systems (15) and (19) in the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(5)853, 84CHEC-I(6)715, 84CHEC-I(6)729>.

Seven heteroatoms (10 π -electron systems)



Six heteroatoms (10 π -electron systems)



Six heteroatoms (12 π -electron systems)

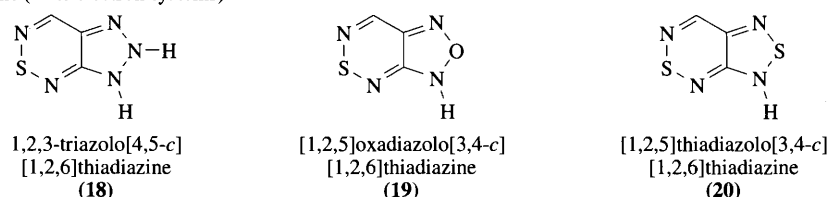


Figure 1 Parent fully conjugated ring systems of known compounds.

7.14.2 THEORETICAL METHODS

There is little to report on the application of molecular orbital calculations to this class of heterocycles. Yamaguchi *et al.* <91AX(C)590> have observed that the semiempirical AM1 method underestimates the double bond character of the bicyclic C—C bond in 2-phenyl-1,2,3-triazolo[4,5-*e*][1,2,3,4]tetrazine (24) (Table 1). The AM1 method has been reported to overestimate bond lengths in other nitrogen heterocycles <92JCS(P1)2779>, and this is possibly attributable to an overestimation of core-repulsion energies for multinitrogen systems.

Ab initio calculations using an STO-3G basis set on the 7-amino-1,2,3-triazolo[4,5-*c*][1,2,6]thiadiazine-5,5-dioxide tautomers (21)–(23) and the derived anions and dianion together with related *N*-methyl and *N*-amino derivatives have been reported <92H(34)1399>. Calculated geometries are in reasonable agreement with data available from x-ray crystallography (Section 7.14.3.1.2). The sulfur atom is calculated to be out of the plane defined by the other ring atoms in agreement with experimental findings. Relative stabilities and dipole moments of various isomers, including the tautomers (21)–(23) (Figure 2), were calculated and compared with experimental findings. Calculated relative stability in the gas phase differs from that observed in solution probably due to the effect of solvation (see also Section 7.14.3.5).

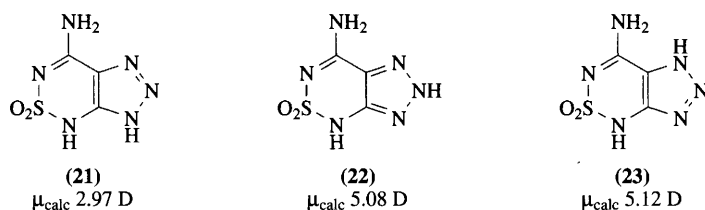


Figure 2 Calculated dipole moments.

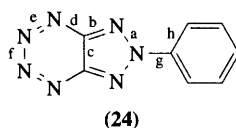
7.14.3 EXPERIMENTAL STRUCTURAL METHODS

7.14.3.1 X-ray Diffraction

7.14.3.1.1 1,2,3-Triazolo[4,5-e][1,2,3,4]tetrazines (11)

The structure of 2-phenyl-1,2,3-triazolo[4,5-e][1,2,3,4]tetrazine (**24**) (Table 1) has been determined at room temperature <88CC1608> and at 153 K <91AX(C)590>. This structure is of particular interest because of the high nitrogen content of the parent ring system ($\text{C}_2\text{HN}_7 = \text{ca } 80\% \text{ N}$) and its relationship to the unknown 1,2,3,4-tetrazine ring system. Selected structural parameters derived from the low temperature diffraction study are shown in Table 1. The heterocyclic system is essentially planar and co-planar with the 2-phenyl substituent. The geometry suggests a heteroaromatic structure with extensive delocalization of π -electrons together with attractive interactions between the *ortho*-hydrogen atoms of the phenyl substituent and the nitrogen atoms at positions 1 and 3. There is good agreement between the observed geometry and that determined for 2-phenyl-1,2,3-triazolo[4,5-*b*]pyrazine <90AX(C)1751>.

Table 1 X-ray structure of 2-phenyl-1,2,3-triazolo[4,5-e][1,2,3,4]tetrazine.



Bond lengths (Å)								Ref
<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>	<i>h</i>	
1.335	1.344	1.383	1.332	1.323	1.388	1.444	1.385	91AXC590

Bond and torsion angles (deg.)							
<i>ab</i>	<i>bc</i>	<i>cd</i>	<i>de</i>	<i>ef</i>	<i>ag</i>	<i>gh</i>	<i>agh</i>
101.3	108.9	122.8	115.5	122.3	120.6	117.9	1.4

7.14.3.1.2 1,2,3-Triazolo-, [1,2,5]oxadiazolo- and [1,2,5]thiadiazolo[1,2,6]thiadiazines (18)–(20)

A wealth of x-ray diffraction data is available on this group of heterocycles and selected structural parameters are summarized in Table 2. In all the systems having generalized structures (**25**) or (**26**), the six-membered ring has an envelope conformation with the sulfur atom out of the plane (*ca* 0.2–0.5 Å) defined by the other five atoms. The five-membered rings are planar and quasiplanar with the nonsulfur atoms of the six-membered ring. The study of compound (**25**; $\text{R}^1 = \text{NH}_2$, $\text{R}^2 = \text{H}$,

X = NH) and its monohydrate showed it to crystallize as the *2H,4H* tautomer. The structure of the 1,7-diamino derivative (**26**; R¹ = NH₂, R² = H, X = NNH₂) has been confirmed by x-ray diffraction, and the essential structural features are similar to those in the isomeric structures (**25**).

Table 2 X-ray structure of bicyclic 1,2,6-thiadiazine-1,1-dioxide derivatives (**25**) and (**26**).



Structure	Derivative			Bond lengths (Å)											Ref.
	R ¹	R ²	X	a	b	c	d	e	f	g	h	i	j	k	
(25)	NH ₂	H	NH	1.32	1.34	1.40	1.33	1.35	1.45	1.33	1.58	1.67	1.38	1.44	75AX(B)1427
(25)	NH ₂	H	NH ^a	1.31	1.34	1.39	1.33	1.33	1.44	1.33	1.59 ₅	1.64	1.38	1.43	75AX(B)2445
(25)	NH ₂	Me	NMe	1.31	1.35	1.39	1.33	1.35	1.43	1.33	1.60	1.67	1.38	1.43	82AX(B)2296
(25)	NH ₂	H	O	1.37	1.30	1.42	1.31	1.41	1.46	1.32	1.59	1.67 ⁵	1.36	1.43	75AX(B)2310
(25)	O ⁻ K ⁺	Me	S	1.64	1.31	1.42	1.31	1.66	1.48	1.35	1.56	1.67	1.38	1.43	84AX(C)80
(26)	NH ₂	H	NNH ₂	1.32 ₅	1.36	1.37	1.35	1.33	1.44	1.33	1.60	1.65	1.38	1.43	92H(34)1399

Structure	Derivative			Bond angles (deg.)											Ref.
	R ¹	R ²	X	ab	bc	cd	de	ae	cf	fg	gh	hi	ij	cj	
(25)	NH ₂	H	NH	103.0	108.8	109.6	102.0	116.6	121.8	119.6	124.8	108.2	117.1	124.5	75AX(B)1427
(25)	NH ₂	H	NH ^a	102.8	108.1	109.8	101.9	117.3	122.3	118.8	122.0	106.2	114.9	123.0	75AX(B)2245
(25)	NH ₂	Me	NMe	102.8	108.4	110.1	101.8	116.9	122.3	119.4	123.7	106.4	114.7	124.4	82AX(B)2296
(25)	NH ₂	H	O	105.4	109.8	109.5	104.0	111.5	122.3	119.3	124.6	106.4	117.3	122.4	75AX(B)2310
(25)	O ⁻ K ⁺	Me	S	106.8	113.9	115.1	105.6	98.6	123.1	1117.3	127.3	108.7	119.5	122.7	84AX(C)80
(26)	NH ₂	H	NNH ₂	117.7	103.3	109.9	107.8	107.3	123.1	118.2	122.3	105.7	115.1	123.4	92H(34)1399

^aMonohydrate.

7.14.3.1.3 [1,2,3,4]Tetrasilino[5,6-c][1,2,5]oxadisiloles (**13**)

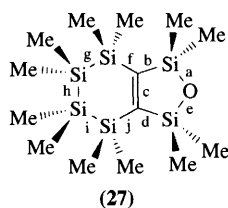
The structure of the duodecamethyl derivative (**27**) has been reported <93OM803>, selected geometrical parameters are shown in Table 3 and confirm the structure as a bicyclic alkene.

7.14.3.2 NMR Spectroscopy

Proton NMR data for a number of derivatives has been reported. These spectra are useful for identifying conventional ring substituents (e.g. Ph, Me, NH₂), but are not diagnostic of the bicyclic ring systems and are not documented here.

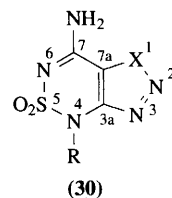
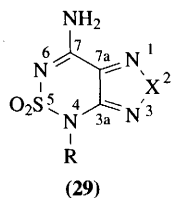
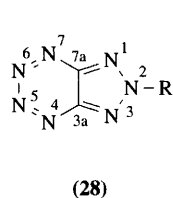
Carbon-13 and nitrogen-15 NMR spectra of several systems have been reported <86MRC444, 91JCS(P1)2045, 92H(34)1399> and details are given in Table 4. The singlet at 145.7 ppm due to the C-3a and C-7a carbon atoms in the ¹³C NMR spectrum of 2-phenyl-1,2,3-triazolo[4,5-d][1,2,3,4]tetrazine (**28**; R = Ph) (Table 4) is consistent with its symmetrical polyaza structure, and corresponds well with the C-3a shifts in the systems (**29**) and (**30**). In compounds (**29**; R = Me, X = O or S) the C-3a signal appears as a quartet (*J* (¹³C¹H) = 3.1 Hz) due to long range coupling with the *N*(4)-Me substituent, thus allowing an unequivocal assignment of the C-3a and C-7 signals.

In the ¹⁵N NMR spectrum of the systems (**29**; X = O or S) the chemical shifts of the nitrogens at position 1 correspond reasonably well with the nitrogen signals in benzo[*c*]-1,2,5-oxadiazole (−35.6 ppm) and benzo[*c*]-1,2,5-thiadiazole (49.1 ppm). The nitrogens at position 3 appear to be deshielded by the effect of nitrogen at position 4. In the thiadiazine rings the “pyridine-like” nitrogens at

Table 3 X-ray structure of 1,1,2,2,3,3,4,4,5,5,7,7-duodecamethyl-1,2,3,4-tetrasilino[5,6-*c*][1,2,5]oxadisilol (27).

Bond lengths (Å)										Ref.
<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>	<i>h</i>	<i>i</i>	<i>j</i>	
1.64	1.88	1.37	1.89	1.64	1.89	2.34	2.33	2.33	1.89	93OM803

Bond and torsion angles (deg.)							
<i>ab</i>	<i>ae</i>	<i>bc</i>	<i>cd</i>	<i>de</i>	<i>cf</i>	<i>cj</i>	<i>fg</i>
100.6	115.2	112.0	111.6	100.5	127.5	127.5	115.5
<i>gh</i>	<i>hi</i>	<i>ij</i>	<i>fcj</i>	<i>bcj</i>	<i>bcd</i>		
107.3	104.5	111.9	2.7	168.0	3.5		

Table 4 Carbon-13 and nitrogen-15 NMR chemical shifts.

Structure	Derivative		Carbon-13 Chemical shifts (ppm) ^a				Ref.
	<i>R</i>	<i>X</i>	<i>C</i> -3a	<i>C</i> -7	<i>C</i> -7a	<i>C</i> (Me)	
(28)	Ph		145.7		145.7		91JCS(P1)2045
(29)	H	NH	148.4	155.1	120.8		92H(34)1399
(29)	Me	NMe	151.8	154.3	121.1	38.7 & 40.3	92H(34)1399
(29)	H	O	152.7	150.1	134.4		86MRC444
(29)	Me	O	154.2	150.0	135.2	31.6	86MRC444
(29)	Me	S	156.6	152.4	133.8	30.6	86MRC444
(30)	H	NNH ₂	150.0	151.8	108.8		92H(34)1399

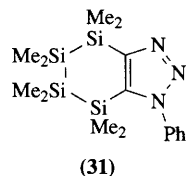
^aChemical shifts expressed in ppm from TMS.

Nitrogen-15 Chemical shifts (ppm) ^b							
<i>R</i>	<i>X</i>	<i>N</i> -1	<i>N</i> -2	<i>N</i> -3	<i>N</i> -4	<i>N</i> -6	<i>N</i> (NH ₂)
(29)	H	NH	53.4		269.2		281.9
(29)	Me	NMe	51.7	136.5	84.0	279.0	278.4
(29)	H	O	-35.7		6.6	270.3	173.9
(29)	Me	O	-37.9		7.6	276.4	181.8
(29)	Me	S	32.6		98.8	258.4	188.8
(30)	H	NNH ₂	78.6	15.8	69.2	268.5	184.6
							283.4 & 298.7

^bChemical shifts expressed in ppm from MeNO₂.

position 6 appear within the range 158–190 ppm, and the “pyrrole-like” nitrogens at position 4 are at higher field and in the range 258–279 ppm.

Silicon-29 and carbon-13 spectra have been reported for the silicon heterocycles (27) and (31) and fully support the assigned structures <92OM1009>.



7.14.3.3 Mass Spectrometry

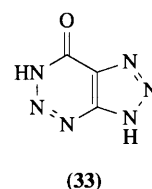
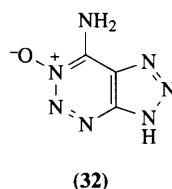
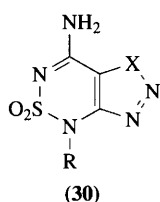
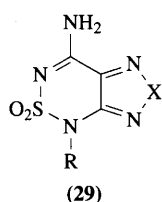
High resolution mass spectrometry (HRMS) confirmed the constitution of the silicon heterocycles (27) and (31). The molecular ion ($M^{\cdot+}$) of compound (31) (m/z 388) shows fragment ions at m/z 373 ($M^{\cdot+} - \text{Me}$) and m/z 315 ($M^{\cdot+} - (\text{Me} + \text{SiMe}_2)$); the molecular ion of compound (27) (m/z 375) shows fragment ions at m/z 347 ($M^{\cdot+} - \text{N}_2$) and m/z 332 ($M^{\cdot+} - (\text{N}_2 + \text{Me})$). Information on the mass spectra of other molecules which fall within the scope of this chapter have not been reported.

7.14.3.4 IR and UV Spectroscopy

Significant IR studies have not been reported. Substantially more data is available on UV spectra and the spectra of simple systems are summarized in Table 5. The UV spectra of a number of glucosyl and ribosyl derivatives having the general structure (29) have also been reported <82JHC305, 84MI 714-01>.

The derivatives (29; $R = \text{H}$) are acidic (pK_a ca 1–3), and only at high pH is the UV spectrum of

Table 5 Ultra-violet spectra.



Structure	Derivative		Solvent (pH)	λ_{max} (nm)(log ϵ)	Ref.
(29)	H	NH	H ₂ O (1)	225(4.0), 242(3.9), 292(3.8)	84MI 714-01
(29)	H	NPh	H ₂ O	202(3.2), 249(3.2), 253(3.0)	77JHC427
(29)	H	NMe	H ₂ O	225(4.0), 250(3.9), 293(3.9)	84MI 714-01
(29)	H	O	H ₂ O(–2)	265(3.7)	76JHC793
			H ₂ O(4)	265(3.6), 335(3.3)	
			H ₂ O(14)	285(3.5), 335(3.4)	
(29)	H	S	H ₂ O (1)	223(3.9), 310(3.7)	79JMC944
			H ₂ O (7.4)	232(3.0), 285(3.4), 357(3.6)	
			H ₂ O (12)	232(4.0), 285(3.4), 357(3.6)	
(29)	Me	S	H ₂ O	233(4.3), 281(4.0), 325(4.1)	84MI 714-01
(30)	H	NNH ₂	H ₂ O	210(3.8), 222(sh), 245(3.7), 322(3.7)	92H(34)1399
(32)			H ₂ O (2)	218(–), 245(–), 277(–), 362(–)	60JA3189
			H ₂ O (5)	225(–), 241(–), 276(–), 348(–)	
			H ₂ O (12.5)	221(–), 240(sh), 280(sh), 370(–)	
(33)			0.1NHCl	264(3.8)	61JOC2396
			H ₂ O (7)	278(3.7)	
			0.1 N NaOH	259(3.6), 294(3.9)	

the neutral molecule obtained. The similarity of the spectrum of the unsubstituted derivative (**29**; R = H, X = NH) at pH 1 and that of the dimethyl derivative (**29**; R = Me, X = NMe) suggests that, in aqueous solution, the most stable tautomer (**29**) is that which is also observed in the solid state (Section 7.14.3.1.2). On the basis that the UV spectrum of the unsubstituted thiadiazolo [1,2,6]thiadiazine (**29**; R = H, X = S) at pH 1 is different to its *N*-methyl derivative (**29**; R = Me, X = S), it has been suggested that this molecule exists in solution as the 3-*H* tautomer. This may be the case but the supporting evidence is weak <84MI 714-01>.

7.14.3.5 Dipole Moments

No dipole moment measurements have been reported but calculated values (*ab initio*) for some molecules including the tautomers (**21**)–(**23**) have been determined (Figure 2) <92H(34)1399>. The energetically preferred tautomer has been shown to have structure (**22**) by x-ray crystallography, UV, and NMR methods, although the tautomer (**21**) was calculated to be the lowest in energy. It was concluded that, as in the case of nitroimidazoles <89NJC151>, solvation favors the tautomers with the largest dipole moment, (e.g. (**22**)). The alternative tautomer (**23**) was calculated to have a much higher energy, and solvation energy is presumably not sufficient to favor its formation.

7.14.4 THERMODYNAMIC ASPECTS

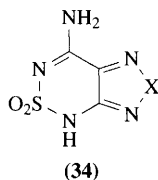
Too little is known about this area of heterocyclic chemistry to offer any meaningful generalizations on boiling points, melting points, solubilities, or chromatographic behavior.

The geometry of the triazolo[4,5-*e*][1,2,3,4]tetrazine (**24**) (Section 7.14.3.1.1) is consistent with aromatic stabilization of the rings but, as might be expected for a heterocycle with a high nitrogen content, it decomposes explosively upon heating or impact <91JCS(P1)2045>. Similarly, the triazolotriazine (**33**) (Table 5) is reported to undergo explosive decomposition on heating <61JOC2396, 66JMC733>.

Using an expert computer program developed to identify high explosives, the heat of formation of the 4,6-dioxide of [1,2,5]oxadiazolo[3,4-*e*][1,2,3,4]tetrazine (**2**; X = O) has been calculated <92MI 714-01>.

The [1,2,6]thiadiazine-5,5-dioxide derivatives of general structure (**34**) (Table 6) are acidic compounds due to a combination of the stabilizing effects of the sulfone function and the aza-conjugation. Measured pK_a values are tabulated in Table 6. The first pK_a values of the triazolo[1,2,6]thiadiazine-5,5-dioxide (**34**; X = NH) and the *N*-phenyl derivative (**34**; X = NPh) suggests that the thiadiazine proton of the former molecule is the most acidic. However, this view has been revised on the basis of quantum mechanical calculations, which suggest that the triazole proton is the most acidic <92H(34)1399>. The thiadiazolo[1,2,6]thiadiazole-5,5-dioxide (**34**; X = S) has comparable acidity to the *N*-phenyl derivative (**34**; X = NPh) but the oxadiazolo [1,2,6]thiadiazole-5,5-dioxide (**34**; X = O) is significantly more acidic, and this can be attributed to the greater electronegativity of oxygen.

Table 6 pK_a Values.

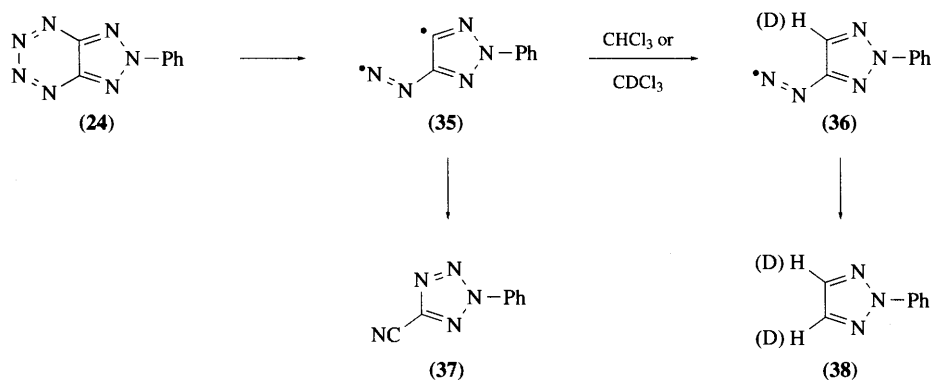


<i>X</i>	pK_a (1)	pK_a (2)	Ref.
NH	2.26	8.70	77JHC427
NPh	3.21		77JHC427
O	1.68	12.96	76JHC793
S	3.2		79JMC944

7.14.5 REACTIVITY OF FULLY CONJUGATED RINGS

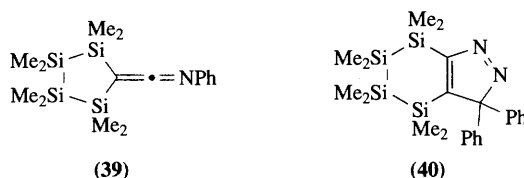
7.14.5.1 Thermal Decomposition

The triazolotetrazine (**24**) decomposes in CH_2Cl_2 or CHCl_3 solution at room temperature with loss of nitrogen to give the 5-cyanotetrazole (**37**) and the 1,2,3-triazole (**38**). In CDCl_3 solution deuterium is incorporated at the 4 and 5 positions of the triazole product (**38**), and a mechanism involving the radical intermediates (**35**) and (**36**) has been proposed (Scheme 1) <88CC1608, 91JCS(P1)2045>.



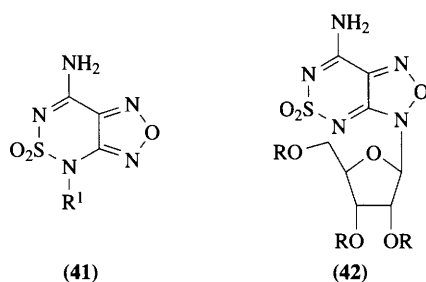
Scheme 1

Upon heating to 300°C the 1,2,3,4-tetrasilino[5,6-*d*]-1,2,3-triazole (**31**) rearranges with loss of nitrogen to give the ketenimine (**39**) in quantitative yield. In a similar reaction the derivative (**40**), which is not isolated, gives the corresponding allene <92OM1009, 93OM803>.

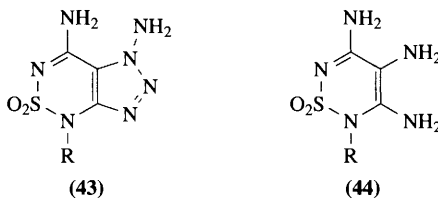


7.14.5.2 Electrophilic Attack at Nitrogen

Alkylation of the oxadiazolo[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide (**41**; $\text{R}^1 = \text{H}$) using 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl bromide and mercuric cyanide is reported to give the 3-ribofuranosyl derivative (**42**; $\text{R} = \text{PhCO}$) (12%) as the minor product in addition to the 4-substituted derivative (**41**; $\text{R}^1 = 2,3,5\text{-tri-}O\text{-benzoyl-}\beta\text{-D-ribofuranosyl}$) (64%) (see Section 7.14.6.1) <82JHC305>.



N-Amination of the triazolothiadiazine (**22**) using *o*-mesitylenesulfonylhydroxylamine under alkaline conditions resulted in formation (30%) of the 1-amino derivative (**43**). The structure of this product has been confirmed by x-ray crystallography (Table 2) <92H(34)1399>.



7.14.5.3 Reduction

The 7-amino[1,2,5]oxadiazolo[1,2,6]thiadiazine 5,5-dioxides (**41**) can be reduced, either catalytically using Pd/C or chemically using Zn dust in acetic acid, to the 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxides (**44**) in good yield <76JHC793, 77MI 714-01, 78MI 714-01, 81H(16)525, 82JHC305>.

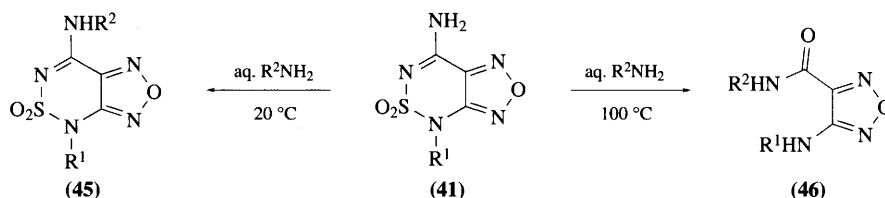
7.14.6 REACTIVITY OF NONCONJUGATED RINGS

7.14.6.1 Electrophilic Attack at Nitrogen

Alkylations of derivatives with the general structure (**29**; R = H) using various reagents, including dimethyl sulfate and glucopyranosyl bromides, have been reported. The product is usually the 4-substituted derivative, (e.g. **29**; R = Me). The triazolothiadiazines (**29**; R = H, X = NH) give 2,4-dialkylated products (**29**; X = NR). In the case of the oxadiazolothiadiazine (**29**; R = H, X = O), a small amount of 3-alkylation has also been observed (see Section 7.14.5.2) <77MI 714-01, 78MI 714-01, 82JHC305, 84MI 714-01>.

7.14.6.2 Nucleophilic Attack at Carbon

Treatment of the derivatives (**41**) with aqueous solutions of primary amines at room temperature results in transamination (**41** → **45**) (Scheme 2). Under more vigorous conditions, ring opening and hydrolysis occur giving the furazan derivatives (**46**). The products (**45**) and (**46**) can be rationalized as being formed by alternative fragmentations of a common tetrahedral intermediate generated by nucleophilic attack by the amine at position 7 <77MI 714-01, 83H(20)2351>.

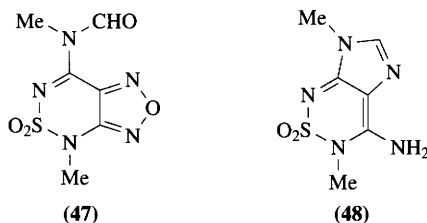


Scheme 2

In a similar manner, reaction of the derivatives (**41**; R¹ = H, Me) with sodium hydroxide gives the corresponding 7-hydroxy-[1,2,5]oxadiazolo[3,4-*c*][1,2,5]thiadiazine 5,5-dioxides, as sodium salts, and the 3-aminofurazan-4-carboxylic acids <83H(20)2351>.

7.14.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Formylation of the oxadiazolothiadiazine (**45**; $R^1 = R^2 = \text{Me}$), using formic acid/acetic anhydride gives the *N*-formyl derivative (**47**) which upon reduction (Zn/AcOH) and subsequent heating gives the imidazo[1,2,6]thiadiazine (**48**) <77MI 714-01, 81H(16)525>. This reaction (**47**) $\rightarrow$ (**48**) occurs via a 4,5-diamino-1,2,6-thiadiazine 1,1-dioxide, (*cf* (**44**) Section 7.14.5.3) which is not isolated.



7.14.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Standard transformations of substituents such as, for example, deprotection of sugars are not reported here. No reactions in which the heterocyclic system plays an influential role in determining the product have been described.

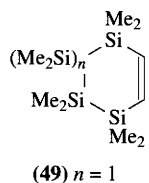
7.14.9 RING SYNTHESSES FROM TWO COMPONENTS

The syntheses of the diverse systems covered by this chapter are discussed in the same order as their parent structures are presented in Figure 1 (see Section 7.14.1).

7.14.9.1 Seven Heteroatoms (10π)

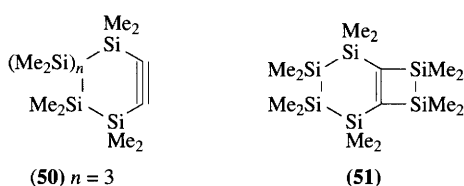
7.14.9.1.1 [1,2,3,4]Tetrasilino[5,6-d]-1,2,3-triazoles (**12**)

1,3-Dipolar cycloaddition of phenylazide to octamethyl-1,2,3,4-tetrasilacyclohex-5-yne (**49**) in hexane solution at room temperature gives a quantitative yield of the crystalline adduct (**31**) <92OM1009, 93OM803>.



7.14.9.1.2 [1,2,3,4]Tetrasilino[5,6-c][1,2,5]oxadisiloles (**13**)

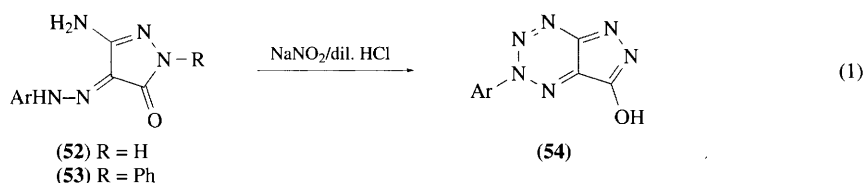
The derivative (**27**) (mp $48-94^\circ\text{C}$) has been prepared in low yield ($\leq 2.5\%$) either by heating the alkyne (**49**) in boiling decane or by irradiation (254 nm) of a hexane solution of the alkyne (**50**) in the presence of excess ($6\times$) Et_3SiH . Both routes are considered to involve oxidation of the intermediate (**51**) <92OM1009, 93OM803>.



7.14.9.2 Six Heteroatoms (10 π)

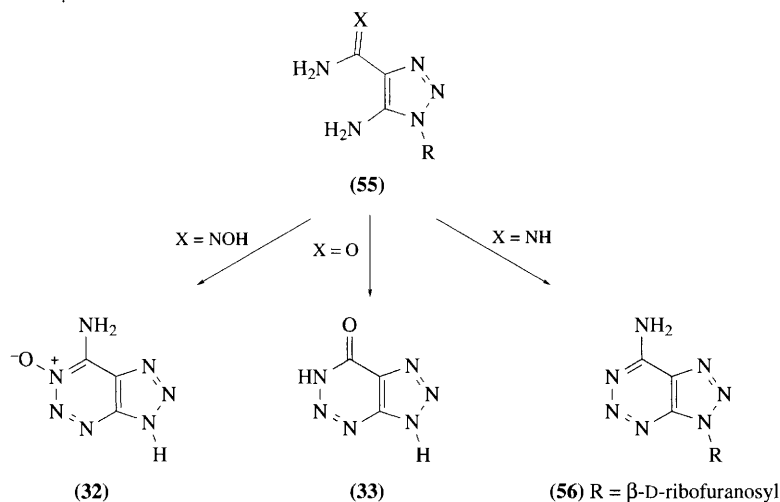
7.14.9.2.1 Pyrazolo[3,4-e][1,2,3,4]tetrazines (14)

The derivatives (**54**; Ar = Ph, *p*SO₃HC₆H₄) have been obtained as crystalline products in good yield by diazotization of the amines (**52**) (Equation (1)). The intermediate diazonium salts could not be isolated <79ZN(B)275, 80MI 714-01>. Using a similar approach, but starting from the amines (**53**), 2,5-diaryl derivatives have been obtained <93MI 714-01>.



7.14.9.2.2 1,2,3-Triazolo[4,5-d][1,2,3]triazines (15)

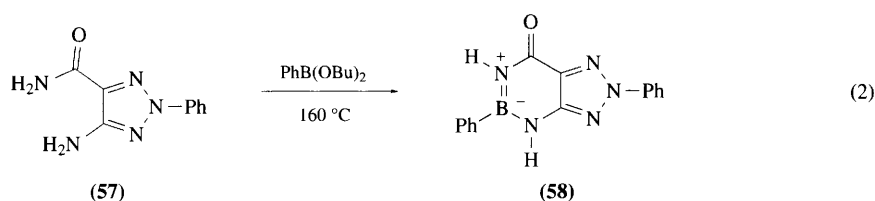
The derivatives (**32**), (**33**), and (**56**) have been prepared by cyclization of the diazonium salts of the appropriate 5-amino-1,2,3-triazoles (**55**) (Scheme 3). 2,8-Diazaadenine-1-*N*-oxide (**32**) is formed in 60% yield from the amidoxime (**55**; X = NOH, R = H), which is made by hydrolysis of 8-azaadenine-1-*N*-oxide <60JA3189>. 2,8-Diazahypoxanthine (**33**) was obtained as a dihydrate in good yield by diazotization of the carboxamide (**55**; X = O, R = H). The intermediate diazonium salt could be isolated and cyclized rapidly under alkaline conditions <61JOC2396, 66JMC733>. 2,8-Diazaadenosine (**56**) is formed in low yield by diazotization of the carboxamidine (**55**; X = NH, R = β -D-ribofuranosyl) <72JMC182>.



Scheme 3

7.14.9.2.3 1,2,3-Triazolo[4,5-c][1,2,6]boradiazines (16)

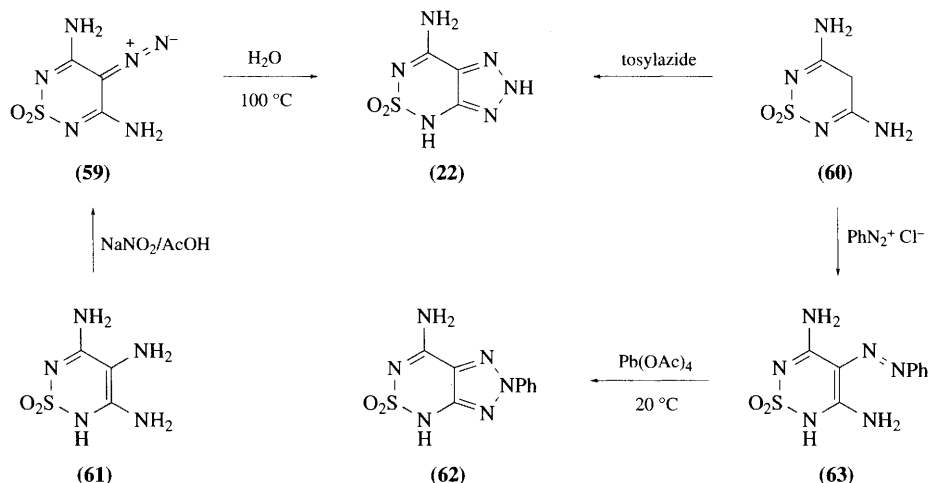
Reaction of the amine (**57**) with dibutylphenylboronate (PhB(OBu)₂) at 160°C has been reported to give the crystalline derivative (**58**) in 23% yield <61JA2708, B-64MI 714-01> (Equation (2)).



7.14.9.3 Six Heteroatoms (12 π)

7.14.9.3.1 1,2,3-Triazolo[4,5-c][1,2,6]thiadiazines (18)

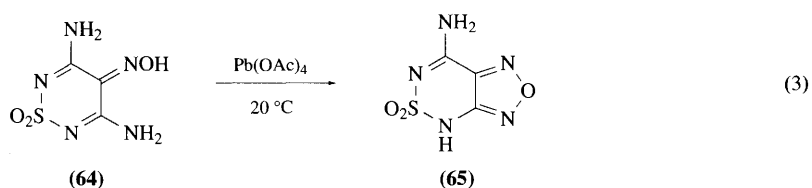
The derivative (22) has been prepared in two ways (Scheme 4). The diazo compound (59), made by diazotization of the 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide (61), cyclizes upon heating in water to give the bicyclic heterocycle (22) in 80% yield. Alternatively, the same product (22) has been obtained by treatment of the 3,5-diamino derivative (60) with tosylazide. With phenyldiazonium chloride, the diamine (60) gives the diazo compound (63) which, upon oxidation with lead tetraacetate, gives the 2-phenyl derivative (62). Attempts to oxidize the corresponding *m*-Cl and *p*-NO₂ phenyl compounds failed <77JHC427, 77MI 714-01>.



Scheme 4

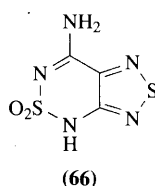
7.14.9.3.2 [1,2,5]Oxadiazolo[3,4-c][1,2,6]thiadiazines (19)

Lead tetraacetate oxidation of the oxime (64) in glacial acetic acid at room temperature gives the yellow crystalline derivative (65) in good yield (Equation (3)) <76JHC793, 76MI 714-01, 77MI 714-01>.



7.14.9.3.3 [1,2,5]Thiadiazolo[3,4-c][1,2,6]thiadiazines (20)

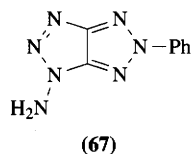
Compound (66) has been obtained in 57% yield by heating 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide (61) with *N*-thionylaniline (PhNSO) in pyridine solution at reflux temperature for three hours <79JMC944>.



7.14.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

7.14.10.1 1,2,3-Triazolo[4,5-*e*][1,2,3,4]tetrazines (11)

2-Phenyl-1,2,3-triazolo[4,5-*e*][1,2,3,4]tetrazine (**24**) has been prepared in 81% yield by lead tetraacetate oxidation of the 1-amino-5-phenyltriazolotriazole (**67**) in CH_2Cl_2 solution at 0°C . Reddish flakes of this unstable product were obtained after chromatography at -30°C <88CC1608, 91JCS(P1)2045>.



7.14.11 APPLICATIONS

No useful applications have been reported for the molecules described in this chapter. Because of the relationship of the parent bicyclic ring system to that of purines, a limited number of investigations of biological activity have been reported <72JMC182>. The triazolo[4,5-*d*]triazine (**33**) (2,8-diazahypoxanthine) has been reported to cause moderate inhibition of tumor growth in mice <65MI 714-01, 66JMC733> and to be a competitive inhibitor of uricase <73BP2237>. 3-(2,3,5-Tri-*O*-benzoyl- β -D-ribofuranosyl)-7-amino[1,2,5]oxadiazolo[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide (**42**; R = PhCO) has been reported to show "interesting" cytostatic activity against HeLa cells <84MI 714-01>.

7.15

Bicyclic 6–6 Systems: Two Heteroatoms 1 : 1

STEPHEN P. STANFORTH

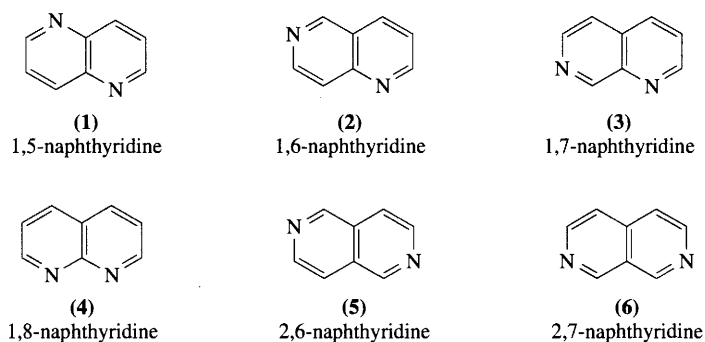
University of Northumbria at Newcastle, UK

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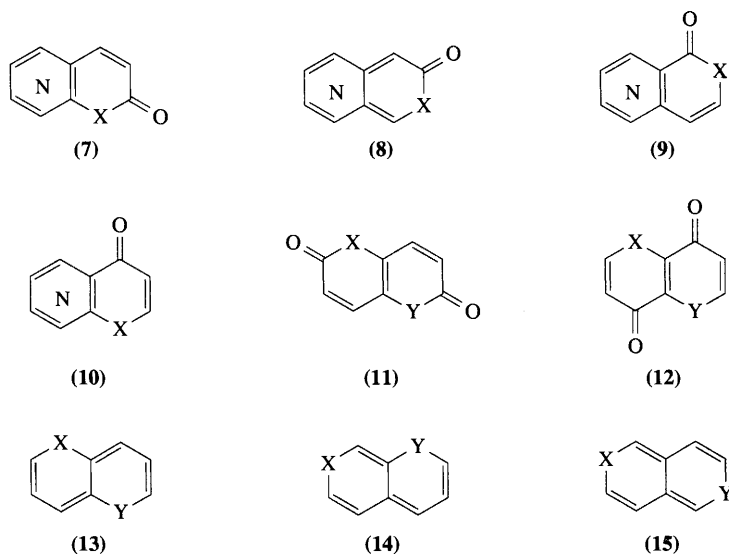
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7.15.1 INTRODUCTION

This chapter provides an update of the six isomeric naphthyridines (1)–(6), which were considered in detail in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and broad coverage of other 6-6 heterocyclic systems which were not considered to any significant extent in CHEC-I (84CHEC-I(2)581). The enormous volume of literature relating to 6-6 heterocycles inevitably requires selectivity regarding the types of systems that can be discussed in a chapter of this length, and consequently benzo derivatives of 6-6 systems have not been included in the main text, however some representative examples of important molecules in this category are given in Section 7.15.12.



The range of heterocyclic systems can be appreciated by considering the fusion of two appropriate monocyclic heterocycles to produce a bicyclic molecule. Thus, fusion of two pyridine rings in all possible combinations gives the naphthyridines (1)–(6). These six heterocycles are all 10π systems without any exocyclic conjugation. Fusion of pyridine with 2-pyridone will give 12 naphthyridone isomers represented by the general formulae (7)–(9) ($X = \text{NH}$). These 12 heterocycles are examples of 12π systems with exocyclic conjugation. Fusion of pyridine with 4-pyridone gives four isomeric naphthyridones represented by the general formula (10; $X = \text{NH}$) which are similarly 12π systems with exocyclic conjugation. Nineteen isomeric naphthyridiones can be generated by fusion of two 2/4-pyridones and diones (11; $X = \text{NH}$) and (12; $X = \text{NH}$) are two representative examples. These dione derivatives are 14π systems with exocyclic conjugation.



When sulfur and oxygen are considered as heteroatoms in fully conjugated 6-6 systems without exocyclic conjugation, the general structures (13)–(15) can be drawn. These structures are however, 12π systems and formally anti-aromatic, consequently, heterocycles possessing oxygen and sulfur as heteroatoms with two fully conjugated rings are invariably associated with exocyclic conjugation, for example, heterocycles (7)–(12) (X, Y = O, S).

An extensive range of heterocyclic systems with either one or no fully conjugated rings can be formulated by fusion of two appropriate monocyclic heterocycles. For the latter category of heterocycles, a saturated bridgehead can give either *cis* or *trans* fusion.

Oxygen has been used as an example of an exocyclic substituent in heterocycles (7)–(12) but other groups such as imine, thiocarbonyl, and substituted methylene are common. The majority of 6-6 heterocycles are associated with nitrogen, oxygen, and sulfur as heteroatoms; other heteroatoms such as selenium and phosphorus are less common.

Heterocycles (1)–(6) are listed in *Chemical Abstracts* as naphthyridines but these compounds are frequently referred to as diazanaphthalenes or pyridopyridines. Heterocycles (7)–(12) are named as naphthyridones or naphthyridiones as appropriate. Most other heterocycles are named according to the two component heterocyclic rings, for example, compounds (11) and (12) are pyranopyrans (X = Y = O), pyranothiopyrans (X = O, Y = S) and thiopyranothiopyrans (X = Y = S). When a benzene ring is replaced by a pyridine ring in natural products, the resulting heterocycles are frequently named as aza derivatives of the natural product. For example, heterocycles (7; X = O) are azacoumarins. Heterocycles with either one or no fully conjugated rings are usually named as dihydro, tetrahydro, etc. derivatives of the corresponding fully conjugated system. Fully saturated heterocycles are sometimes named as heteroderivatives of bicyclo[4.4.0]decane.

The literature relating heterocycles with one or two fully conjugated rings is extensive and is mostly associated with ring synthesis. The chemistry of pyranopyran and pyranopyridine derivatives which are not associated with any fully conjugated rings is also extensive because these heterocycles are present in numerous natural products, and some representative examples are included in this chapter (see Sections 7.15.8, 7.15.10.2, and 7.15.12).

The chemistry and physical properties of 1,7-naphthyridines (3) <82H(19)363> and of heterocycles (1)–(6) <83AHC(33)147> have been reviewed. The reactions of heterocycles (1)–(6) with nitrogen nucleophiles have also been reviewed <83AHC(33)95>. Reviews covering pyranopyridines <87AKZ104> and pyranopyrans <75MI 715-01> have been published.

7.15.2 THEORETICAL METHODS

The π – π^* spectra of naphthyridines (1)–(6) have been calculated, and there is a good correlation between theoretical and experimental data <82IJC(B)334>. INDO–PSDCI (partial single and double bond configuration interaction) calculations have been performed on naphthyridines (1), (2), and (4) and correlated with their picosecond excited state singlet–singlet absorption spectra. Calculated INDO–PSDCI wave functions have been used to predict intersystem crossing rates <86JCP(84)6790>.

Heats of atomization, resonance energies and π -dipole moments have been calculated for naphthyridines (1)–(6) <79IJC(B)610>.

Perturbation Molecular Orbital (PMO) theory has been used to account for the regioselectivity of the reaction of naphthyridines (1)–(6) with amide and dimethyl anions. The reaction with the amide ion (a hard nucleophile) is under charge control, whereas the reaction with the dimethyl ion (a soft nucleophile) is determined by the distribution of the LUMO <91PJC1449>.

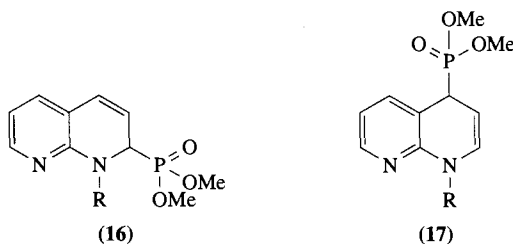
The resonance energy per electron for the sulfur-containing heterocycles (13)–(15) (X = Y = S) have been determined. The values are -0.005β , -0.008β , and -0.012β , respectively. These values, when compared with thiophene (0.032β), indicate these isomers (13)–(15) are not aromatic <73JA3907>.

7.15.3 EXPERIMENTAL STRUCTURAL METHODS

7.15.3.1 NMR Spectroscopy

Proton and ^{13}C -NMR spectroscopy has been used to detect the σ -adducts formed between the reaction of naphthyridines and the amide ion <83AHC(33)95>. Proton, ^{13}C , and ^{31}P NMR spectroscopy has been used to elucidate the nature of the product formed between 1,8-naphthyridine (4), trimethylphosphite and an appropriate acid chloride in a Reissert reaction. 1,2-Addition is determined to

have occurred giving adducts of the general structure (16) rather than the 1,4-addition products (17) <86BCJ2362>.

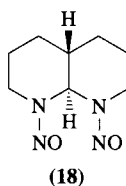


7.15.3.2 ESR Spectroscopy

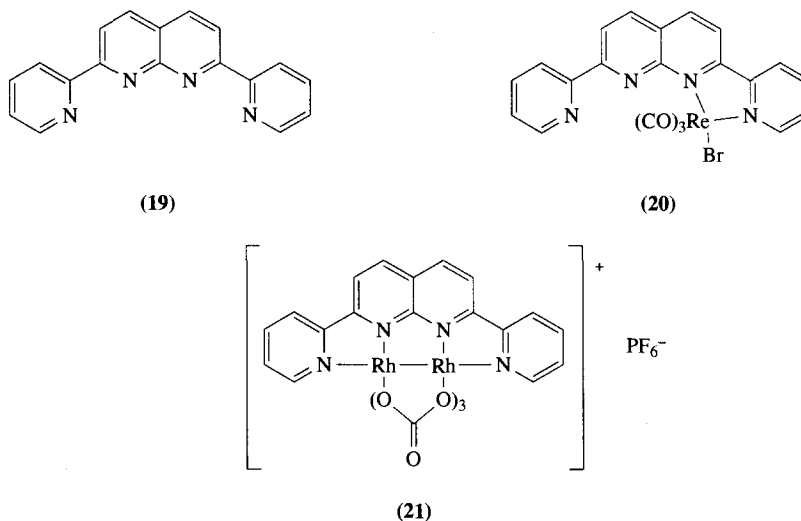
The ESR spectra of the lowest excited triplet states of several naphthyridines in ethanol glasses and stretched polyvinyl alcohol films at 77 K have been determined <87JMR(71)303>. A comparison of the calculated and experimental ESR spectral hyperfine coupling of radical anions has been reported <83ZN(A)415>.

7.15.3.3 X-ray Crystallography

An x-ray study of *trans*-1,8-dinitrosooctahydronaphthyridine (18) reveals a *syn, anti*-conformation of the nitroso groups. The rings in compound (18) adopt a chair, twist-boat conformation.



2,7-Bis(2-pyridyl)-1,8-naphthyridine (BPNP) (19) has attracted interest as a ligand. BPNP (19) reacts with $[\text{Re}(\text{CO})_3\text{Br}(\text{THF})_2]$ to give the complex (20) in which the rhenium atom is chelated to one naphthyridine nitrogen and one pyridyl nitrogen. The distance between the rhenium atom and the remote naphthyridine nitrogen atom is 3.32 Å, indicating that there is no bonding between these atoms. Steric demands preclude coordination of the rhenium atom to both naphthyridine nitrogen atoms <83ICA29>. In contrast, BPNP (19) reacts with tetrakis(μ -aceto)dirhodium(II) giving, after treatment with ammonium hexafluorophosphate, a complex (21) in which the BPNP moiety is behaving as a tetradentate ligand <83IC1147>.



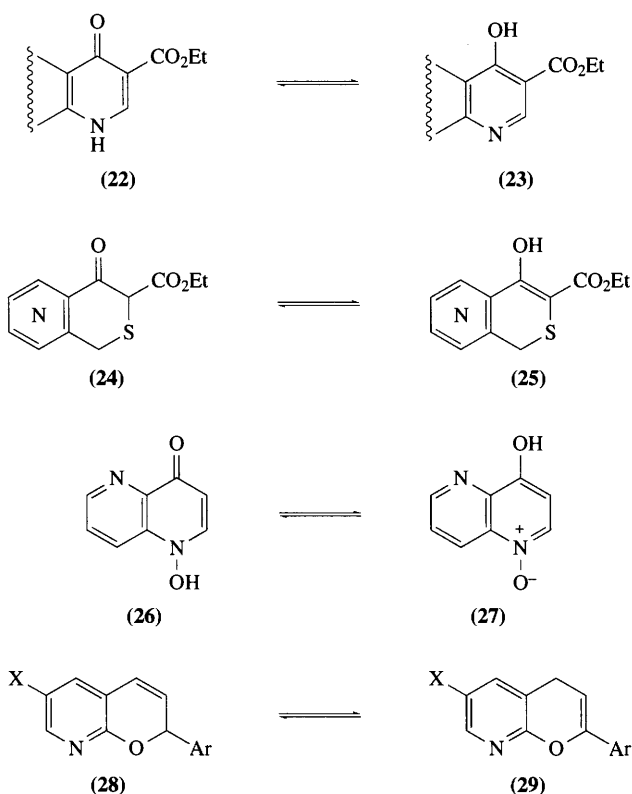
7.15.3.4 Dipole Moments

The dipole moment of 1,8-naphthyridine (**4**) is determined as 4.10 D in benzene <88JCED9>.

7.15.4 THERMODYNAMIC ASPECTS

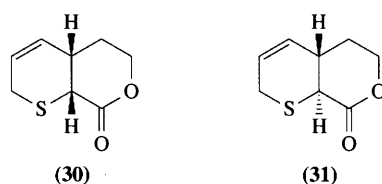
7.15.4.1 Tautomerism

There are numerous compounds associated with the partial structures (**22**) and (**23**) because of their structural similarity to the antibacterial agent nalidixic acid (see Section 7.15.12). Such compounds invariably exist as the tautomer (**22**). The four pyridothiopyran isomers (**24**)/(**25**) exist as the enol tautomers (**25**) <84JCS(P1)1501>. Structure (**12**; X = Y = NH) is the favored tautomer in water <78JOC1331>. The *N*-hydroxy tautomer (**26**) is favored over the corresponding *N*-oxide tautomer (**27**) in the solid state <81KGS792>. Heterocycles (**28**; X = Br) are transformed into their tautomers (**29**) when treated with DBU <85JHC1583>.



7.15.4.2 Epimerization

The *cis* isomer (**30**) is converted by DBU to a 3 : 1 mixture of the *cis* (**30**) and *trans* (**31**) isomers <88JOC2220>.

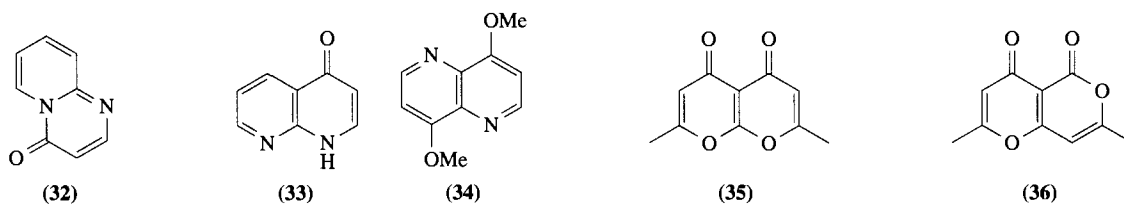


7.15.4.3 Aromaticity

The nonaromatic character of isomers (13)–(15) ($X = Y = S$) has been discussed in Section 7.15.2. Compounds possessing one fully conjugated ring can often be readily dehydrogenated and these reactions are discussed in Section 7.15.6.6.

7.15.4.4 Thermal Isomerization Reactions

Derivatives of the pyridopyrimidones (32) are converted to 1,8-naphthyrid-4-one derivatives (33) when heated (82JHC1017, 83JHC1053, 84JHC407). 4,8-Dimethoxy-1,5-naphthyridine (34) undergoes the Lander rearrangement giving compound (10; $X = NMe$) when heated at 226°C for 10 h (78JOC1331). The pyranopyran derivative (35) cannot be isolated and is transformed into the isomer (36) (61PCS112).

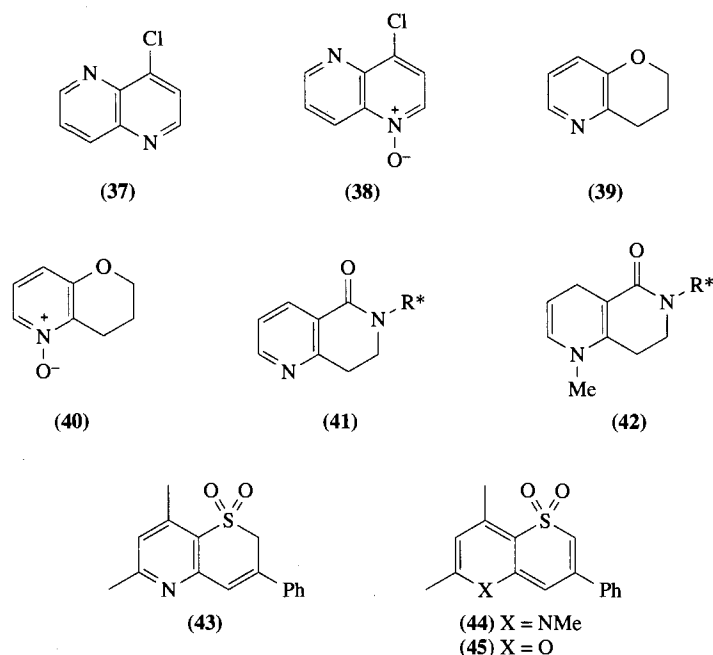


Amination of naphthyridines can be carried out under kinetic or thermodynamic conditions (83AHC(33)95), for example treatment of 1,5-naphthyridine (1) with KNH_2-NH_3 gives addition at C-2 (kinetic adduct) at $-40^\circ C$, and addition at C-4 (thermodynamic adduct) at $10^\circ C$.

7.15.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.15.5.1 Electrophilic Attack at Nitrogen

Oxidation of 4-chloro-1,5-naphthyridine (37) with hydrogen peroxide in the presence of a catalytic quantity of Na_2WO_4 gives the *N*-oxide (38) in good yield (81KGS792). Hydrogen peroxide oxidation of tetrahydropyrano[3,2-*b*]pyridine (39) gives the *N*-oxide (40) in quantitative yield (79H(12)493). Methylation of dihydronaphthyridone derivatives (41; $R^* =$ chiral group) gives, after reduction



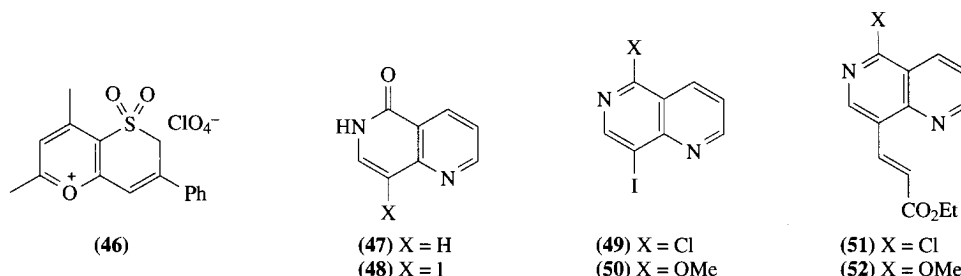
with $\text{Na}_2\text{S}_2\text{O}_4$, the tetrahydronaphthyridones (**42**) which are used as NADH models <91CL125, 91T9369>. The thiopyranopyridine derivative (**43**) gives heterocycle (**44**) after treatment with dimethyl sulfate and then sodium carbonate <74JCS(P2)1389>.

The Reissert product (**16**) has been discussed in Section 7.15.3.1.

7.15.5.2 Electrophilic Attack at Carbon

Protonation of the pyranothiopyran dioxide derivative (**45**) with perchloric acid gives the pyrylium salt (**46**) <74JCS(P2)1389>.

Iodination (I_2/NaOH) of 1,6-naphthyrid-5-one (**47**) gives the iodo derivative (**48**) (70% yield). This compound is converted to 5-chloro-8-iodo-1,6-naphthyridine (**49**) by the action of phosphorus oxychloride (64% yield). Heterocycle (**49**) undergoes a Heck reaction with ethyl acrylate in the presence of palladium acetate as a catalyst giving compound (**51**) (47% yield). Similarly, heterocycle (**50**) (obtained in 98% yield by treating compound (**49**) with sodium methoxide) gives ester (**52**) (88% yield) in a Heck reaction <86CPB2018>.



7.15.5.3 Nucleophilic Attack at Carbon

N-Oxide derivative (**38**) reacts with sodium methoxide and sodium hydroxide to give the substitution products (**53**) and (**26**), respectively in good yield <81KGS792>.

2,6-Dichloro-1,5-naphthyridine (**54**) and 2,7-dichloro-1,8-naphthyridine (**55**) have been used in the synthesis of macrocycles. Thus, reaction of heterocycle (**54**) with hexaethylene glycol and sodium hydride gives the 1:1 adduct (**56**) (60% yield) together with the 2:2 adduct (**57**) (2% yield). Heterocycle (**55**) similarly yields a 1:1 adduct (**58**) (30% yield) and a 2:2 adduct (**59**) (2% yield) <81JOC833>.

The 1,8-naphthyridine derivative (**60**) reacts with LiPPh_2 giving the product (**61**) (55% yield), which has been used as a ligand for rhodium <92JCS(D)2367>.

Derivatives of [1,x]-naphthyridines (**1**)–(**4**) react with a series of chloromethylsulfone derivatives (**62**) in the presence of potassium hydroxide to yield the 2:1 adducts (**63**) (23–77% yield) <91CB577>.

7.15.5.4 Reduction

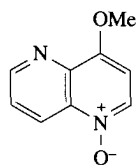
1,5-Naphthyridine (**1**) has been reduced by potassium in the presence of trimethylsilyl chloride to give the dihydro derivative (**64**) (19% yield) <89JOM37>, and 1,8-naphthyridine (**4**) has been reduced with diborane yielding 1,2,3,4-tetrahydronaphthyridine (**65**) (44% yield) <83POL595>. Reduction (H_2/Pd) of heterocycle (**52**) gives the tetrahydro derivative (**66**) (83% yield) <86CPB2018>.

The reduction of heterocycle (**41**) via its methiodide to give compound (**42**) has been noted in Section 7.15.5.1.

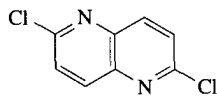
7.15.6 REACTIVITY OF RINGS WHICH ARE NOT FULLY CONJUGATED

7.15.6.1 Electrophilic Attack at Nitrogen

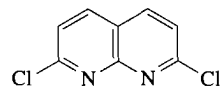
Nitrosation of *trans*-decahydro-1,8-naphthyridine (**67**) gives the dinitroso derivative (**18**) <84JOC1481>. The octahydro-1,8-naphthyridine (**68**) gives the methyl derivative (**69**) (75% yield)



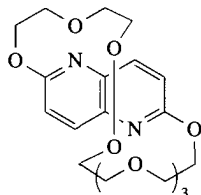
(53)



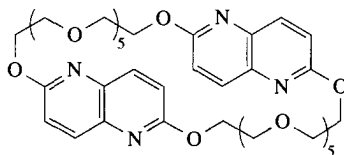
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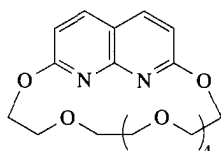
(55)



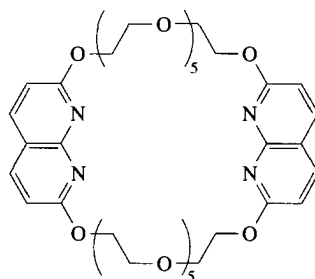
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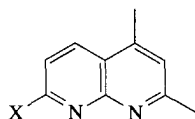
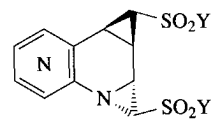
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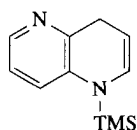
(58)



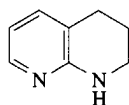
(59)

(60) X = Cl
(61) X = PPh₂(62)
Y = Ph, NMe₂, OCH₂Bu^t

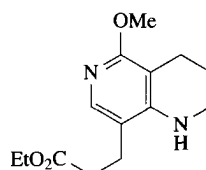
(63)



(64)

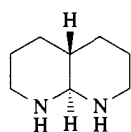


(65)

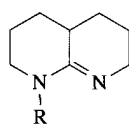
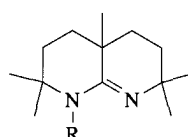


(66)

when treated with methyl iodide and then potassium hydroxide (84JHC583). The pentamethyl derivative (70) can be sulfonated (ClSO₃H or pyridine—SO₃) giving compound (71) (61–88% yield) which has been used as a mild sulfonating agent (83H(20)1531).

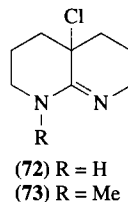


(67)

(68) R = H
(69) R = Me(70) R = H
(71) R = SO₃H

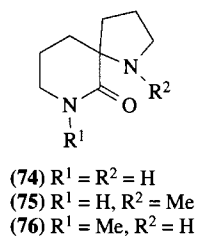
7.15.6.2 Electrophilic Attack at Carbon

Heterocycles (68) and (69) react with carbon tetrachloride in the dark giving the chlorinated products (72) and (73), respectively <84JHC583>.



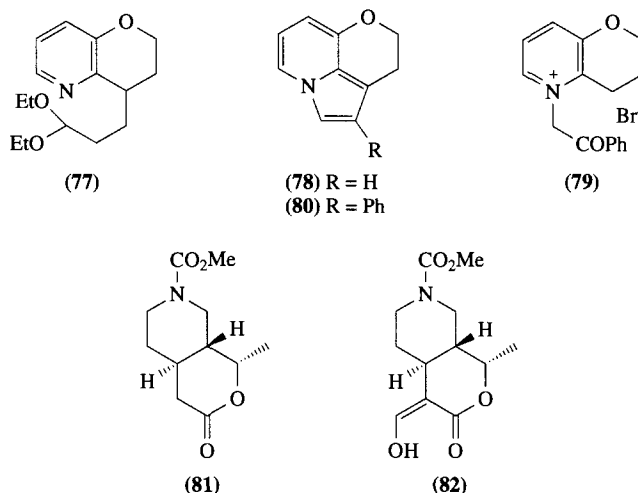
7.15.6.3 Nucleophilic Attack at Carbon

Compound (72) reacts with water yielding the spiro heterocycle (74) (30% yield from compound (68)) and compound (73) gives a 78 : 22 mixture of isomers (75) and (76) in good yield <84JHC583>.



7.15.6.4 Nucleophilic Attack at Hydrogen

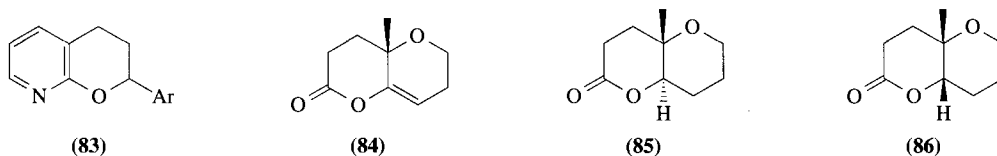
1,2,3,4-Tetrahydropyrano[3,2-*b*]pyridine (39) can be deprotonated by butyllithium and the resulting anion trapped with bromoacetaldehyde diethyl acetal giving compound (77). Treatment of compound (77) with a mixture of acetic anhydride and sodium acetate gives heterocycle (78) (45% yield) <83JHC1613>. Reaction of heterocycle (39) with phenacyl bromide and treatment of the resulting salt (79) with aqueous sodium hydrogen carbonate gives the heterocycle (80) (90% yield) <83JHC1613>.



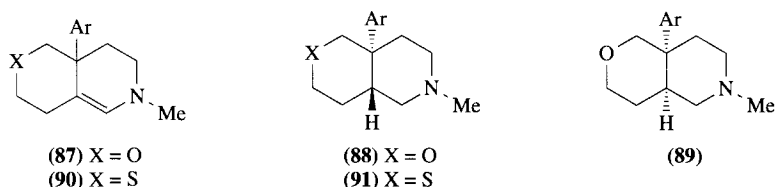
The chiral heterocycle (81) is deprotonated by trityl sodium and the resulting anion trapped with methyl formate giving the hydroxymethylene derivative (82) <92JCS(P1)517>.

7.15.6.5 Reduction

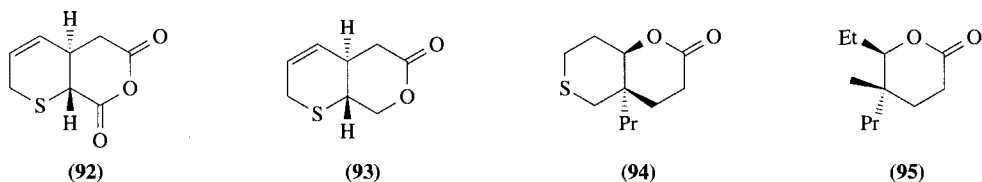
Hydrogenation (Ni/H_2) of compounds (**28**; $\text{X} = \text{H}, \text{Br}$) gives the heterocycles (**83**) (10–80% yield) <85JHC1583>. The chiral pyranopyran derivative (**84**) is hydrogenated (PtO_2/H_2) yielding a 1:2 mixture of the isomers (**85**) and (**86**) <92TA863>.



The enamine moiety of the octahydropyrano[4,3-*c*]pyridine derivative (**87**; $\text{Ar} = 3\text{-methoxyphenyl}$) can be reduced (Pt/H_2) either under neutral conditions yielding the *trans* isomer (**88**) as the major product, or under acidic conditions giving the *cis* isomer (**89**). The thiopyranopyridine derivative (**90**; $\text{Ar} = 3\text{-methoxyphenyl}$) is reduced to the *trans* isomer (**91**) by treatment with methanesulfonic acid and then sodium borohydride <89JCS(P1)1177>.

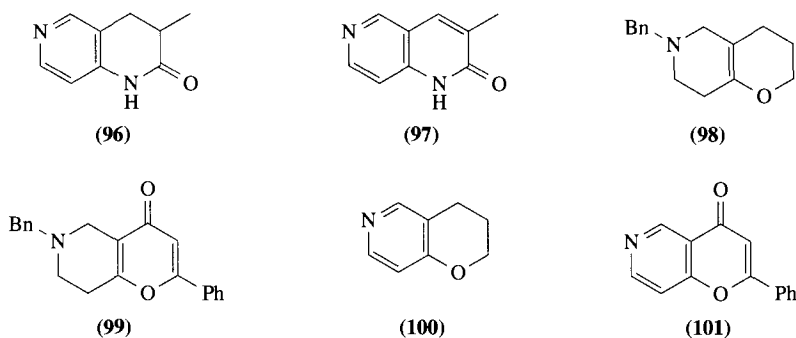


The thiopyranopyrandione derivative (**92**) is reduced by lithium borohydride yielding the product (**93**) in moderate yield <88JCS(P1)663>, and the chiral heterocycle (**94**) gives the chiral 2-pyranone derivative (**95**) when treated with nickel boride <91H(32)1875>.

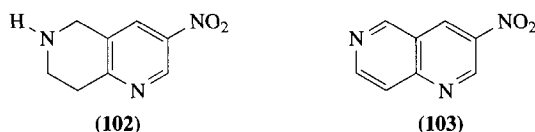


7.15.6.6 Oxidation

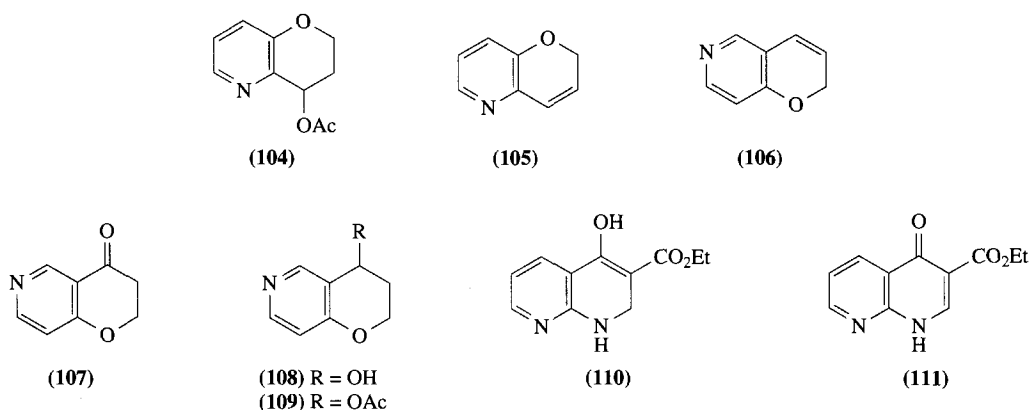
Palladium-mediated dehydrogenation of the dihydronaphthyridine derivative (**96**) gives the naphthyridone derivative (**97**) (69% yield) <91S894>. Dehydrogenation and debenzoylation of heterocycles (**98**) and (**99**) is achieved by heating in the presence of palladium, and gives 1,2,3,4-tetrahydropyrano[3,2-*c*]pyridine (**100**) (85% yield) <79JCR(S)124> and 6-azaflavone (**101**) (84% yield) <87JHC111>, respectively.



Aromatization of the nitro compound (**102**) giving 3-nitro-1,6-naphthyridine (**103**) (24% yield) has been achieved by treatment with iodine <89T2693>.



The overall process of transforming a tetrahydropyran ring into a dihydropyran ring has been realized by two methods. Treatment of the *N*-oxide (**40**) with acetic anhydride gives the acetate derivative (**104**) (70% yield) which upon heating (465°C) yields the dihydropyranopyridine (**105**) (70% yield) <79H(12)493>. The isomeric dihydropyranopyridine (**106**) is obtained from heterocycle (**100**) by a different procedure. Thus, oxidation ($\text{H}_2\text{CrO}_4\text{--AcOH}$) of compound (**100**) yields the ketone (**107**) which is then reduced (LiAlH_4) giving the alcohol (**108**) (65% yield). Compound (**108**) is converted by treatment with acetic anhydride into the acetate (**109**) and subsequent pyrolysis (350–370°C) gives heterocycle (**106**) (73% yield) <79JCR(S)124>.



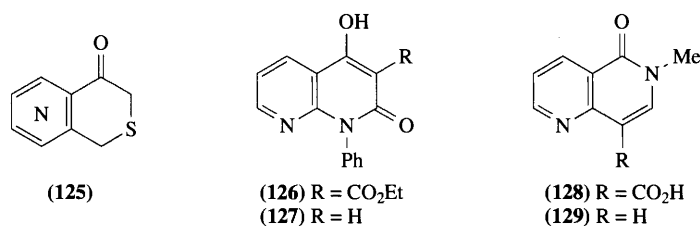
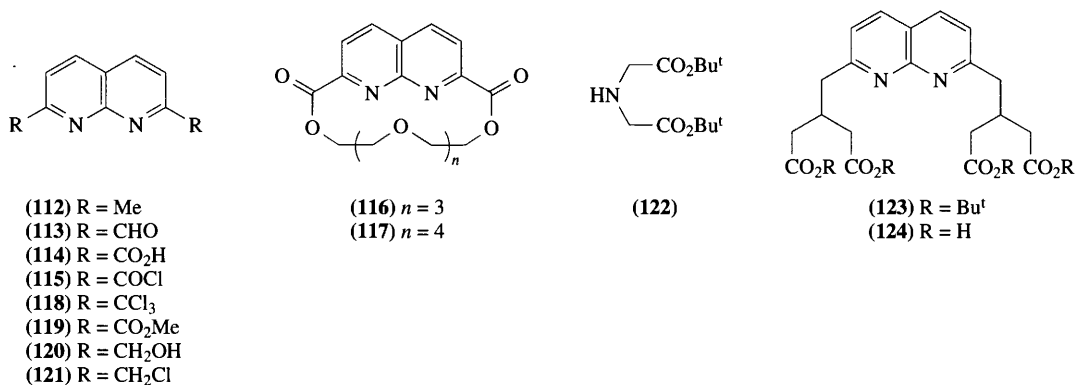
The dihydro-1,8-naphthyridine derivative (**110**) and related compounds can be oxidized by either chloranil or bromine to the corresponding naphthyridones (**111**) <87JHC1333>.

7.15.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.15.7.1 Carbon Substituents

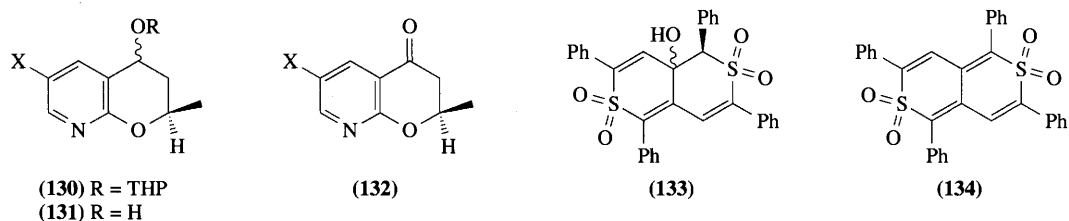
2,7-Dimethyl-1,8-naphthyridine (**112**) is oxidized by selenium dioxide giving the dialdehyde (**113**) (59% yield). Nitric acid oxidation of this dialdehyde (**113**) affords the dicarboxylic acid (**114**) (65% yield) from which the diacid chloride (**115**) (57% yield) is obtained by treatment with thionyl chloride. Reaction of compound (**115**) with an appropriate diol gives the macrocycles (**116**) (35% yield) and (**117**) (69% yield) <82JHC1017>. Chlorination of heterocycle (**112**) yielding the hexachloro derivative (**118**) (98% yield) is achieved using NCS. This compound (**118**) is treated with phosphoric acid and then methanol giving the diester (**119**) (80% yield). Reduction of this diester (**119**) with $\text{NaBH}(\text{OMe})_3$ gives compound (**120**) (55% yield) which is converted into the dichloride derivative (**121**) (7% yield) by the action of phosphorus trichloride <90JOC2838>. Heterocycle (**112**) has also been converted directly into the dichloride (**121**) (18% yield) by treatment with NCS <92HCA1621>. Treatment of compound (**121**) with the amine (**122**) gives the tetraester derivative (**123**) (36% yield) from which the tetracarboxylic acid (**124**) is obtained in quantitative yield by treatment with trifluoroacetic acid <92HCA1621>.

6-6 Heterocycles possessing an ester substituent are frequently the products of ring synthesis. The ester group can then be removed by hydrolysis and decarboxylation. Mild conditions are generally required to achieve the decarboxylation reaction when the ester is part of a β -keto ester moiety (or its enolic tautomer) and representative examples include the conversion of esters (**25**) into heterocycles (**125**) <84JCS(P1)1501> and ester (**126**) into heterocycle (**127**) <92JMC1130>. Severe conditions are often required to achieve decarboxylation in other cases as exemplified by the conversion of acid (**128**) into the naphthyridone (**129**) (77% yield) by heating at 260°C <83JCB916>.



7.15.7.2 Oxygen Substituents

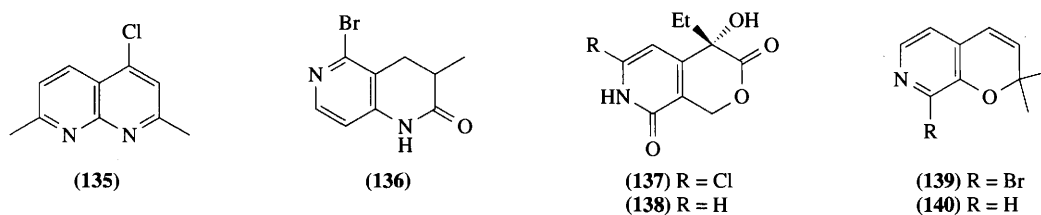
The THP derivatives (**130**; X = H, Cl) have been deprotected and the resulting alcohols (**131**) oxidized with PCC yielding the chiral heterocycles (**132**) <92JOC1930>. Dehydration of a 1:1 mixture of the diastereoisomers (**133**) with phosphorus oxychloride gives the thiopyrano[4,3-*c*]thiopyran derivative (**134**) (48% yield) <84JOC5136>.



The pyrolysis of acetates (**104**) and (**109**) giving the corresponding heterocycles (**105**) and (**106**) and the Lander rearrangement of heterocycle (**34**) giving compound (**12**; X = Y = NMe) has been discussed in Sections 7.15.6.6 and 7.15.4.4, respectively.

7.15.7.3 Halogen Substituents

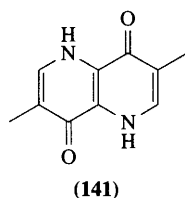
Halogen substituents can be removed either by catalytic hydrogenation or by lithiation, followed by protonation of the resulting lithio derivative. Thus, halogenated heterocycles (**135**)–(**137**) give compounds (**112**) (92% yield) <82JHC1017>, (**96**) (83% yield) <91S894>, and (**138**) (95% yield) <92JA10971>, respectively by the former method. Heterocycle (**139**) gives the pyrano[3,2-*c*]pyridine derivative (**140**) when treated with butyllithium and then water <B-93MI 715-01>.



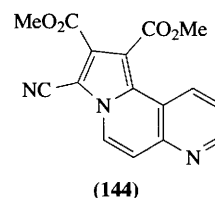
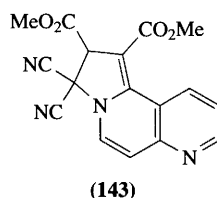
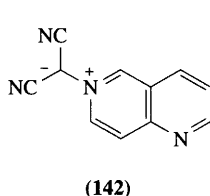
7.15.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The debenzoylation of compounds (**98**) and (**99**) has been considered in Section 7.15.6.6 and the formation of heterocycle (**80**) from salt (**79**) was discussed in Section 7.15.6.4.

When compound (**12**; X = Y = NMe) is heated with methyl iodide, the isomer (**141**) (53% yield) is formed by a *C*-methylation and *N*-demethylation process <77CC87>.



The *N*-methylide (**142**) reacts with DMAD yielding a mixture of the dihydro derivative (**143**) (23% yield) and the fully conjugated tricyclic product (**144**) (44% yield) <93H(36)1945>. Other naphthyridine *N*-methylides behave similarly.



There are numerous examples in alkaloid chemistry in which an *N*-substituted pyranopyridine is subjected to an intramolecular ring closure in order to construct the alkaloid skeleton. The total synthesis of ajmalicine (**145**) and camptothecin (**146**) provide some relevant examples. The pyranopyridine derivative (**147**) is treated with mercuric acetate and then sodium borohydride giving ajmalicine (**145**) (28% yield) <81HCA1663, 92JCS(P1)517>. A second approach to the construction of the indole-pyranopyridine bond involves a Bischler-Napieralski reaction. Thus, treatment of the lactam (**148**) with phosphorus oxychloride and then hydrogenation (H_2/PtO_2) of the resulting iminium salt gives heterocycle (**149**) which is then converted (with inversion of configuration of the lactone methyl substituent) into ajmalicine (**145**) <91JOC2947, 93JCS(P1)539>. Camptothecin (**146**) has been prepared by an intramolecular Heck reaction (59% yield) of the quinoline derivative (**150**) <92JA10971>.

7.15.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

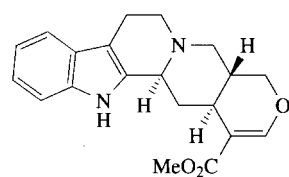
7.15.9.1 Synthesis by Construction of the Second Heterocyclic Ring on to an Existing Heterocycle

7.15.9.1.1 Heteroatom in new ring adjacent to a bridgehead position

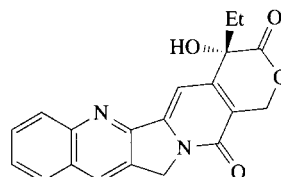
This section considers the formation of a ring represented by the partial structure (**151**). The heterocyclic ring depicted in structure (**151**) is built on to an existing six-membered heterocyclic ring possessing one heteroatom thus forming a bicyclic 6-6 system. The partial structures (**152**)–(**166**) indicate possible methods for construction of the second heterocyclic ring. The following sub-sections consider the formation of structure (**151**) according to the number of component atoms which are required to form the second ring. Structures have been orientated to correspond with the relevant formulae (**152**)–(**166**).

(i) Synthesis of the second ring from [6 + 0] atom fragments

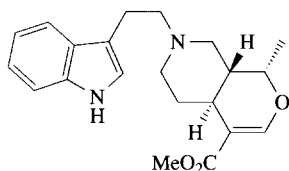
Ring syntheses (**152**) → (**151**) and (**153**) → (**151**) are well represented whereas other intramolecular cyclizations are less common.



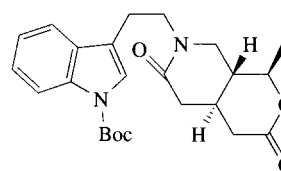
(145) ajmalicine



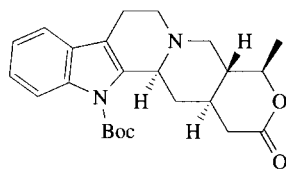
(146) camptothecin



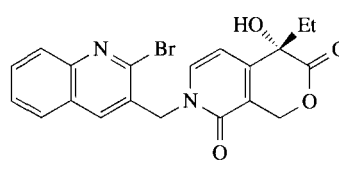
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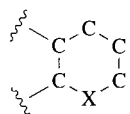
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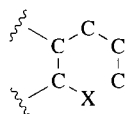
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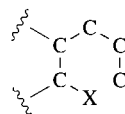
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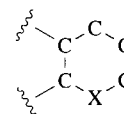
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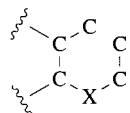
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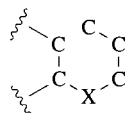
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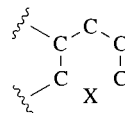
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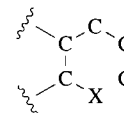
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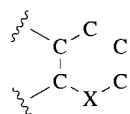
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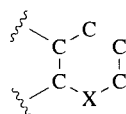
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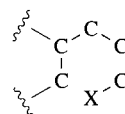
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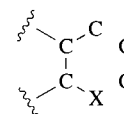
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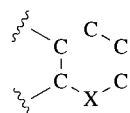
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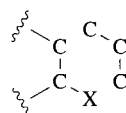
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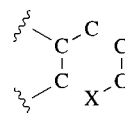
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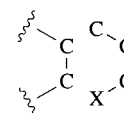
(163)



(164)



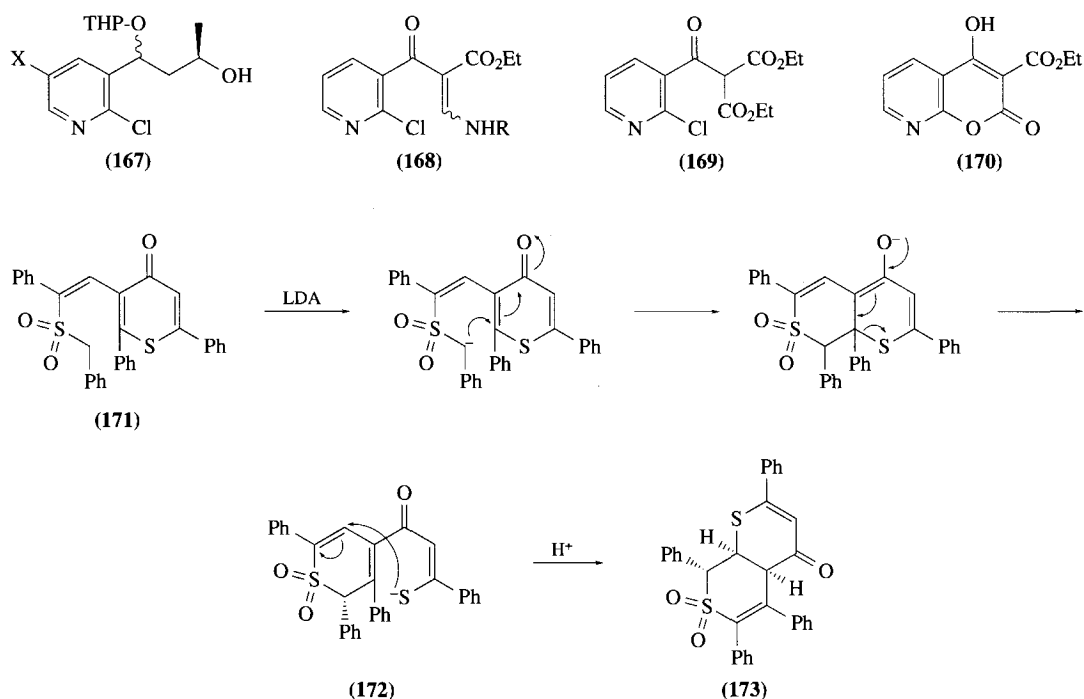
(165)



(166)

Heterocycles (167) and (168) react with sodium hydride yielding the pyrano[2,3-*b*]pyridines (130) <92JOC1930> and 1,8-naphthyridine derivatives (111) <92JMC518> respectively: a related synthesis of tetrahydropyrano[2,3-*b*]pyridines has been reported <71JCS(B)279>. Under acidic conditions, the diester (169) affords heterocycle (170) (44% yield) <93H(35)93>. The sulfone (171) reacts with LDA giving an intermediate (172) which cyclizes yielding the sulfone (173) (Scheme 1) <84JOC5136>.

The amino esters (174; R = H, Me) yield naphthyridones (175) (67–83% yield) when treated with sodium ethoxide <85CPB4764>, whereas the amides (176) and (177) give naphthyridones (178) (86–

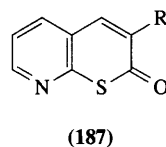
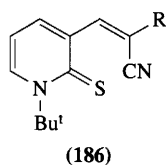
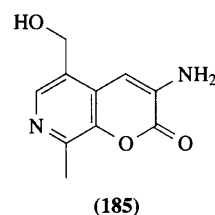
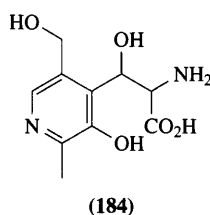
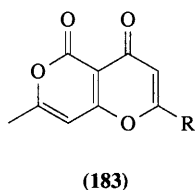
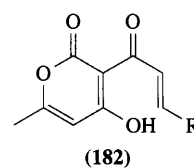
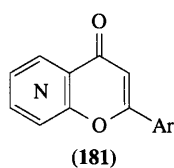
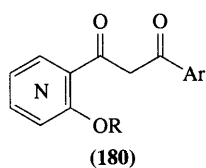
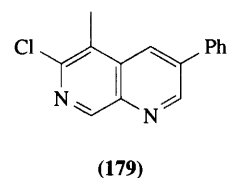
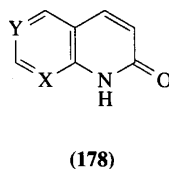
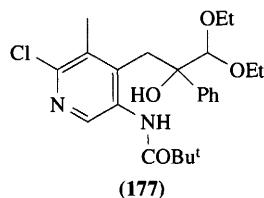
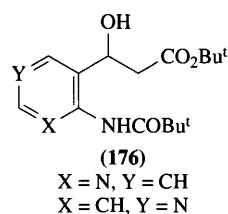
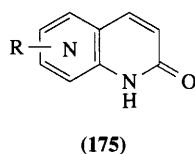
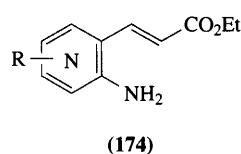


Scheme 1

96% yield) <90JOC4744> and the naphthyridine (**179**) (60% yield) <93SC365> respectively, when treated with HCl. Treatment of the 1,3-diketones (**180**; R = H, Et) with acid results in the formation of azaflavones (**181**) (65–75% yield) <67JCS(C)1836, 70BSF631, 72BSF1435, 91MI 715-01>. Reaction of the heterocycles (**182**) with bromine followed by treatment of the resulting dibromo derivative with a mixture of pyridine and piperidine gives pyranopyrandiones (**183**) (60–77% yield) <88IJC(B)373>. Lactonization of compound (**184**) and subsequent dehydration giving the pyranopyridine (**185**) (50% yield) occurs when compound (**184**) is treated with DCC <70JHC1013>. 2-Thiopyridone derivatives (**186**) cyclize with loss of the Bu^t group, when reacted with HCl yielding thiopyranopyridones (**187**) in moderate to good yields <81JHC1357>.

Allylic alcohol derivatives (**188**), diols (**189**; X = O, S, Se) and the alcohol (**190**) give dihydropyranopyridines (**28**) (27–33% yield) <85JHC1583>, heterocycles (**191**) (50–63% yield) <70BSF642, 72KGS1539>, and the tetrahydropyranopyridine (**39**) (46% yield) <79H(12)493> respectively, when treated with HBr. Reduction of the chiral ketone (**192**) with sodium borohydride gives a 80:20 mixture of compound (**94**) and its epimer <91H(32)1875>. Similarly, the chiral ketone (**193**) gives a mixture of diastereoisomers (**85**) and (**86**) with a variety of reducing agents with best yields of heterocycle (**85**) being obtained using (+)-Ipc₂BH <92TA867>. Mesylation of alcohol (**194**) followed by treatment with NaH gives the fully saturated pyranopyridine derivative (**195**) <89JCS(P1)1187>. Lactone (**196**) yields a mixture of the pyranopyran derivative (**197**) (38% yield) and its epimer (5% yield) when treated with AgBF₄ followed by methoxide <84CJC2493>. The control of stereochemistry in ring formation is elegantly demonstrated by the NaH mediated intramolecular conjugate addition reactions of the *E*-alkene (**198**) and the *Z*-alkene (**199**) giving the *trans*-pyranopyran derivatives (**200**) and (**201**), respectively. *Cis*-pyranopyrans can also be obtained from the appropriate epimers of compounds (**198**) and (**199**). The stereospecificity of these cyclizations has been attributed to the equatorial orientation of the benzyloxy substituent which controls the conformation of the transition state <93TL5467>. The chiral epoxide (**202**) (obtained from D-mannose) gives the pyranopyran (**203**) when treated with TBAF. Heterocycle (**203**) was used in the total synthesis of the polyether natural product, hemibrevetoxin B <92JA7935>.

There are numerous examples of Claisen rearrangements of propargyl derivatives (e.g. (**204**)) which give either a mixture of products (**206**) and (**207**) or solely product (**207**) via the allene intermediates (**205**) (Scheme 2). Thus, the pyridine derivative (**208**) gives heterocycles (**209**) (55% yield) and (**210**) (29% yield) <78HCA2542>, the derivative (**211**) gives the pyranopyridine (**212**) <B-93MI 715-01> and the thiopyran derivative (**213**) gives the thiopyrano[2,3-*b*]thiopyran (**214**) (40% yield) <78S578>.



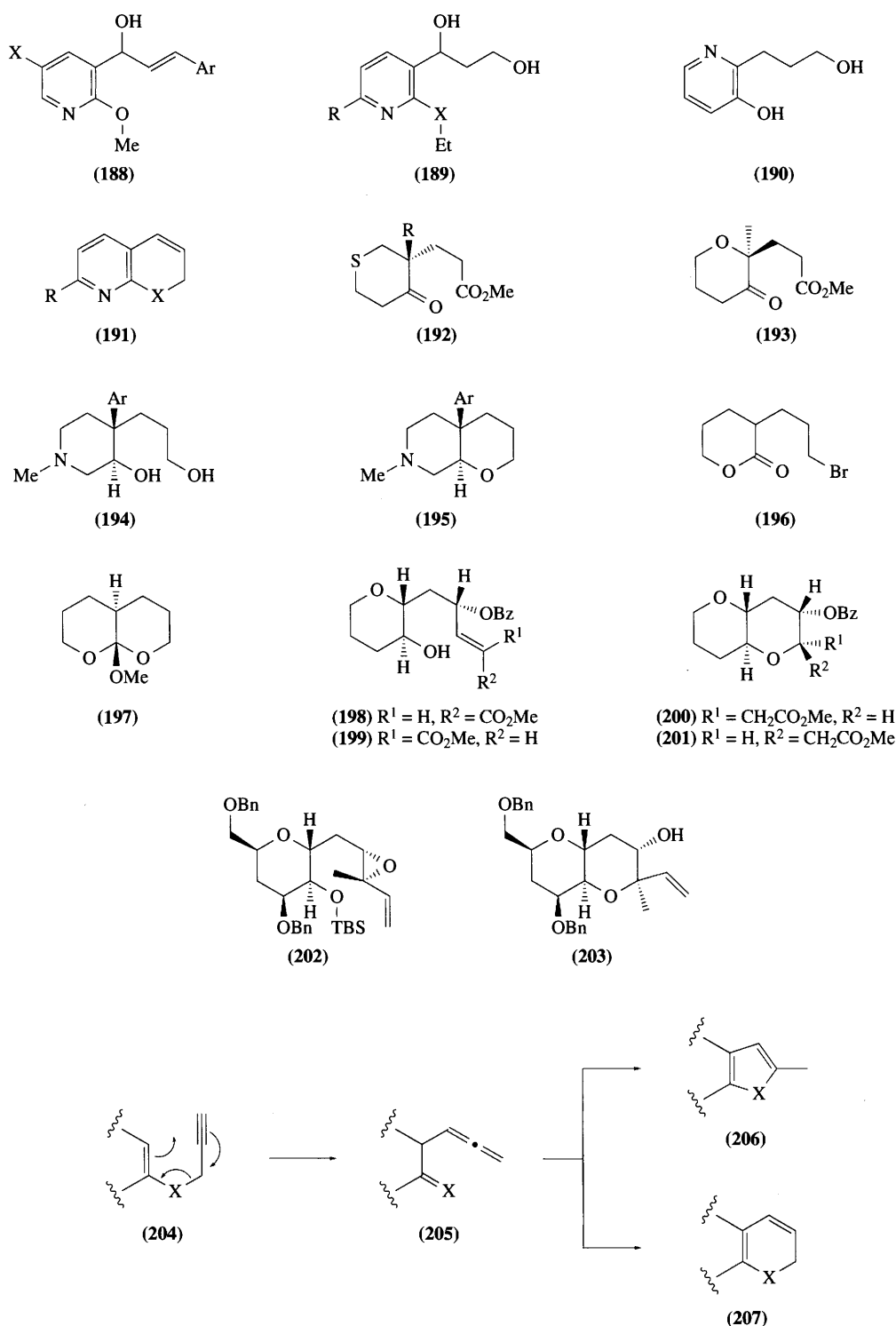
The transformation of esters (215) and (216) giving the corresponding dihydronaphthyridine derivatives (110) and (217) are two examples of cyclizations of the type (155) → (151) <87JHC1333>.

Cyclizations of the type (156) → (151) include the conversion of: (a) carboxylic acids (218; X = O, S) into diones (219) (34% yield) under acidic conditions <74MI 715-01>; (b) pyridine derivative (220) into the pyrano[3,2-*c*]pyridine (221) (72% yield) via an intramolecular Grignard reaction <82JCS(P1)93>; and (c) a 1:1 mixture of diastereoisomers (222) into a 1:1 mixture of diastereoisomeric pyranopyrans (223) via a HSnBu₃-mediated free radical cyclization <93LA629>. The diethyl ethoxymethylenemalonate (EMME) synthesis of 3-ethoxycarbonyl-4-naphthyridone derivatives has been discussed in CHEC-I <84CHEC-I(2)581>.

(ii) Synthesis of the second ring from [5 + 1] atom fragments

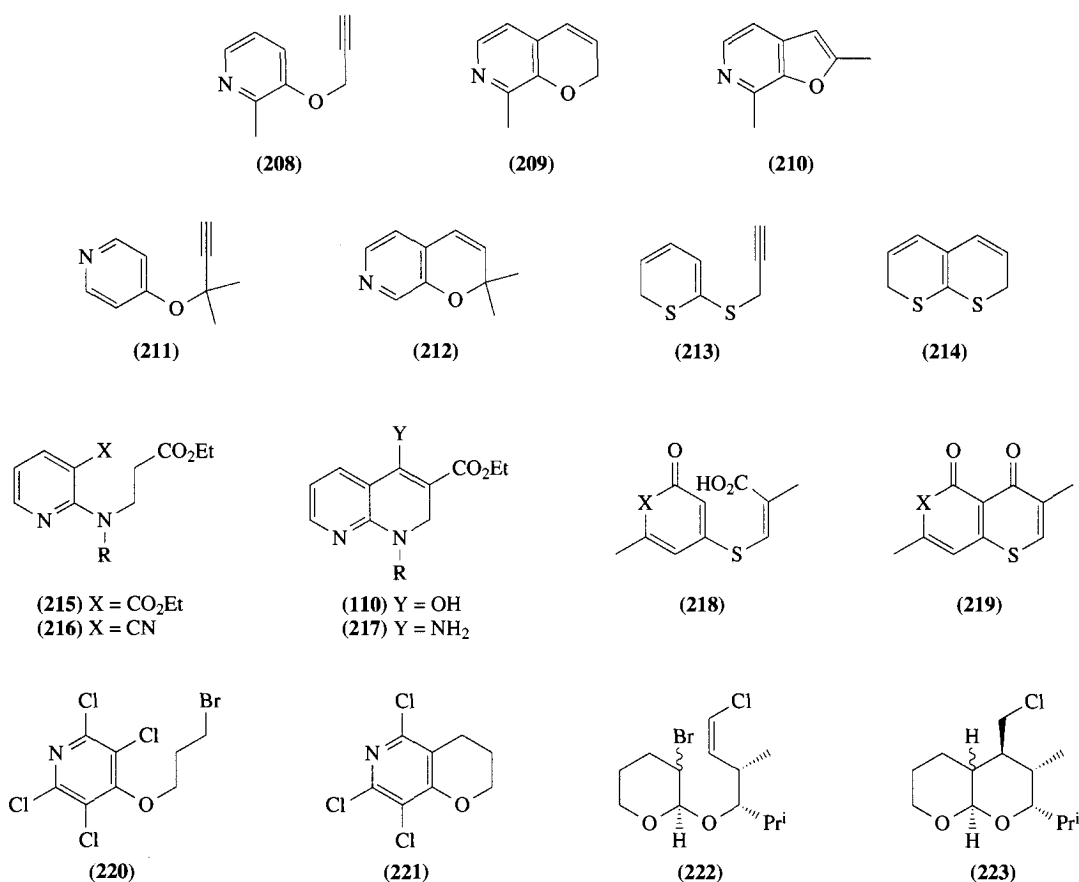
Ring syntheses which use a one-atom component are usually associated with either the transformation (157) → (151) or (158) → (151).

Hydroxylamine can act as a one-atom component as exemplified by the conversion of 1,5-diketones (224; R¹ = Me, R² = R³ = H, X = O and R¹ = H, R² = R³ = Me, X = S) into the fused pyridine derivatives (225) (90% yield and 71% yield, respectively) <74AKZ56>. Other nitrogen nucleophiles include ammonia which converts pyridine derivative (226) into the 1,8-naphthyrid-2-one (227) (74% yield) at 180 °C <85CPB4764>, aniline which reacts with the keto ester (228) yielding



Scheme 2

heterocycles (**229**) (14% yield) <84JMC1271> and amines (R^3NH_2) which participate in a double Michael addition reaction with the dienones (**230**) and (**232**) yielding products (**231**) (33–62%) and (**233**) ($R^3 = Me$) (33–49% yield) <65MI 715-01>. A double Michael addition of phenylphosphine ($PhPH_2$) to the dienone (**234**) yielded the fused phosphole (**235**) <86ZOB2690>. Fused phosphole derivatives (**237**; $R^1, R^2 = H, Me$; $X = O, NMe$) have also been obtained from Mannich bases (**236**) and $PhPH_2$ <82ZOB1919, 83ZOB1757, 84MI 715-01>.

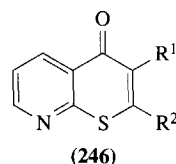
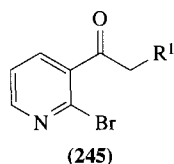
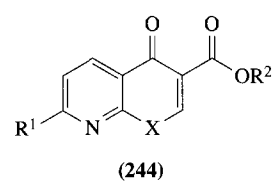
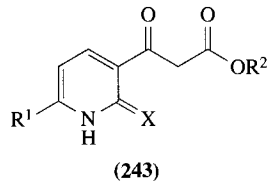
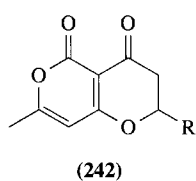
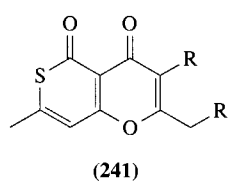
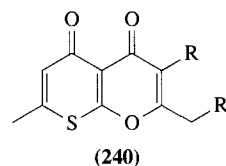
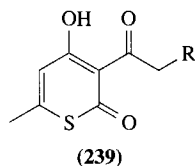
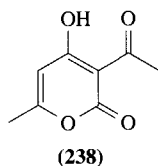
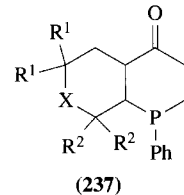
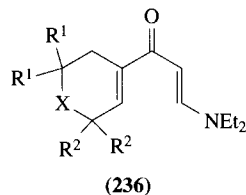
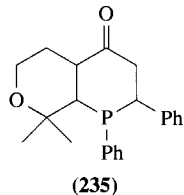
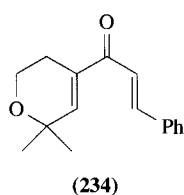
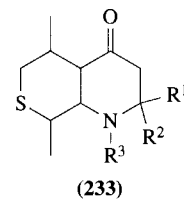
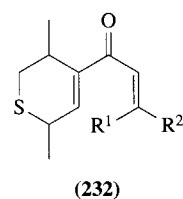
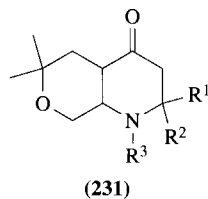
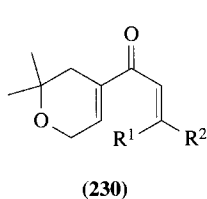
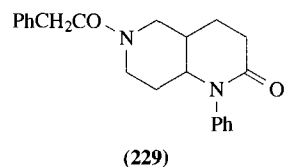
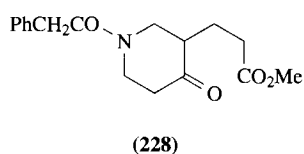
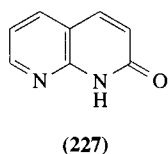
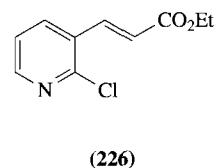
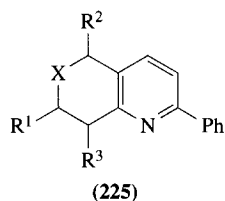
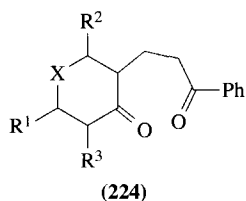


Treatment of dehydroacetic acid (**238**) with a mixture of acetic anhydride and perchloric acid gives the pyranopyran derivative (**35**) as its perchlorate $\langle 61\text{PCS112} \rangle$. Thiopyranone derivatives (**239**) afford a mixture of isomers (**240**) and (**241**) with acid chlorides (RCH_2COCl) and TiCl_4 $\langle 75\text{MI 715-01} \rangle$. Aldehydes (RCHO) and dehydroacetic acid (**238**) give dihydropyranopyrans (**242**) in the presence of piperidine $\langle 85\text{MI 715-01} \rangle$. Heterocycles (**243**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{allyl}$, $\text{X} = \text{O}$ and $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bu}^t$, $\text{X} = \text{S}$) yield products (**244**) (40–50% yield) when treated with methoxymethyleneiminium methanesulfonate ($\text{MeOCH}=\text{NMe}_2^+ \text{MeOSO}_3^-$) $\langle 93\text{H}(35)93 \rangle$.

(iii) *Synthesis of the second ring from [4 + 2] atom fragments*

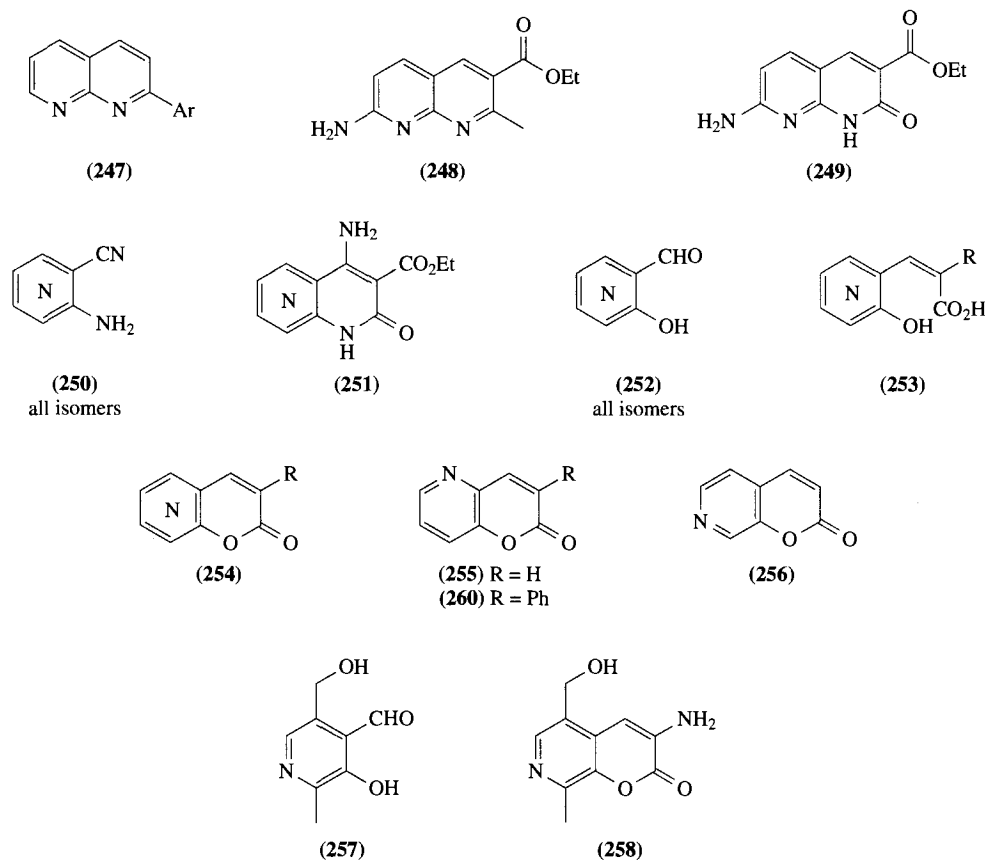
The reaction of the bromopyridine derivative (**245**) with thioesters ($\text{R}^2(\text{EtO})\text{C}=\text{S}$) gives the pyrido[2,3-*b*]thiopyrans (**246**) (59–73% yield) $\langle 89\text{S456} \rangle$ and this transformation corresponds to a synthesis of the general type (**161**) $\rightarrow$ (**151**).

There are many examples of cyclizations of the general type (**162**) $\rightarrow$ (**151**). The condensation of activated methylene compounds with aminopyridine-carbaldehydes giving naphthyridines (Friedländer synthesis) has been reviewed in CHEC-I $\langle 84\text{CHEC-I}(2)581 \rangle$ and the condensation of 2-aminopyridine-3-carbaldehyde with aryl methyl ketones (ArCOMe) in acetic acid solution giving 2-aryl-1,8-naphthyridines (**247**) (78–93% yield) is an additional example of this synthesis $\langle 86\text{JIC443} \rangle$. 2,6-Diaminopyridine-3-carbaldehyde condenses with ethyl acetoacetate in the presence of piperidine affording the aminonaphthyridine derivative (**248**) (80% yield). Other activated methylene compounds participate in similar condensation reactions $\langle 93\text{JOC6625} \rangle$. With diethyl malonate, 2,6-diaminopyridine-3-carbaldehyde yields the aminonaphthyridone (**249**) (70% yield) in the presence of piperidine $\langle 93\text{H}(36)2697 \rangle$ and aminonitriles (**250**) give aminonaphthyridones (**251**) in the presence of sodium ethoxide (36–71% yield) $\langle 90\text{ZC20} \rangle$. Hydroxyaldehydes (**252**) can participate in a Perkin reaction followed by cyclization giving azacoumarin derivatives of general structure (**254**) and, although the initial condensation products (**253**) (cf. structure (**153**)) can often be isolated prior to ring closure, these reactions are considered here because the reagent provides a two-carbon atom



unit. Thus, all four hydroxyaldehyde isomers (**252**) react with either carboxylic acids (RCH_2CO_2H) or their corresponding esters affording azacoumarins (**254**) in moderate to good yields <70JOC3596>. Malonic acid condenses with both 3-hydroxypyridine-2-carbaldehyde and 3-hydroxypyridine-4-carbaldehyde yielding 5-azacoumarin (**255**) (30% yield) <78BSF1> and 7-azacoumarin (**256**) (45%

yield) <90JCS(P1)2409>, respectively. Pyridoxal (**257**) condenses with the methyl ester of glycine giving heterocycle (**258**) (63% yield) <70JHC1031>.



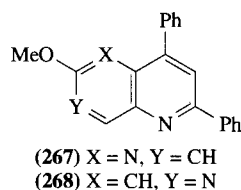
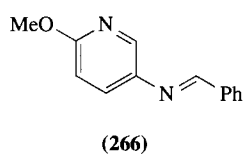
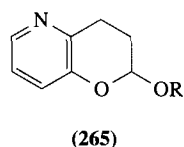
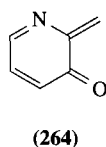
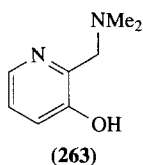
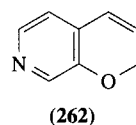
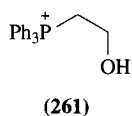
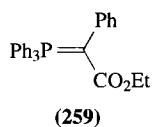
Wittig methodology has been used for preparing pyranopyridine derivatives. Thus, phosphorane (**259**) reacts with 3-hydroxypyridine-2-carbaldehyde giving 3-phenyl-5-azacoumarin (**260**) (72% yield) <93JHC671>. Phosphonium salt (**261**) reacts with 3-hydroxypyridine-4-carbaldehyde in the presence of potassium carbonate giving the dihydropyranopyridine (**262**) and related Wittig reactions have been reported <93S881>. Pyrolysis (220°C) of the pyridine derivative (**263**) in the presence of vinyl ethers gives the tetrahydropyranopyridines (**265**; R = Et, 25% yield and R = Bu^t, 43% yield) via the *ortho* azaquinomethide intermediate (**264**) and a hetero-Diels-Alder reaction <76JHC419>.

Imine (**266**) has been converted into a mixture of the isomeric naphthyridines (**267**) (50% yield) and (**268**) (7% yield) when treated with a mixture of phenylalkyne, chloranil, and FeCl₃ <92JOC1842>. This reaction represents an example of a transformation of the general type (**163**) → (**151**).

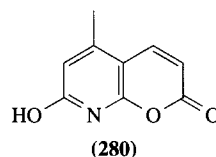
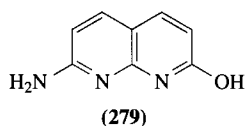
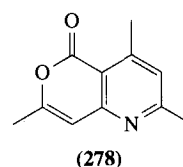
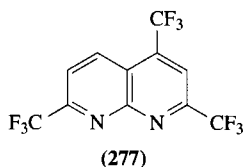
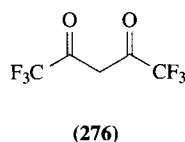
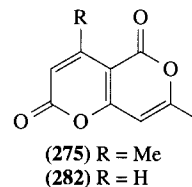
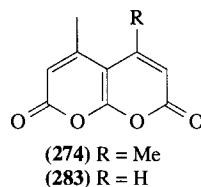
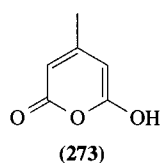
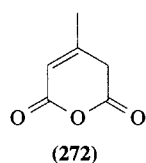
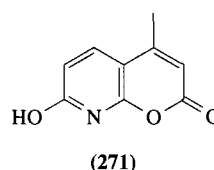
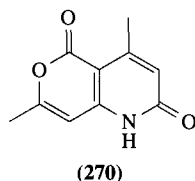
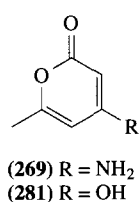
(iv) Synthesis of the second ring from [3 + 3] atom fragments

Transformations of the general type (**164**) → (**151**) are well represented. The Skraup and Conrad-Limpach reactions of aminopyridines giving naphthyridines and naphthyridones, respectively, have been considered in CHEC-I <84CHEC-I(2)581>. The Conrad-Limpach synthesis has also found application in the preparation of pyranopyridines. Thus, the aminopyranone derivative (**269**) reacts with ethyl acetoacetate in the presence of 4-toluenesulfonic acid giving heterocycle (**270**) (16% yield) <93JHC317>. A mixture of ethyl acetoacetate, ZnCl₂ and 2,6-dihydroxypyridine gives heterocycle (**271**) (15% yield) <78JOC1975> and a mixture of ethyl acetoacetate, P₂O₅ and pyranone (**272**)/(**273**) gives the isomeric products (**274**) (21% yield) and (**275**) (19% yield) <72AJC1367>.

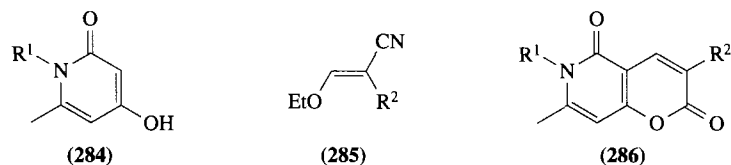
The Combes synthesis has been used for the preparation of fused pyridine derivatives. Thus, 2,6-diaminopyridine reacts with the fluorinated 1,3-diketone (**276**) and PPA giving the naphthyridine derivative (**277**) (95% yield) <86JHC501>, and compound (**269**) reacts with acetylacetone in acetic acid yielding heterocycle (**278**) (52% yield) <93JHC317>. A mixture of malic and sulfuric acids



have frequently been used as a source of three carbon atoms and the transformations of 2,6-diaminopyridine into 2-amino-7-hydroxynaphthyridine (**279**) (97% yield) <81JOC833>, 2,6-dihydroxy-4-methylpyridine into heterocycle (**280**) (50% yield) <34JCS1536>, compound (**281**) into the pyranopyrandonone derivative (**282**) in low yield <68JCS(C)543>, and compound (**272**)/(**273**) into the product (**283**) <72AJC1367> exemplify this approach.

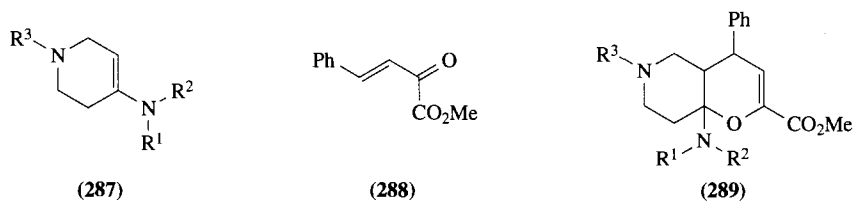


Compounds (**284**) react with the alkenes (**285**) in the presence of sodium ethoxide yielding the products (**286**) (56–64% yield) <78M1075>.



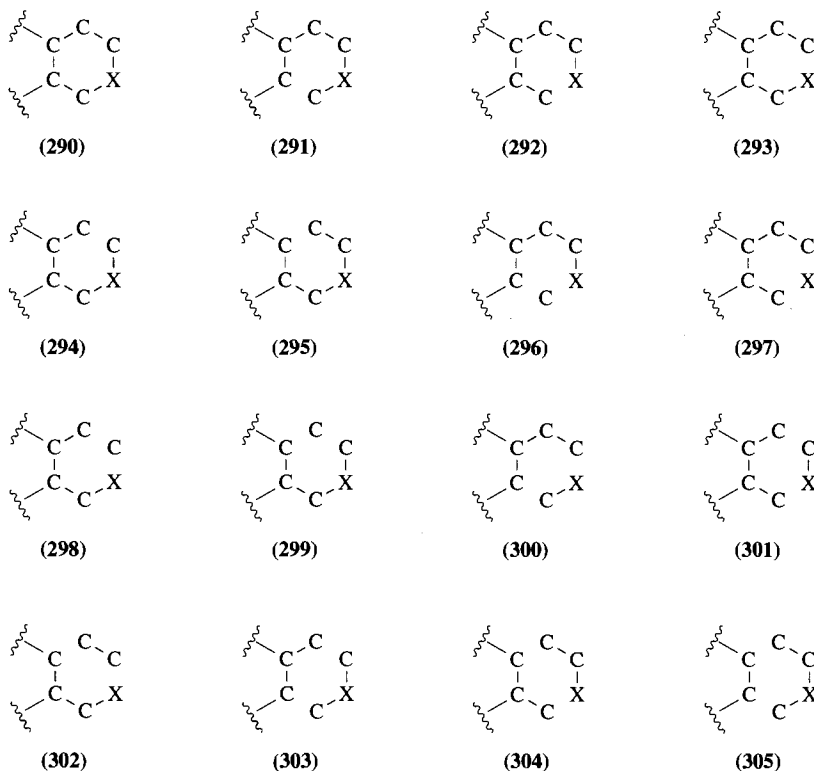
(v) *Synthesis of the second ring from [2 + 4] atom fragments*

The enamine (**287**; $R^3 = \text{Bn}$, $R^1 + R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$) reacts with ethyl benzoylacetate affording heterocycle (**99**) <87JHC111>. Enamines (**287**; $R^3 = \text{Me}$, $R^1, R^2 = \text{various groups}$) react with the ester (**288**) giving products (**289**) in moderate yield and related enamines behave similarly in this hetero-Diels-Alder reaction <85AP(318)648>.



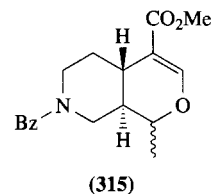
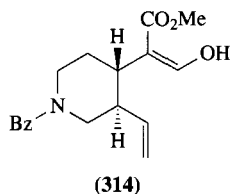
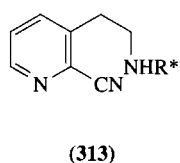
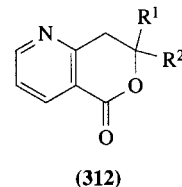
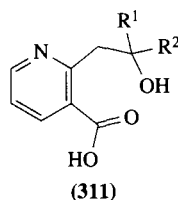
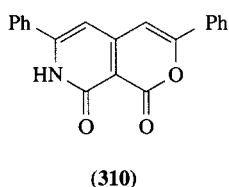
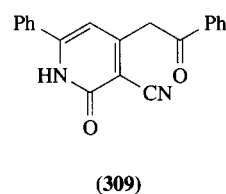
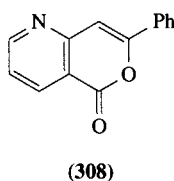
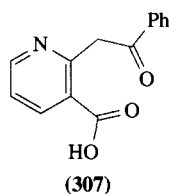
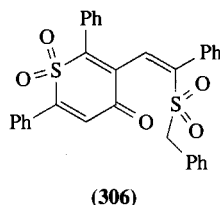
7.15.9.1.2 *Heteroatom in new ring remote from a bridgehead position*

This section considers the formation of a ring represented by the partial structure (**290**); the partial structures (**291**)–(**305**) indicate possible methods for construction of the second heterocyclic ring. The following subsections consider the formation of structure (**290**) according to the number of component atoms which are required to form the second ring. There are relatively few examples of transformations which require either a three- or four-atom component to construct the second ring and hence these transformations have not been considered. Structures have been orientated to correspond with the relevant formulae (**291**)–(**305**).



(i) Synthesis of the second ring from [6 + 0] atom fragments

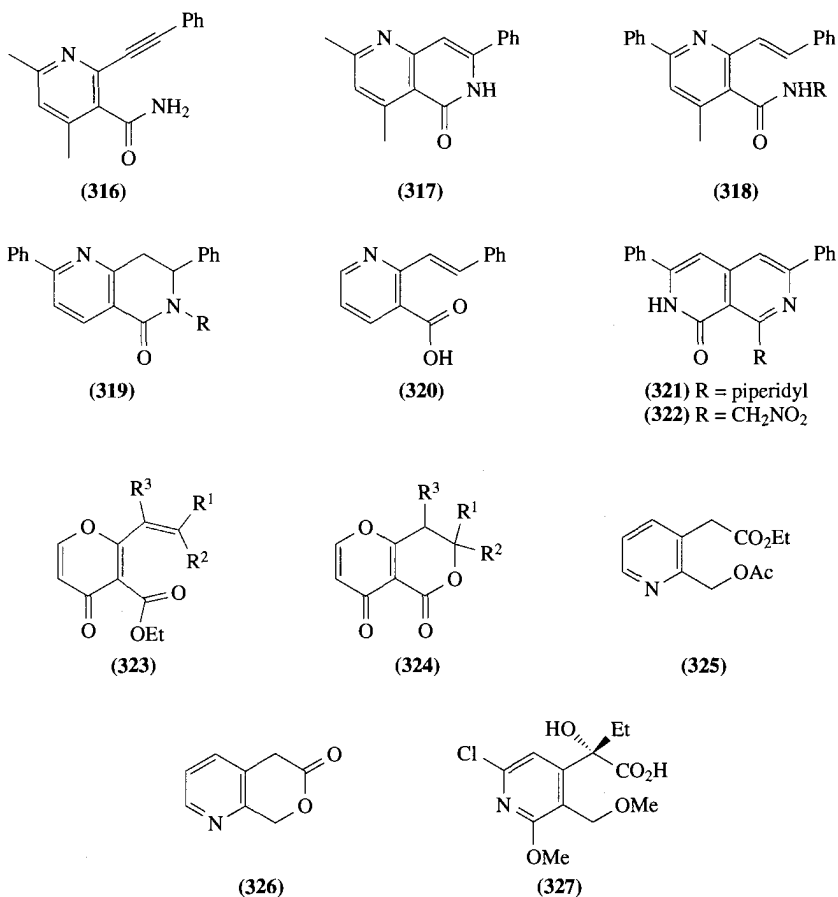
Sulfone (306) cyclizes in the presence of DBU yielding the diastereoisomers (133) in good yield <84JOC5136>: this transformation is an example of a cyclization of the type (291) → (290). Note the difference between this mode of cyclization and that depicted in Scheme 1.



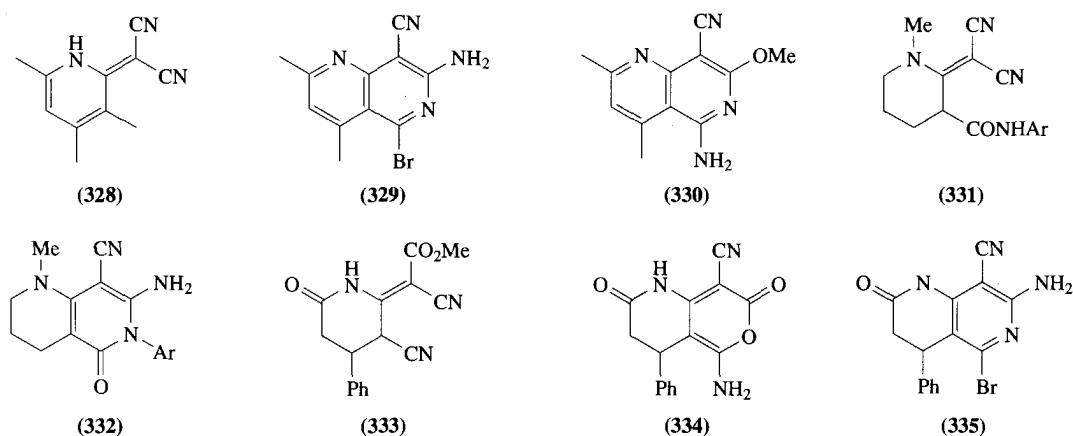
Examples of transformations of the general type (292) → (290) include: (a) cyclization of ketones (307) and (309) in aqueous acid affording products (308) <92SC1239> and (310) <70JHC495>, respectively; (b) cyclization of hydroxyacid derivatives (311) giving heterocycles (312) <92SC1239>; (c) cyclization of aminonitrile (313) in aqueous ethanol yielding product (41; R* = chiral group) <91CL125, 91T9369>; and (d) the reaction of enol (314) with Hg(OAc)₂ and then NaBH₄ yielding the pyranopyridine derivative (315) (70% yield) as a mixture of epimers. This heterocycle (315) was subsequently used in the synthesis of ajmalicine (145) <81HCA1663>.

Cyclizations of the general type (293) → (290) are well represented. The alkyne (316) gives the naphthyridone (317) (88% yield) when treated with sodium ethoxide and isomers of compound (316) undergo a similar reaction <85CPB626>. Dihydronaphthyridone derivatives have been obtained from alkenes and the reaction of compounds (318) with ppa giving naphthyridones (319) (33–66% yield) illustrates this reaction <84ZOB2083>. The pyranopyridone (308) has also been obtained by reaction of the alkene (320) with bromine <62JCS4528>. Ketone (309) gives naphthyridones (321) and (322) when treated with piperidine and the anion of nitromethane, respectively <70JHC495>. Alkene (323; R¹ – R³ = H, Me) gives the dihydropyranopyrans (324) (40–80% yield) when treated with ppa <82S1107>. Dihydropyranopyrans have also been obtained from derivatized hydroxy acids. Thus, compound (325) reacts with ethanolic KOH giving product (326) in low yield <60CPB427> and the chiral acid (327) gives lactone (137) (77% yield) when treated with TMSI <92JA10971>. Lactone (137) has been subsequently used in the synthesis of camptothecin (146).

The cyclizations of 2-(dicyanomethylene)-3-cyanopyridine derivatives, such as compound (328), have been discussed in CHEC-I <84CHEC-I(2)581> but continue to attract interest. Thus, compound (328) gives the naphthyridine derivative (329) (39% yield) with HBr and product (330) (16% yield)

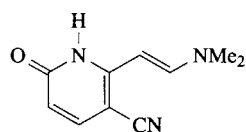


with sodium methoxide $\langle 83H(20)2405 \rangle$. Related reactions include the conversion of compounds (331) into heterocycles (332) (76–99% yield) with sodium ethoxide $\langle 86H(24)1247 \rangle$ and the transformation of compound (333) into either heterocycle (334) (94% yield) with HBr in dioxane at reflux temperature or products (334) (10% yield) and (335) (57% yield) with HBr in benzene at room temperature $\langle 93H(36)1 \rangle$.

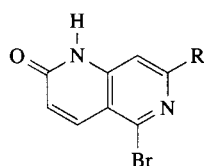
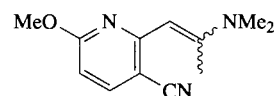


The cyclization of enamionitriles in the presence of HBr has also been covered in CHEC-I $\langle 84CHEC-I(2)581 \rangle$, and further examples of this reaction include the transformations of compounds (336), (338), and (340) into naphthyridones (337) (94% yield) $\langle 92JMC4858 \rangle$, (339) (62% yield) $\langle 91S894 \rangle$, and (136) (95% yield) $\langle 91S894 \rangle$ respectively.

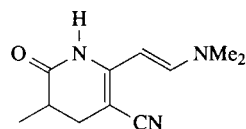
The diesters (341) participate in a Dieckmann condensation giving heterocycles (25) (60–70% yield) $\langle 84JCS(P1)1501 \rangle$ and this is a transformation of the general type (294) $\rightarrow$ (290).



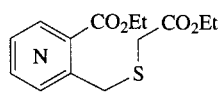
(336)

(337) R = H
(339) R = Me

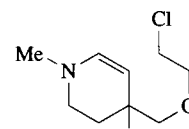
(338)



(340)



(341)

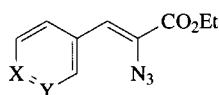
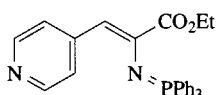


(342)

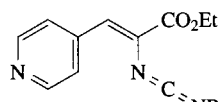
Enamine (342; Ar = 3-methoxyphenyl) reacts with NaI in acetonitrile at 80°C giving the pyrano-pyridine derivative (87) (40% yield) <89JCS(P1)1177> and this represents an example of a transformation of the general type (295) → (290).

(ii) Synthesis of the second ring from [5 + 1] atom fragments

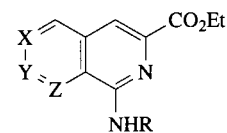
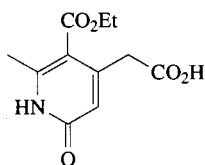
Isocyanates have provided one carbon atom in transformations of the general type (296) → (290). Thus, azide (343) reacts with triphenylphosphine in a Staudinger reaction giving phosphorane (344) which is then treated with isocyanates (RNCO; R = benzyl or aryl) giving naphthyridines (346) (50–59% yield) via the carbodiimide (345). The cyclization (345) → (346) occurred in toluene at 160°C <92T4601>. Azide (347) undergoes a similar sequence of reactions yielding a 1:1 mixture of isomeric naphthyridines (348) and (349) (44–47% yield).

(343) X = N, Y = CH
(347) X = CH, Y = N

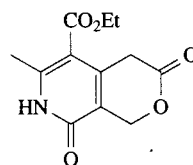
(344)



(345)

(346) X = Z = CH, Y = N
(348) X = N, Y = Z = CH
(349) X = Y = CH, Z = N

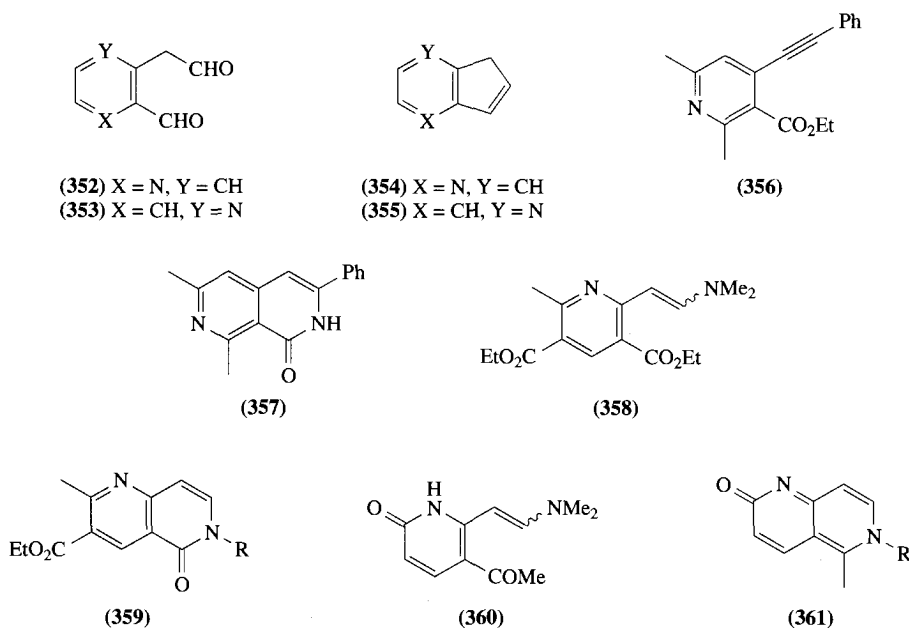
(350)



(351)

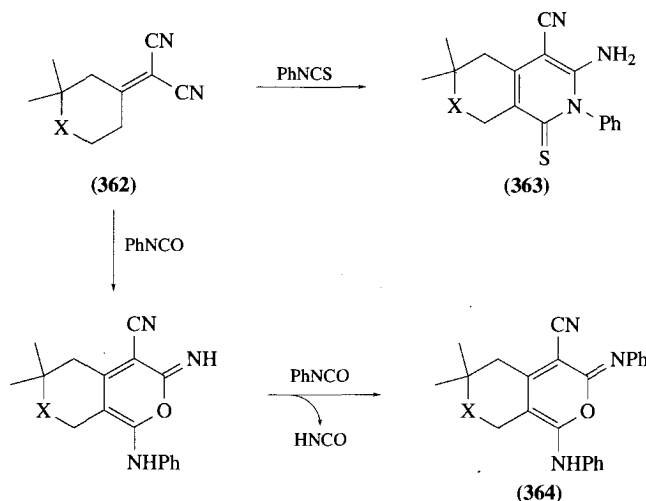
The pyridine derivative (350) gives heterocycle (351) (31% yield) when treated with chloromethyl methyl ether (MeOCH₂Cl) in acetic acid <71JA5575>.

Ammonia and amines can provide the X component in transformations of the general type (297) → (290). A mixture of aldehydes (352) and (353) (obtained by ozonolysis of a mixture of 5*H*-1-pyridinine (354) and 7*H*-1-pyridinine (355)) gives 1,7-naphthyridine (3) (47% yield) and 1,6-naphthyridine (2) (24% yield) with aqueous ammonia <84CC265>. Pyridine derivative (356) gives naphthyridine (357) (85% yield) with ammonia in ethanol <85CPB626> and enamine (358) yields heterocycle (359; R = H) (64% yield) with ammonia <86JCS(P1)753> and heterocycles (359; R = aryl) in good yields with appropriate primary amines <89JHC1755>. Enamine (360) affords products of general structure (361; R = 4-MeOC₆H₄, NMe₂, NH₂) (51–90% yield) with appropriate nucleophiles <92S279>.



(iii) Synthesis of the second ring from [4 + 2] atom fragments

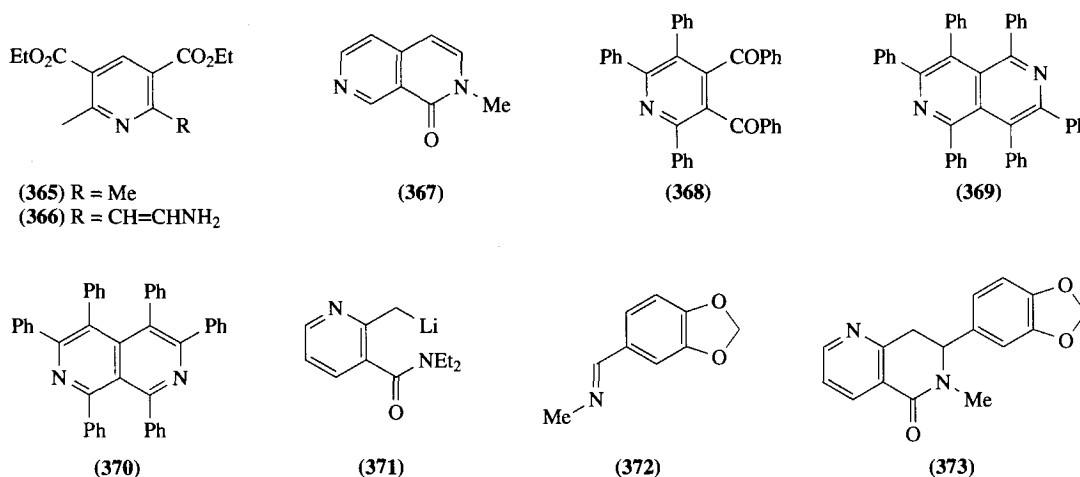
The dicyanomethylene derivatives (**362**; X = O, S) react with phenylisothiocyanate yielding the products (**363**; X = O) (70% yield) and (**363**; X = S) (76% yield) <87KGS989>. These reactions are examples of transformations of the general type (**300**) → (**290**). With phenylisocyanate the reaction takes a different course and products (**364**) are obtained (Scheme 3).



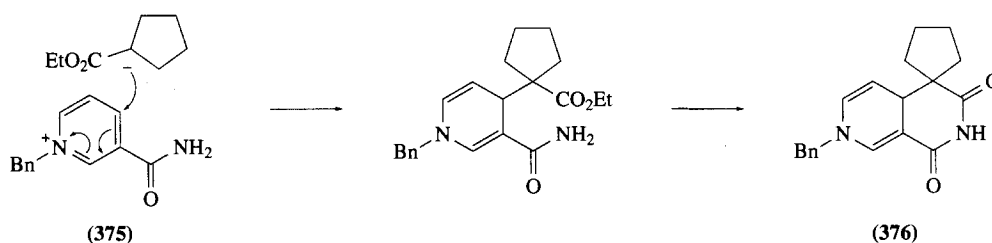
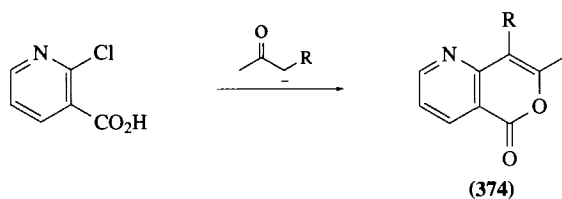
Scheme 3

1,3,5-Triazine has provided the C—X fragment in transformations of the general type (**301**) → (**290**). Thus, pyridine derivative (**365**) reacts with this triazine in the presence of sodium ethoxide giving heterocycle (**359**; R = H) (80% yield) via the intermediate enamine (**366**) which is not isolated <86JCS(P1)753>. 4-Substituted derivatives of pyridine (**365**) participate in a similar reaction <89JHC1755> as do 1,4-dihydropyridine derivatives of 4-substituted pyridines (**365**) <86S859>. The Vilsmeier reaction of 4-methylpyridine-3-carboxylic acid gives the naphthyridine (**367**) (58% yield) <83TL4607> for which a mechanism has been proposed. 2-Methylpyridine-3-carboxylic acid participates in a similar reaction. The diketone (**368**) gives a mixture of perphenylated naphthyridines (**369**) and (**370**) with benzylamine in moderate yields <83JHC971>. The lithio derivative (**371**) and imine (**372**) give heterocycle (**373**) (55% yield) <87JOC5378>.

2-Chloropyridine-3-carboxylic acid reacts with either the anion of acetylacetone or ethyl aceto-



acetate in toluene at reflux (Scheme 4) giving pyranopyridines (**374**; R = COMe, CO₂Et) (46–47% yield) <89IJC(B)173>. Pyridinium derivative (**375**) gives heterocycle (**376**) (51% yield) with the anion of ethyl cyclopentanecarboxylate (Scheme 5) and related compounds give similar products <82T2741>. The reactions illustrated in Schemes 4 and 5 correspond to transformations of the general type (**302**) → (**290**).

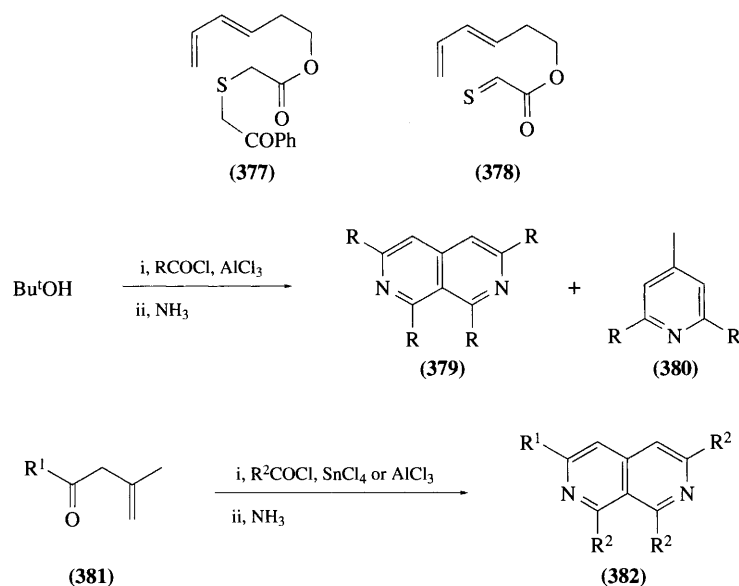


7.15.9.2 Synthesis From Acyclic Precursors

Photolysis of diene (**377**) affords heterocycle (**30**) (36% yield) via the thioaldehyde (**378**) which undergoes an intramolecular hetero-Diels–Alder reaction <88JOC2220>.

Friedel–Crafts acylation of *t*-butanol (Scheme 6) followed by treatment with ammonia gives a mixture of 2,7-naphthyridines (**379**; R = Me, Et, Prⁿ, Prⁱ, Bu) and pyridines (**380**) (38–91% yield) <84BSF449>. Heterocycles (**379**) are the major products in these reactions and pyrylium salts have been proposed as reaction intermediates. Unsymmetrical naphthyridines (**382**) have been obtained as the major products of the reaction of alkenones (**381**) under similar conditions (Scheme 6) <84BSF454>.

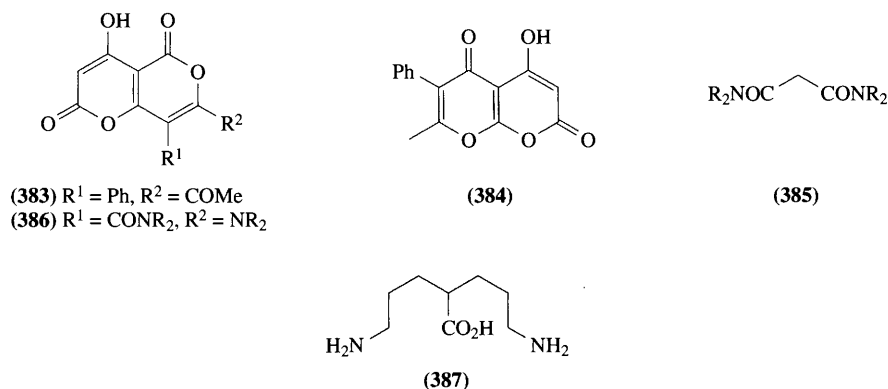
Benzoylacetone reacts with carbon suboxide in the presence of sulfuric acid as a catalyst yielding a mixture of pyranopyran derivatives (**383**) and (**384**) <67M2431>. In a related reaction, malonyl



Scheme 6

dichloride (a carbon suboxide equivalent) reacts with amides (385; R = Et, Ph) giving pyranopyrans (386) in good yield <93CB841>.

Heterocycle (68) (71% yield) is obtained by heating diamine (387) in toluene in the presence of 4-toluenesulfonic acid <84JHC583>.

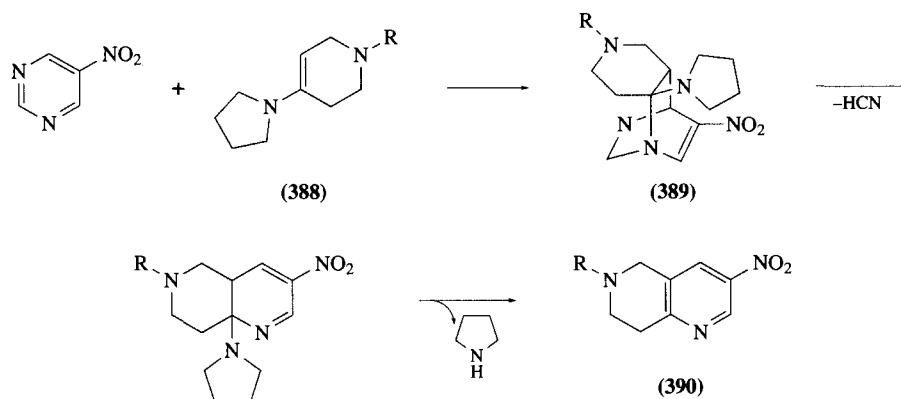


7.15.10 RING SYNTHESSES BY TRANSFORMATIONS OF OTHER RINGS

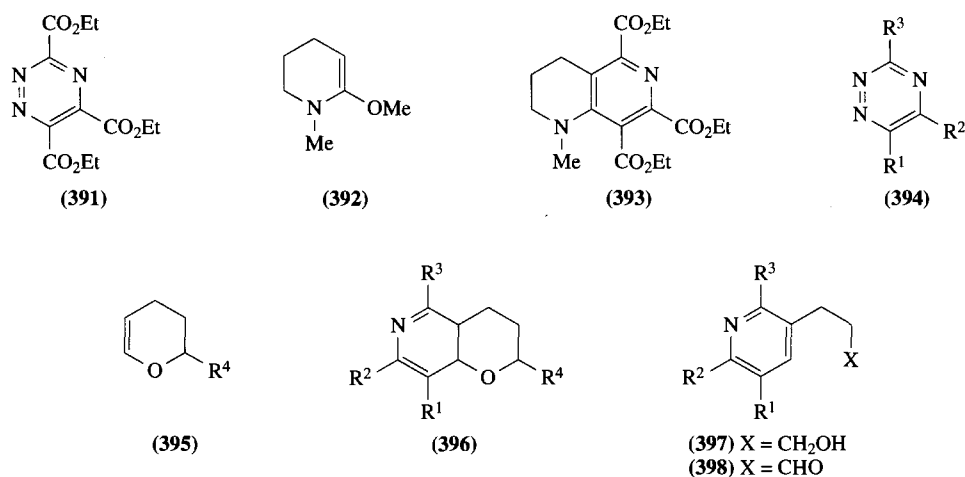
7.15.10.1 Hetero-Diels-Alder Reactions

7.15.10.1.1 Intermolecular reactions

5-Nitropyrimidine reacts with enamines (388; R = Me, COMe) giving the tetrahydronaphthyridines (390; R = Me, 16% yield; R = COMe, 48% yield) via the cycloadduct (389) (Scheme 7) <89T2693>. Triazine (391) reacts with heterocycle (392) giving product (393) (83% yield) in a related reaction <86CB3600>. Triazines of general structure (394) react with vinyl ethers (395) yielding the intermediates (396) which fragment affording the alcohols (397; R⁴ = H) or the aldehydes (398; R⁴ = OMe, OEt) <93T5277>.

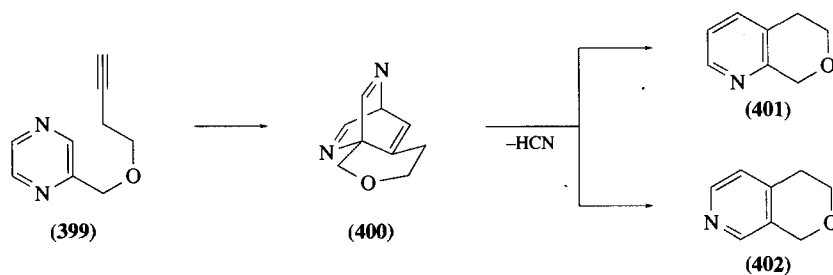


Scheme 7



7.15.10.1.2 Intramolecular reactions

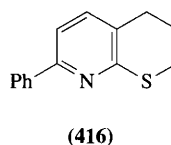
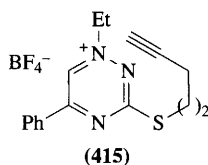
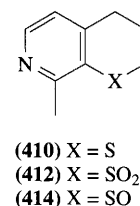
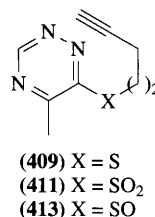
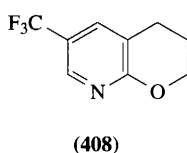
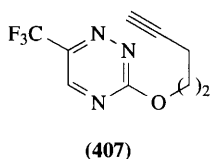
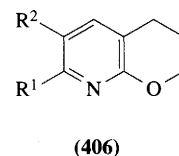
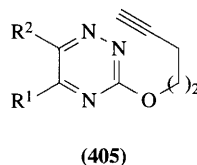
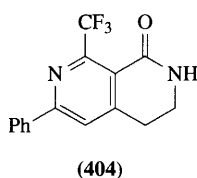
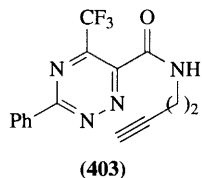
Diazine (399) undergoes an intramolecular Diels–Alder reaction (195°C, 135 h) yielding the intermediate (400) which fragments giving a mixture of the isomeric pyranopyridines (401) (40% yield) and (402) (22% yield) (Scheme 8) <89T6211>. In the presence of TFA this reaction proceeds at 72°C and gives heterocycle (402) (85% yield) <89T6519>.



Scheme 8

Triazine (403) gives the naphthyridone derivative (404) (95% yield) in diphenyl ether under reflux <90CZ381>. Triazines (405; R¹, R² = alkyl, aryl) give tetrahydropyranopyridines (406) in good yield at 200°C <87T5145> and triazine (407) gives heterocycle (408) (30% yield) when heated in diphenyl ether <92AP(325)349>. When triazine (409) is heated (64 h) in bromobenzene at reflux, the thio-pyranopyridine derivative (410) (57% yield) is obtained <89JOC4984>. The sulfone derivative (411)

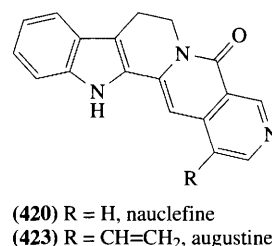
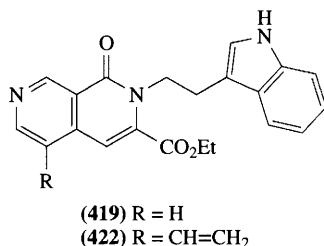
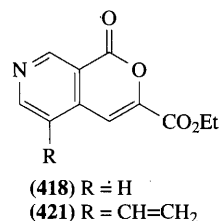
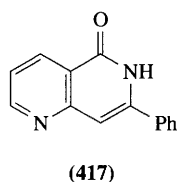
gives an excellent yield (99%) of the corresponding product (**412**) after 12 h at reflux in bromobenzene but, in contrast, the sulfoxide (**413**) gives only a trace of product (**414**). Salt (**415**) gives the tetrahydrothiopyranopyridine derivative (**416**) (40% yield) in dioxane at reflux <89T6499>.



7.15.10.2 Other Ring Transformations

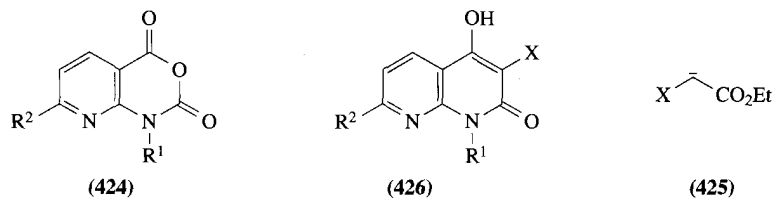
The thermal isomerization (**32**) → (**33**) has been discussed in Section 7.15.4.4.

Fused pyranone derivatives are converted into the corresponding fused pyridone derivatives by the action of an appropriate amine. Thus, heterocycle (**308**) yields naphthyridone (**417**) in moderate yield when reacted with ethanolic ammonia solution <62JCS4528>. Compound (**418**) and tryptamine gives the indole derivative (**419**) (82% yield) <76H(4)247>, which was used in the synthesis of nauclefine (**420**), and compound (**421**) and tryptamine gave heterocycle (**422**) (80% yield) <75H(3)627>, which was used in the synthesis of angustine (**423**).

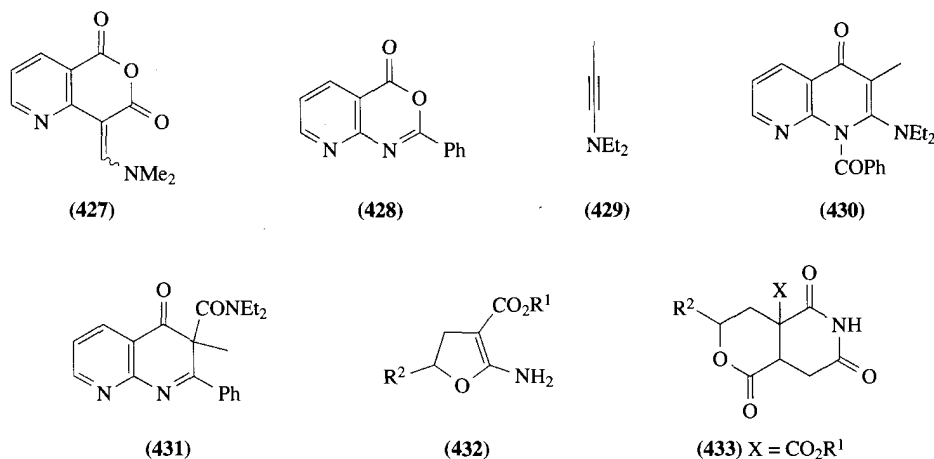


Heterocycle (**45**) reacts with ammonium acetate yielding product (**43**) and with methylamine giving product (**44**); other nucleophiles (e.g. aniline, H₂S) behave similarly <74JCS(P1)1389>.

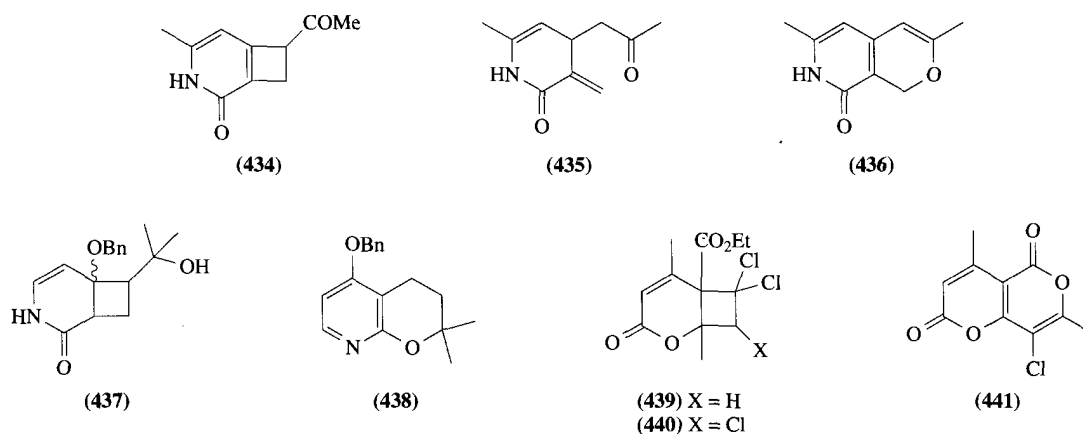
Aza derivatives (**424**) of isatoic anhydride react with anions of esters (**425**; X = NO₂, CO₂Et) giving naphthyridones (**426**), generally in good yield <85JHC193, 91JHC2029, 92JMC1130, 92JMC4866>.



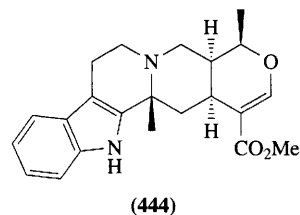
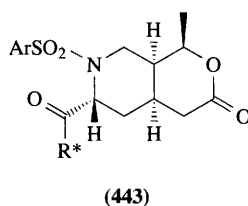
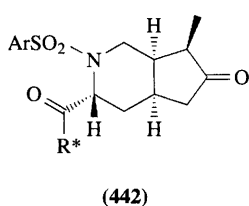
Heterocycle (**427**) gives naphthyridone (**128**) (69% yield) in a Vilsmeier reaction <83JJC(B)916>. Compound (**428**) and alkyne (**429**) yield product (**430**) (75% yield) in acetonitrile at 110°C and product (**431**) (58% yield) in toluene at 110°C <87CB1427>. Maleic anhydride reacts with enamine (**432**; R¹ = Me, Et; R² = H, Me) giving pyranopyridtriones (**433**) (9–27% yield) <80S698>, and a mechanism has been proposed for this transformation.



Fused cyclobutane derivatives can yield 6-6 heterocycles. Thus, compound (**434**) gives the dihydropyranopyridine derivative (**436**) (28% yield) in xylene at reflux temperature via the intermediate (**435**) <82CL1361>, cyclobutane (**437**) gives heterocycle (**438**) (25% yield) as the major product when treated with SnCl₄ <82CPB1531> and compounds (**439**) and (**440**) afford products (**275**) and (**441**), respectively, with DBU and either methanol or ethanol <92JHC387>.



Bayer–Villiger oxidation of the cyclopentanone derivative (**442**; R* = chiral auxiliary) with MCPA gives the saturated pyranopyridone derivative (**443**) which has been used in the total synthesis of the heteroyohimbine alkaloid, 3-isoraunicine (**444**) <91JA9660>.



7.15.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISONS OF THE VARIOUS ROUTES AVAILABLE

There are numerous ways of preparing heterocycles of general structure (151). Intramolecular cyclizations of the general type (153) → (151) and (156) → (151) are commonly encountered, and the former mode of cyclization is the most common method for preparing fully saturated heterocycles. The latter mode of cyclization includes the EMME synthesis. Transformations of the general type (162) → (151) (Friedländer synthesis) are popular because of the availability of a wide range of appropriate two carbon atom components which are used to construct the second ring. Transformations of the general type (164) → (151) are associated with a diverse variety of reactions (Skraup, Combes, Conrad-Limpach, and malic acid syntheses) and, since structures (164) and appropriate three carbon atom components are readily available, these methods for the preparation of fully conjugated 6-6 systems are extremely common.

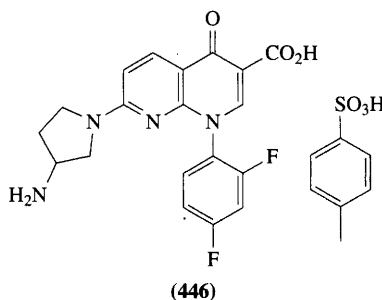
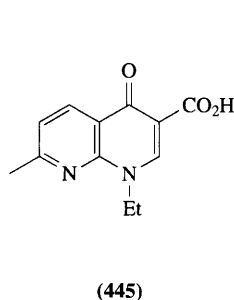
In contrast, there are fewer general methods for preparing heterocycles (290): these compounds are usually prepared by cyclizations of the general type (292) → (290) and (293) → (290).

Fused pyridone derivatives are commonly prepared from the corresponding fused pyranone derivative and an amine.

Tetrahydronaphthyridines, tetrahydropyranopyridines, and tetrahydrothiopyranopyridines are available via hetero-Diels-Alder reactions (Section 7.15.10.1).

7.15.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Medicinally important naphthyridine derivatives such as analogues of the antibacterial agent naladixic acid (445) <91MI 715-02> have been discussed in CHEC-I <84CHEC-I(2)581> and in another review <83AHC147>. Tosufloxacin tosylate (446) is an example of a nalidixic acid analogue.

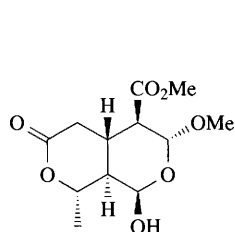


The naphthyridine ring system is found in numerous alkaloids, nauclefine (420) <76H(4)247> and angustine (423) <75H(3)627> being two relevant examples.

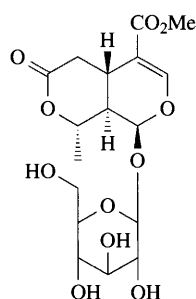
The pyranopyridine ring system is also present in numerous alkaloids, two examples are ajmalicine (145) <92JCS(P1)517> and camptothecin (146) <92JA10971>. The *trans* 8a-aryloctahydropyrano[4,3-*c*]pyridine (88) and related compounds have been prepared as morphine analogues <89JCS(P1)1177>.

There are many natural products associated with the pyranopyran ring system. Examples include the iridoid terpene xylomollin (447) <86JA6802> and the secoiridoid glucoside kingisidic acid (448) <93P1071>. Monobenzopyranopyran derivatives include aflatoxins G₁ (449) and G₂ (450) which are metabolites of the mould *Aspergillus flavus* <94JOC3775>. The dibenzopyranopyran ring system <75MI 715-01> commonly occurs in natural products, and one example from rotenoid chemistry is the

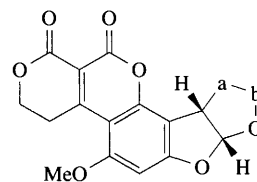
insecticidal agent rotenone (**451**) <79COC(4)763, 84MI 715-02>. There is also an extensive and diverse number of complex polycyclic ethers which possess a fully saturated pyranopyran moiety, examples include the marine neurotoxin hemibrevetoxin B (**452**) <92JA7935> and related compounds such as brevetoxin A and brevetoxin B <86JA7855, 87JA2184>.



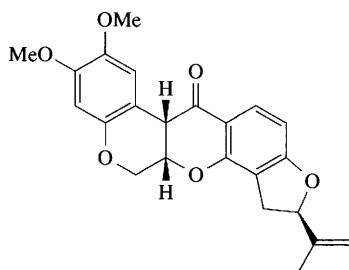
(447)



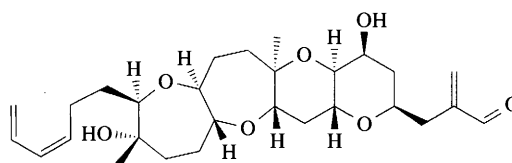
(448)



(449) a-b = CH=CH

(450) a-b = CH₂CH₂

(451)



(452)

7.16

Bicyclic 6-6 Systems: Three Heteroatoms 1 : 2

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7.16.1 INTRODUCTION

This chapter deals with the chemistry of bicyclic 6-6 systems containing three heteroatoms distributed 1:2 in the two rings. The commonest heteroatoms are nitrogen, oxygen, and sulfur. Consequently, a great number of heterocycles can be expected under such a heading. The scope of the present chapter covers fused pyrido-, pyrano-, and thiopyrano rings with heterocyclic rings containing two nitrogen, one nitrogen and one oxygen as well as one nitrogen and one sulfur atom. The literature of pyrido[x,y-z][1,n]diazines, oxazines, and thiazines, as well as pyrano- and thiopyrano[x,y-z][1,n]diazines, oxazines, and thiazines, from 1982 to 1993 is considered. The notation x,y and z indicates the face of fusion, whereas n indicates the relative positions of the two heteroatoms on the corresponding ring. Fusion of a benzo ring onto a pyridine ring leads to a class of compounds which are reported in *Chemical Abstracts* as diazinoquinolines and diazinoisoquinolines.

Heterocycles with two oxygen or sulfur atoms in one of the rings, i.e., dioxane and dioxolanes as well as their thia analogues have not been considered in this chapter; many such ring systems are in the carbohydrate series in the form of acetals.

The relevant chapter in the first edition of *Comprehensive Heterocyclic Chemistry* (84CHEC-I(2)199) dealt only with pyridodiazines. Other reviews relevant to this topic have dealt with pyridopyrimidines (92CHE1) and pyrano- and thiopyranopyrimidines (92CHE119). According to the relative numbers of publications, the pyridopyrimidines constitute the greatest area of interest, particularly those with [2,3-*d*] ring fusion.

There are six, four, and two possible isomeric structures for each of the pyrido-, pyrano-, and thiopyrano[x,y-*z*]pyridazine, pyrimidine, and pyrazine systems, respectively, which are shown in Figure 1.

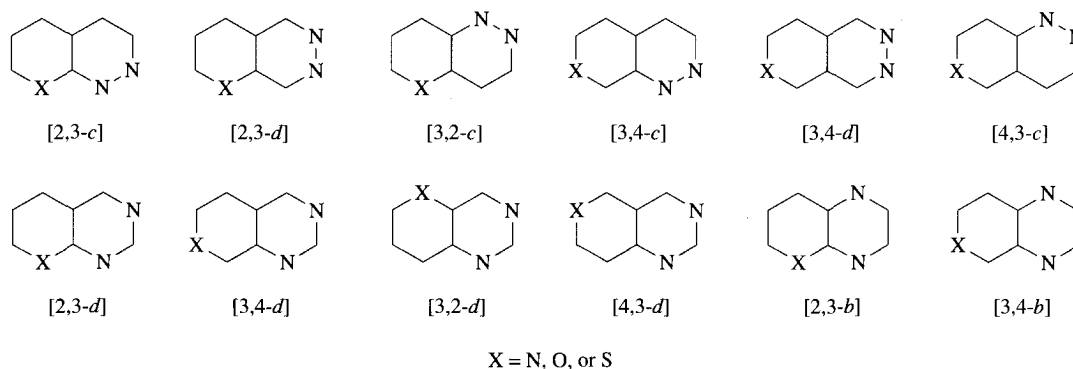


Figure 1

By considering the possible locations of the three heteroatoms and fusion of the bicyclic 6-6 system of pyrido[x,y-*z*][1,*n*]oxazines and thiazines, it is possible to write 24 isomers for each of the oxygen and sulfur analogues. The same number of isomeric structures holds also for the pyrano- as well as the thiopyrano[x,y-*z*][1,*n*]oxazines and thiazines. Fusion of a benzo ring on bond [*e*] or bond [*d*] of the former system and on bond [*e*] of the second system will lead to 12 isomeric structures in each case for each heteroatom. Each of the 12 structures could be divided into 6, 4, and 2 structures belonging to the [1,2], [1,3] and [1,4]oxazines and thiazines, respectively.

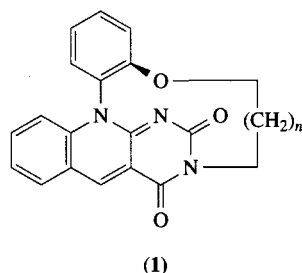
7.16.2 THEORETICAL METHODS

The reactivity of the four parent bicyclic pyridopyrimidines has been correlated. The net charges on particular carbon and nitrogen atoms were calculated by the semiempirical MNDO method. From the calculated data it appears that the unsubstituted isomeric pyridopyrimidines will be attacked by nucleophiles at position 2 in the following order of decreasing reactivity: [3,4-*d*] ≥ [3,2-*d*] > [2,3-*d*] > [4,3-*d*]. For position 4 the following order appears to operate: [3,4-*d*] > [2,3-*d*] ≥ [3,2-*d*] > [4,3-*d*] (87M399). It should be mentioned, however, that the [4,3-*d*] system was found to be the most reactive under acidic conditions (pH 2) where, after covalent hydration, ring opening occurs with great ease. Except for the [3,2-*d*] system, it appears that nucleophilic attack would preferentially take place at position 4, rather than at 2. There are also small differences in total energies of these systems and calculations predict that the [4,3-*d*] and [3,2-*d*] systems are the most stable of the four isomeric bicycles.

The significant acidity of the methyl groups in 1-aryl-2-methyl-1,4-dihydro-4-pyrido[2,3-*d*]pyrimidinones agrees with calculations that were carried out using the Hückel method (91KGS1397).

Calculations using the Hückel method for 1-aryl-2-acetyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4-ones show that the keto form is energetically more favorable than the enol form (88KGS1649). *Ab initio* MO calculations on 10-phenylisoalloxazine suggest that compound (1) with the smaller angle (θ) between the isoalloxazine ring and the 10-phenyl ring is destabilized by steric hindrance (89JA4928, 89JA4935).

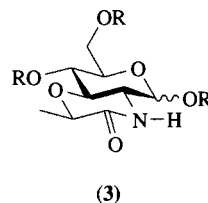
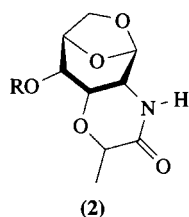
The induced circular dichroism (ICD) spectra of the (β -CD)_n complexes of pyrido[2,3-*b*]pyrazines have been measured. The polarization analysis and spectral assignments were made by comparing the theoretical results calculated using the CNDO/S-CI approximation with the observed ICD spectra (82JA7059).



7.16.3 EXPERIMENTAL STRUCTURAL METHODS

7.16.3.1 X-Ray Diffraction

X-ray crystallographic studies of 5-deazaflavinophanes (1) established that the dihedral angle (θ) is 76.5° (89JA4928, 89JA4935). X-ray crystallographic analysis of 6,7,8-trichloro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine has been reported (92H(34)1539). X-ray analysis of compound (2; R = CH₃CO) confirmed its presence in a highly distorted conformation which on opening gives a glucopyranose moiety which adopts the ⁴C₁ conformation as in structure (3) (93CAR(241)131).

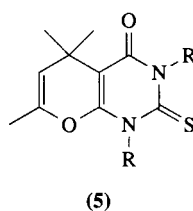
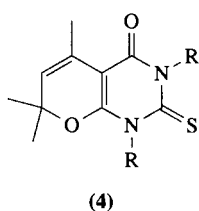


7.16.3.2 NMR Spectroscopy

NMR spectra have been used frequently to elucidate and/or confirm the structures of these heterocycles, but little or no systematic study had been done. A detailed study of ¹³C NMR spectra by distortionless enhancement by polarization transfer (DEPT), inverse ¹H-¹³C coherence transfer experiments (HMQC and HMBC) and by INADEQUATE of factor *F*₀ has been reported (91JBC9622). The ¹³C NMR spectra of a series of pyrido[4,3-*d*]pyrimidines were interpreted on the basis of a detailed study of other analogues (91JCS(P2)1559). Carbon-13 NMR spectroscopy has been used to indicate the site of alkylation of pyrido[2,3-*c*]pyridazin-4-ones (90CPB3359).

The anisotropy effect of the carbonyl group in 7-aryl-5-phenyl-1,2,3,4-tetrahydro-2-thio-4-oxo-pyrido[2,3-*d*]pyrimidine causes a low-field shift of the protons of the aryl group linked to C-5, which was used to determine the orientation during the cyclization process of its formation (92JHC1045).

Proton NMR differentiated between the isomeric structures (4) and (5) (90T3953) and ¹³C NMR concluded that the main difference between these structures is in the chemical shifts of the tertiary carbon atoms at C-7 and C-5 (90T3953).

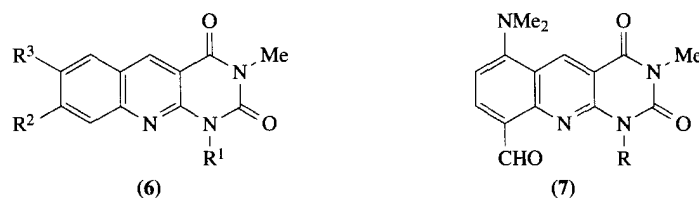


7.16.3.3 Mass Spectrometry

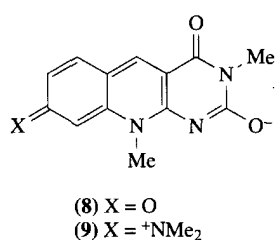
Little work has been done on the detailed study of the fragmentation patterns of these heterocycles. The fragmentation patterns of pyridopyrimidine-2,4-diones have been reported <86H(24)2201>. The electron impact fragmentation of pyranooxazines was studied <84MI 716-01, 89MI 716-02>. A possible mechanism for the loss of CO₂ from the 4,5-dioxopyrano[3,4-*e*][1,3]oxazine ring has been reported <89MI 716-01>. Mass spectra of 2-amino-4*H*-pyrido[4,3-*d*][1,3]thiazines suggest a method for tautomer identification <89OMS(24)517>.

7.16.3.4 UV, IR, and Photoelectron Spectroscopy

UV spectra were used to study tautomeric forms (see Section 7.16.4.2). The properties of substituted 5-deazaalloxazines (6) and (7) were investigated to provide a basis for the interpretation of pH effects on the spectroscopic properties of donor-substituted 5-deazaalloxazines in comparison with naturally occurring 5-deazaflavins.



With regard to their UV and visible spectra in various states of ionization, the 8-dimethylamino- and 8-hydroxydeazaalloxazines were found to be comparable with the substituted 5-deazaflavins (8) and (9), respectively <82AP(315)959>. 5-Deazaalloxazines substituted at C-8 exhibited red-shifted light absorption spectra <85JHC873>. Photophysical and photochemical properties of deazaflavin (3,10-dimethylpyrimido[4,5-*b*]quinoline-2,4-(3*H*,10*H*)-dione) and some of its 1,5-dihydro derivatives have been investigated. Contrary to earlier reports, the photodimer of deazaflavin is nonluminescent throughout the temperature range 77–295 K <83AJC1873>. Excitation of deazaflavin in the presence of oxalate anion causes photodimerization via a possible triplet excimer of deazaflavin. The lowest excited triplet (*T*₁) states of pyrido[2,3-*b*]pyrazine in three environments were studied <87JPC1754>.



The fluorescence excitation and emission maximum of pyrido[2,3-*d*]pyridazine-1,4-(2*H*,3*H*)-dione are found at 285 and 380 nm, respectively <83MI 716-01>.

IR spectra have frequently been used as a method for confirming structures <90CPB3359>.

7.16.3.5 ESR Spectroscopy

When potassium metal was added to a DMF solution of 3,10-dimethyl-5-deazaflavin, the ESR spectrum of the corresponding radical anion was observed, although very short-lived. A Hückel calculation on this radical anion gave the spin densities <87JHC251>. The application of 5-deazaflavin in the reduction of redox enzymes has a serious drawback. The wavelength needed (300–400 nm) corresponds to an energy level high enough to destroy the protein enzyme with time <85JHC841>.

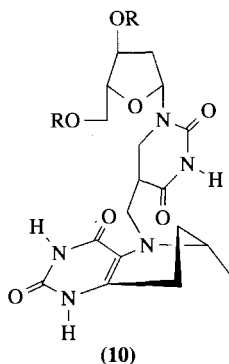
7.16.4 THERMODYNAMIC ASPECTS

7.16.4.1 Conformation

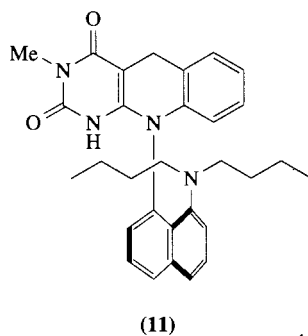
The interatomic distances, bond lengths, bond angles, and torsion angles of the energetically most favorable conformer of (pyridylcarbamoyl)pyrido[3,2-*e*][1,2]thiazine dioxide was determined by application of computer-assisted drug design (CADD) software. The results show that the pyridine ring plane is roughly parallel to that of the pyridothiazine moiety owing to restricted rotation about the C—CO bond <88MI 716-01>.

5-Methyl-2-[(2,3,4-tri-*O*-acetyl- β -D-arabinopyranosyl)thio]-3,4-dihydro-7*H*-pyrano[2,3-*d*]pyrimidine-4,7-dione is orthorhombic. The sugar ring is in a $^4C_1$ chair conformation and makes dihedral angles of 74.5° and 75.7° with the pyran and pyrimidine rings. The sulfur atom occupies an axial position on the sugar ring and lies 246.19 pm out of the corresponding mean plane <93AX626>.

The ^1H NMR spectrum of compound (10; R = CH₃CO) shows the presence of two diastereoisomers. A series of decoupling experiments was performed to detect the conformation of the molecule <82JOC4391>.

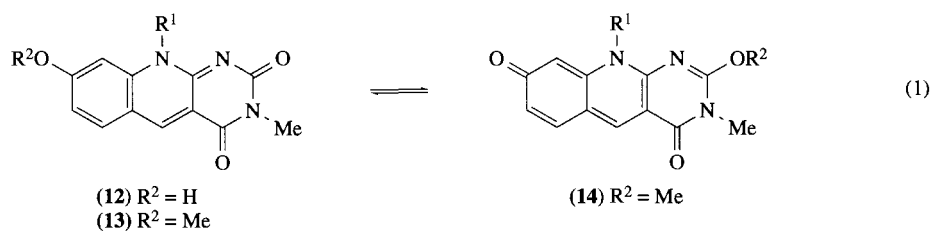


The central ring of compound (11) adopts a fixed boat or half-boat conformation and the proton at lower magnetic field occupies a (pseudo) equatorial position and that at higher field a (pseudo)axial position; consequently, the molecule adopts a bent conformation <90CL1197>.



7.16.4.2 Tautomerism

The existence of paraquinoid-phenolic tautomerism in an ethanolic solution of the derivatives (12) was found (Equation (1)); reaction with diazomethane gives the isomers (13) and (14) <83CL713>.

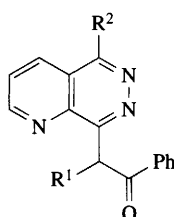


The ^1H NMR and UV spectra of 1-aryl-2-acetyl(2-phenacyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4-ones indicated their existence in two tautomeric forms with strong intramolecular hydrogen bonds <88KGS1649, 91KGS1397>.

7.16.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.16.5.1 Pyrido[x,y-*z*]pyridazines

Reaction of 1,4-dichloropyrido[2,3-*d*]pyridazine with acetophenone in the presence of NaH afforded a mixture of di- and monobenzoylmethyl derivatives (**15**) and (**16**), respectively, while reaction with phenylethylketone afforded only the monosubstituted derivative (**17**) <83YZ623>.

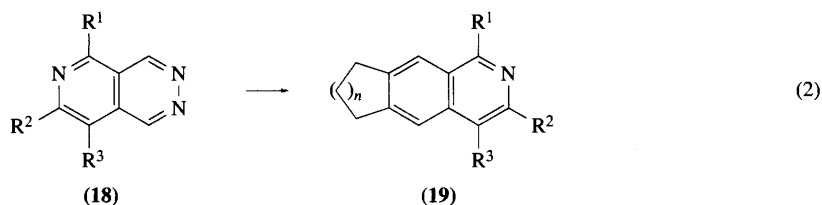


(**15**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_2\text{COPh}$

(**16**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Cl}$

(**17**) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Cl}$

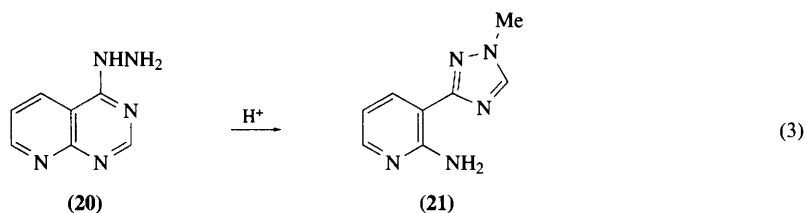
Employment of pyrido[3,4-*d*]pyridazine derivatives (**18**) as azadienes in inverse electron-demand Diels–Alder reactions with 1-pyrrolidino-1-cyclopentene, or its six-membered homologue, provides a good route to the isoquinolines (**19**) after aromatization of the dihydroisoquinoline intermediates (Equation (2)) <92TL7173>.



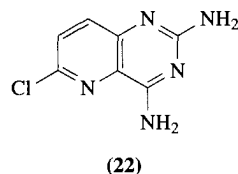
Oxidation of 5-phenylpyrido[2,3-*d*]pyridazine with MCPBA gave the respective 7-oxide, whose reactions with nucleophiles afforded the 8-substituted products <83YZ631>.

7.16.5.2 Pyrido[x,y-*z*]pyrimidines

Thermolysis of the hydrazine (**20**) in toluene–methanol catalyzed by TFA led to a translocative rearrangement to give the 2-aminopyridine derivative (**21**) (Equation (3)) <88JOC5309>.

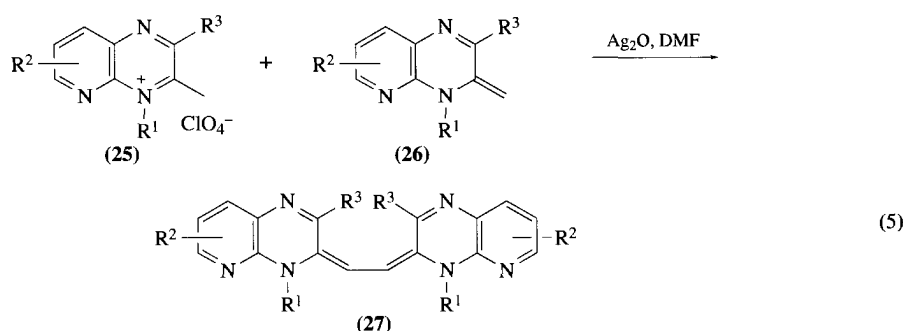
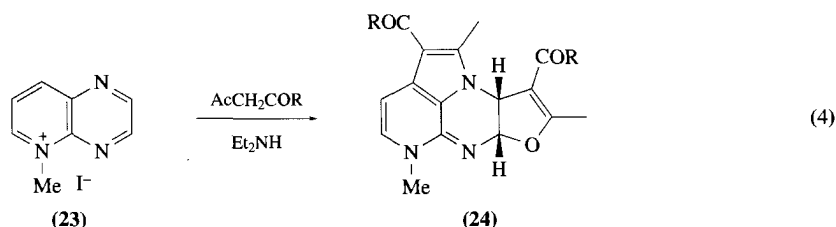


Oxidation of compound (22) with peroxytrifluoroacetic acid gave the corresponding *N*(5)-oxide, which reacted with piperidine to give the piperido derivative <85JMC248>.



7.16.5.3 Pyrido[x,y-z]pyrazines

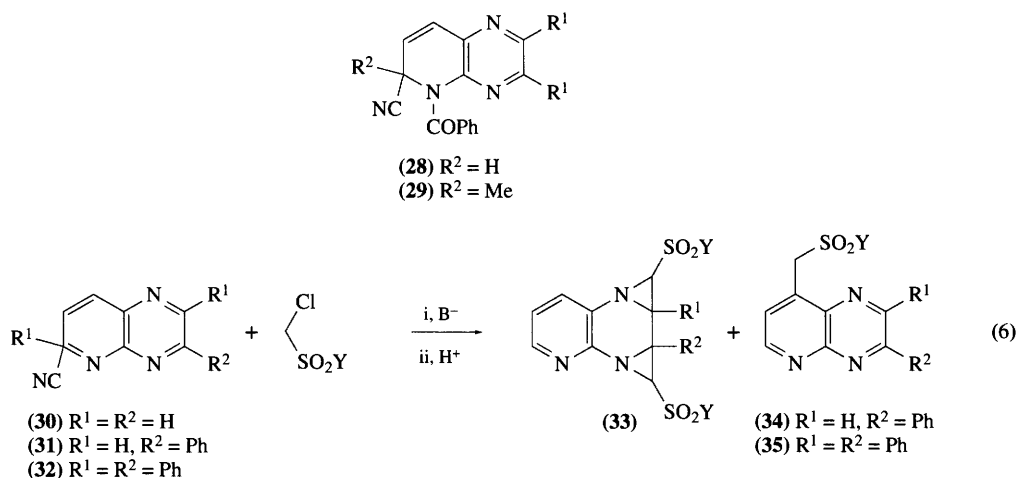
Quaternization at N-4 of pyrido[2,3-*b*]pyrazines using MeI gives the pyridopyrazinium salts <82KFZ1329>, which undergo addition of hydroxide ion at C-3 to give the respective mono-adduct <86KGS1380>. Reaction of the pyrido[2,3-*b*]pyrazinium cation (23) with β -diketones gave the derivatives (24) (Equation (4)) <81KGS1543>. The reaction of the perchlorate (25) with (26) gave (27) (Equation (5)) <81HCA2665>.



Reduction of pyrido[2,3-*b*]pyrazines with NaBH_4 gives, according to the substituents, 1,2- or 5,6-dihydro or 1,2,3,4-tetrahydro derivatives <88CJC1500>. Their catalytic hydrogenation using Pd/C in ethanol leads to mixtures of the 1,2,3,4- and 5,6,7,8-tetrahydro derivatives. Reduction of the unsubstituted heterocycle takes place on the pyrazine ring and that of the 2,3-diphenyl derivative takes place on the pyridine ring. In acetic acid this reduction gives only 1,2,3,4-tetrahydro derivatives. The observed selectivity could result from the isomerization of the partially hydrogenated intermediates <82CJC2785>.

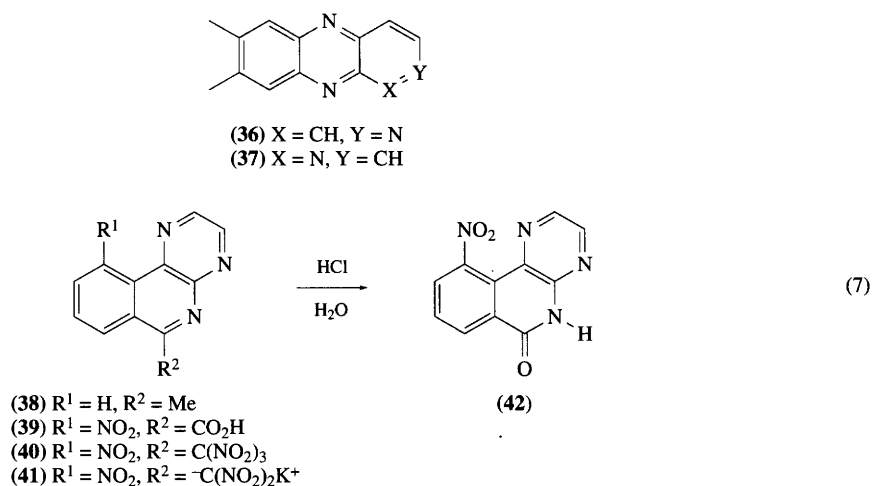
Reduction of 5,7-diaminopyrido[3,4-*b*]pyrazine with NaBH_4 gives the 1,2-dihydro derivative whose enantiomers can be separated by reaction with (*R*)-1-(1-naphthyl)ethylisocyanate <89JMC2089, 89JMC2363>. Reduction of the *N*-oxides with sodium dithionite gives the deoxygenated product <92SI206>.

Pyrido[2,3-*b*]pyrazines give Reissert compounds (28) by the action of TMS-CN-BzCl and subsequent methylation gives the derivatives (29) <82JHC425>. Carbanions of α -haloalkyl(aryl)sulfones, sulfonates, and sulfonamides react with the 5-azaquinoxaline (pyrido[2,3-*b*]pyrazine) (30) to give (33) (Equation (6)) <88MI 716-05, 91CB577>. In the σ adducts of the carbanions with (31) and (32) the negative charge is more efficiently delocalized, so that the annulation is accompanied by the formation of small quantities of derivatives (34) and (35), respectively. The use of strong base (Bu^tOK) shifted the reaction towards elimination, leading to (34) or (35) <91CB577>. In the case of compound (30), to obtain the elimination product the reaction has to be done at low temperature and with excess Bu^tOK <88T1721>.



7.16.5.4 Benzo Derivatives of the Pyridodiazines

Electrochemical reduction of the derivative (36) in H_2O -MeOH gave the 5,10-dihydro derivative, whereas reduction of either (36) or (37) with $NaBH_4$ or $LiAlH_4$ gave the respective 1,2,3,4-tetrahydro or 1,2-dihydro derivatives. Compound (36) reacts with $MeMgBr$ to give 1,7,8-trimethylpyrido[3,4-*b*]quinoxaline <88CJC1500>. Nitration of compound (38) introduced a nitro group at position 10 together with oxidation of the 6-methyl group to give the acid (39). Nitration at room temperature gave the nitro compound (40), whose reaction with KI gave the salt (41) which upon boiling in HCl gave the acid (42) (Equation (7)) <92AJC2083>.



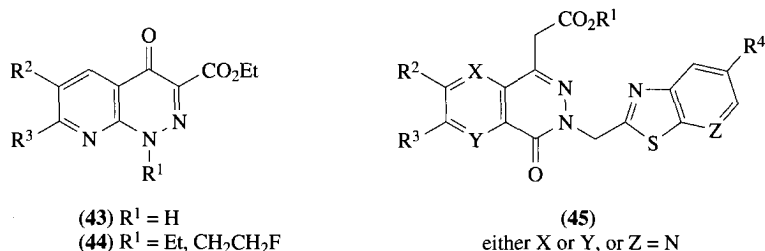
7.16.6 REACTIVITY OF NONCONJUGATED RINGS

7.16.6.1 Pyrido[x,y-z]pyridazines

7.16.6.1.1 Electrophilic attack at ring nitrogen

Alkylation of the derivative (43) with EtI or with 2-fluoroethyltosylate occurred at N-1 rather than at O-4 to give (44; $R^1 = Et, CH_2CH_2F$) <87JHC55, 90CPB3359>. Alkylation of *t*-butyl 5-oxo-6*H*-

pyrido[2,3-*d*]pyridazin-8-yl-acetate with 2-chloromethyl-5-trifluoromethylbenzothiazole gave (45) <90EUP401981, 90USP4954629>.



Oxidation of pyrido[2,3-*d*]pyridazine-5,8-dione with peracetic acid gave the *N*(1)-oxide <84AJC87>, which could also be obtained by reaction of pyridine-2,3-dicarboxylate 1-oxide with hydrazine hydrate. Similarly, the pyrido[3,4-*d*]pyridazine-1,4-dione was oxidized to the 6-oxide.

7.16.6.1.2 Nucleophilic attack at ring carbon

Deoxygenation of the 4-oxo position in pyrido[2,3-*c*]pyridazin-4-ones can be effected by NaBH₄-BF₃·Et₂O <90CPB3359>.

7.16.6.2 Pyrido[x,y-*z*]pyrimidines

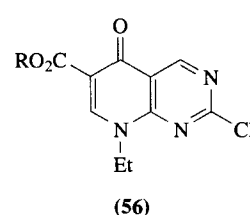
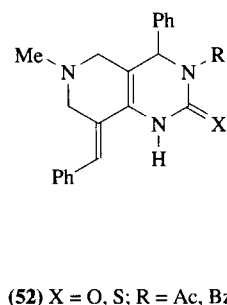
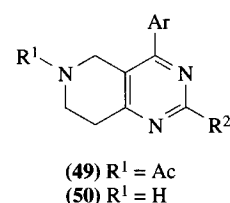
7.16.6.2.1 Electrophilic attack at ring nitrogen

Methylation of 1-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-2-one with dimethylcarbonate in DMF gives the corresponding N-3 methylated product <82JAP5760352>. Ethylation of the 8-position gave the *N*-ethyl derivatives <82JAP(K)8248984>. The 4-oxo analogues react with diethylaminoethyl chloride, 2-hydroxy-3-morpholinopropyl chloride or *N*-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole to give the *N*-3-alkylated derivatives <86MIP136563, 87MIP136564, 92EUP481614>. Alkylation of 3-substituted pyrido[2,3-*d*]pyrimidine-2,4-diones gives the corresponding N-1 substituted derivatives <90FES101>. Mannich reaction of 3,4-dihydropyrido[2,3-*d*]pyrimidin-4-one with piperidine and formaldehyde gave (46) <84MIP126441, 86MIP136561>. Alkylation at N-6 of pyrido[4,3-*d*]pyrimidine (47) gives the derivatives (48) <90JHC1885>. The *N*(6)-acetyl group in the amides (49) is removed by hydrochloric acid (49) → (50) and subsequent alkylation gives the *N*(6)-alkyl derivatives <92EJM655>. Alkylation of 6-methyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)dione with 5-chloromethyluracil took place at N-5 <82JOC4391>. Similarly, alkylation with 5-(bromo-methyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine gave products (51) <82JOC4391, 82TL1431, 84JMC1710, 88MI 716-02>. Acylation of 2-oxo(thiooxo)pyrido[4,3-*d*]pyrimidine derivatives with Ac₂O or PhCOCl afforded the derivatives (52) <85PHA536>.

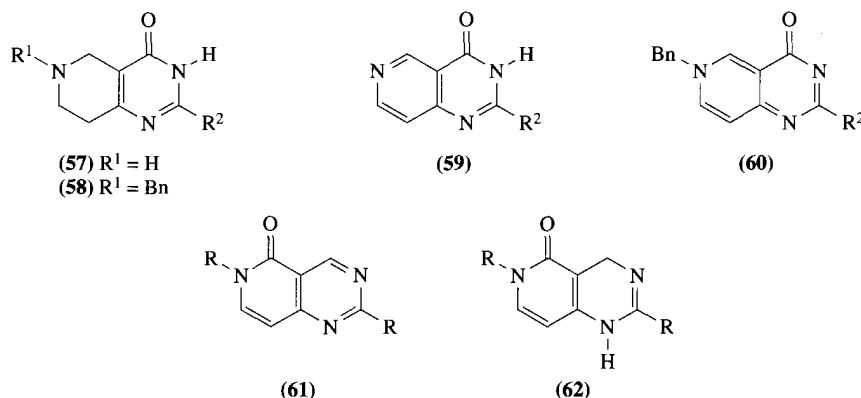
Catalytic hydrogenation of 2-isobutyl-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol did not give the expected debenzylated derivative, but reaction with ethyl chloroformate gave the 6-carbethoxy derivative <86EGP241257, 88PHA475>.

7.16.6.2.2 Electrophilic attack at ring carbon

Michael addition of compounds (53) to chalcones afforded the derivatives (54) <92AP(325)341>. Oxidation of 5-alkyloxy-7,8-dihydropyridopyrimidine-6-carboxylate (KMnO₄/H⁺) gives 5-oxo-5,8-dihydropyridopyrimidine-6-carboxylate <87MIP86105062>. Dehydrogenation of the 3,4-position in pyrido[2,3-*d*]pyrimidin-2-ones (MnO₂) <83SAP8206106> and the 6,7-positions in 6-carbethoxy-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-5-ones (iodobenzene diacetate) has been reported <89JAP(K)0116782>. Photooxidation of (55) gave (56) <87MIP86105080>.



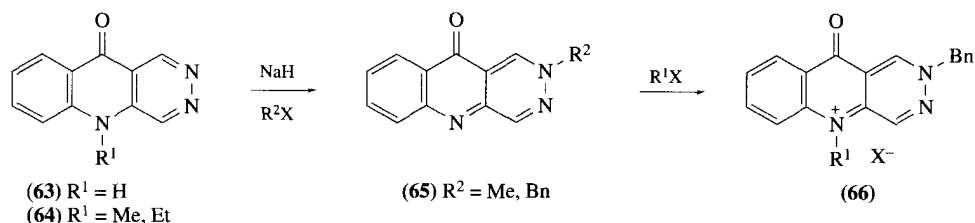
The pyrimidinium salt of 2,3-(1*H*,4*H*)dioxopyrido[3,4-*b*]pyrazine was obtained during its acylation (<92MIP9222556>). During the preparation of an (*S*)-1,2-dihydropyrido[3,4-*b*]pyrazine derivative by hydrogenation, over-reduction took place giving (2*S*,3*RS*)-1,2,3,4-tetrahydropyridopyrazine (<92JMC4809>). Nitration of pyrido[2,3-*b*]pyrazine-2,3-dione using fuming nitric acid in AcOH–Ac₂O afforded the 6-nitro derivative (<92JAP(K)04178385>).



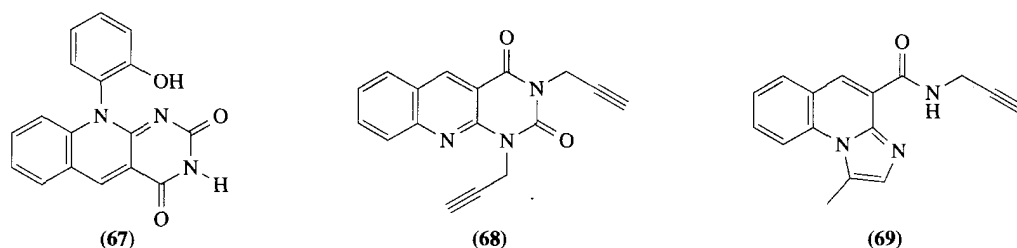
7.16.6.4 Benzo Fused Pyrido[x,y-z][1,n]diazines

7.16.6.4.1 Electrophilic attack at ring nitrogen

Alkylation of compound (63) using MeI–NaH or BnBr–NaH gave no substitution at N-5 but instead N-2 substituted compounds (65) were obtained (Scheme 1). Further alkylation of compound (65; $R^2 = Bn$) using Me_2SO_4 , EtI or ICH_2CO_2Et gave the corresponding 2,5-dialkylated derivatives (66), which were debenzylated (66) $\rightarrow$ (64) by $AlCl_3$ –PhMe [88JCS(P1)401, 89H(29)1309]. Alkylation of compound (67) with alkylidene dibromides afforded the derivatives (1) [89JA4928, 89JA4935]. 10-Ethylpyrimido[4,5-*b*]quinolin-4-one derivatives can be quaternized by EtI at position 10 [84GEP3233604]. Methylation of pyrimido[4,5-*c*]quinoline-1,3-dione using MeI gave the 2,4-dimethyl derivative [86AP(319)382]. Alkylation of 3-alkyl-2-oxopyrido[4,3,2-*de*]quinazoline with $BrCH_2CO_2Et$ took place at position 1 [90JAP(K)02111762]. Reaction of the dialkyne derivative (68) with formic acid gave compound (69) [88JHC677].

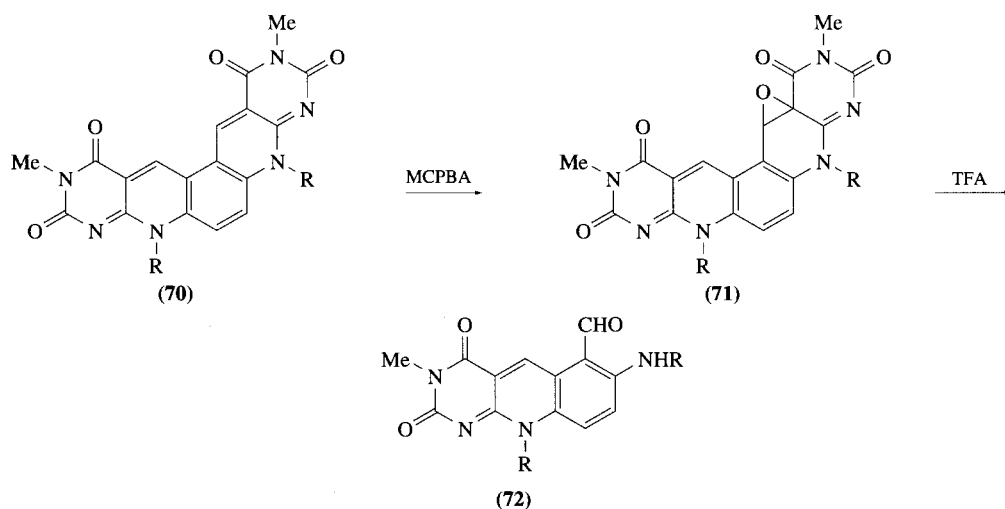


Scheme 1



7.16.6.4.2 Electrophilic attack at ring carbon

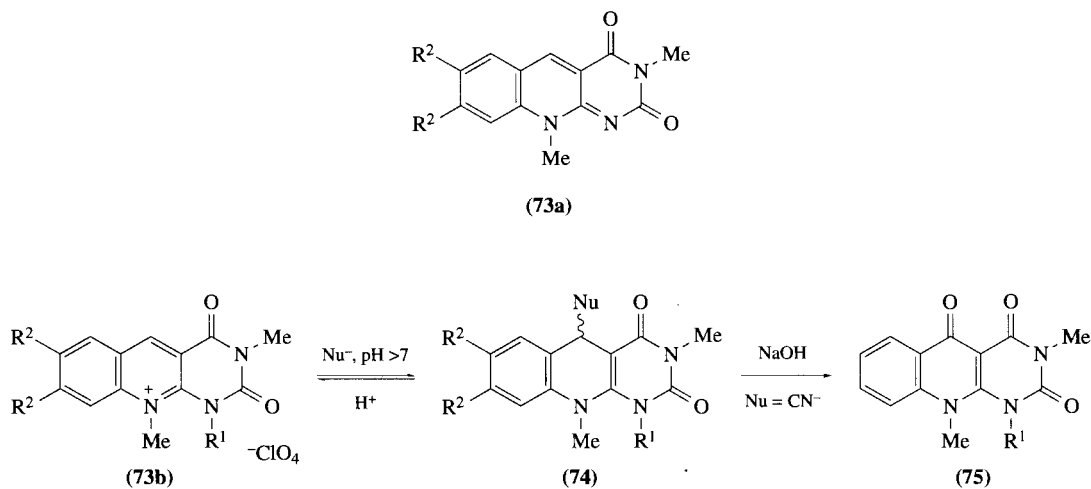
Epoxidation of derivative (70) with MCPBA gave the epoxides (71) which with TFA gave the aldehydes (72) (Scheme 2) [86CPB2653]. Reaction of 1,5-dihydro-5-deazaflavins with MCPBA gives 4a,5-dihydro-4a-hydroxy-5-deazaflavins, whose base-catalyzed hydrolysis gives the corresponding 9,9a-dihydrooxazolo[4,5-*b*]quinolin-2(4*H*)-ones [84CPB3761].



Scheme 2

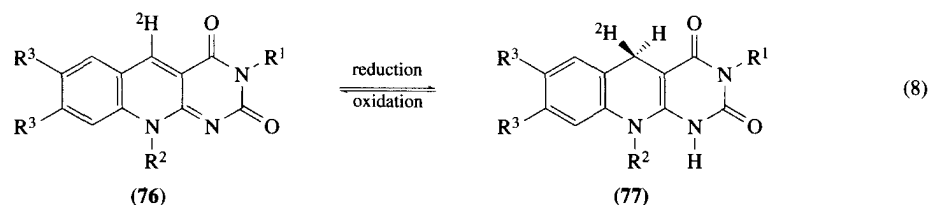
7.16.6.4.3 Nucleophilic attack at ring carbon

Nucleophilic addition to the derivatives (73a) and their salts (73b) takes place reversibly at position-5 to give the adducts (74) (Scheme 3). Reaction of alkali with either (73a; $R^2 = H$) or (74; $R^2 = H$) gives (75). Autooxidation or oxidation of the derivative (74; $R^1 = H$) gives the corresponding 5-substituted-5-deazaflavin <89AP(322)271, 90AP(323)67, 92JHC763>. Opening of the pyrimidine ring of compound (73a) occurs at pH 11–13 <90AP(323)67>.

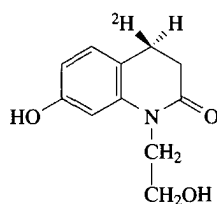


Scheme 3

Hydrocyanation of 10-(8-*N,N*-dibutylaminonaphthyl-1-yl)-5-deazaflavin in the presence of $Me_3N^+Cl^-$ in DMF and subsequent air oxidation afforded the 5-nitrile, whose diastereomers were separated and reduced to 1,5-dihydro-5-deazaflavin, which upon oxidation by air gave 5-deazaflavin <89TL7431>. The *o*-substituted aryl group at N-3 of compounds (76) gives an important effect on the asymmetric “(net) hydride transfer” reaction from 1-benzyl-1,4-dihydronicotinamide to C-5 to give the reduced products (77) (Equation (8)). The larger substituents increase the chiral recognition ability of the 5-deazaflavin enantiomers <92TL3169, 92TL7173>. 5-Dezaaisoalloxazines with 2'-substituted aryl group at N-10 invariably racemize when they are reduced to 1,5-dihydro forms. The easy rotation in the reduced state is due to their presence in a bent form, whereas the oxidized form is planar <88JCS(P1)313>. Reduction with a CF_3 group at C-5 can be achieved with $NaBH_3CN$ and the reverse process is achieved by heating in DMSO <84AP(317)42>.

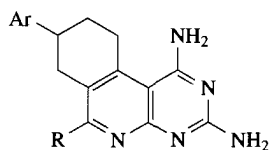


Reduction of the derivatives (76) by a selenium-containing hydrogenase from *Methanococcus vannielii* gave the (*R*)-isomers (77) as confirmed by its degradation to (78) <85PNA(82)1364>. A direct hydride equivalent transfer from C-1 of alcoholates to C-5 of 5-deazaflavins was confirmed by deuteration <87JHC251>.

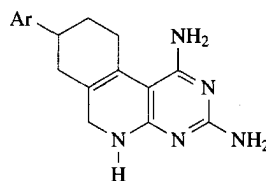


(78)

Reaction of a 5-alkoxy derivative with NaBD₄ gave the 5,5-dideutero derivative exclusively <87JHC251>. Reduction of the compounds (79) with borane in THF gave the amines (81), whose oxidation with DDQ in AcOH afforded the derivatives (80) <92JMC320>.



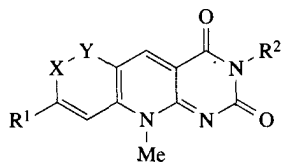
(79) R = OH
(80) R = H



(81)

7.16.6.4.4 Photochemical reactions

Prolonged illumination (blue fluorescent lamp) of the derivatives (82) in the presence of triethanolamine as electron donor led to (83), whereas using ethylenediaminetetraacetate or oxalate led to an additional dimeric product <86CC1385, 87AP(320)1238, 88JHC375>.



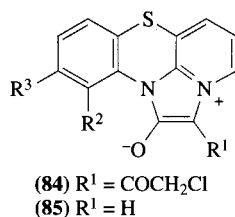
(82) X-Y = CH=CH
(83) X-Y = CH₂-CH₂

7.16.6.5 Pyrido[x,y-z][1,n]oxazines and Thiazines

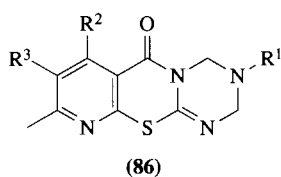
7.16.6.5.1 Electrophilic attack at ring nitrogen

Alkylation of 2*H*-3-substituted 4-hydroxy-5,7-dimethylpyrido[3,2-*e*][1,2]thiazine 1,1-dioxide with alkyl halides or dimethyl sulfate afforded the *N*(2)-methyl derivatives <86FES819, 86FES892,

88MIP143077). *N*-Alkylation of 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine derivatives with alkyl halides in either DMF or toluene containing NaH gave the corresponding *N*(4)-alkyl derivatives (82MI 716-01, 83YZ857, 83YZ1247). Alkylation also occurred with 2-dialkylamino-1-chloroethanes (83ACH487, 83YZ835, 84JAP(K)5948489). Similarly, alkylation of the respective 3-ones took place at *N*-4 (83YZ143, 84JAP(K)5948489). Condensation of pyrido[3,2-*b*][1,4]thiazine(10*H*-1-azaphenothiazines) with chloroacetic acid and chloroacetic anhydride in dioxan gave the meso-ionic compounds (84), which can be hydrolyzed to the derivatives (85) (84JHC1239). Acylation of pyrido[3,2-*b*][1,4]oxazines with acid chlorides gave the 4-acyl derivatives (83YZ1247).



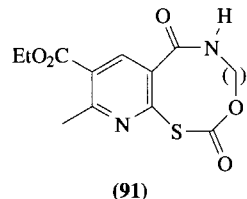
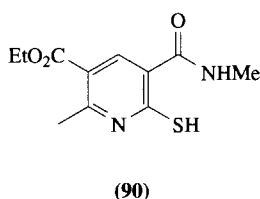
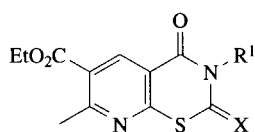
Mannich reaction on 3*H*-2-imino-7-methyl-4-oxopyrido[3,2-*e*][1,3]thiazine-5- or 6-carboxylate gave the corresponding 3-aminomethyl derivatives (85FES58). Use of primary amines in the presence of excess formaldehyde gave the derivatives (86) via cyclization of hydroxymethyl intermediates (85FES65). Heating (86) with Ac_2O gave the *N*-acetyl derivative.



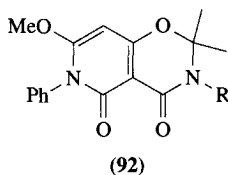
7.16.6.5.2 Nucleophilic attack at ring carbon

The kinetics of hydrolysis of 1,2-dihydropyrido[2,3-*d*][1,3]oxazin-4-one pro-drugs has been investigated: they are readily hydrolyzed to their parent acids, which are used as drugs (91AP(324)821). Reaction of the anions of ethyl nitroacetate or diethylmalonate with pyrido[2,3-*d*][1,3]oxazin-4-ones (azaisatoic anhydride) in DMA afforded 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-4(5*H*)-one (91JHC2029) or the respective 3-(ethoxycarbonyl) derivative (92JMC1130). Pyrido[2,3-*d*][1,3]oxazin-4-ones undergo ring opening with alkynic amines to give the respective nicotinamide derivatives, which are intermediates in the synthesis of pyrido[2,3-*d*]pyrimidines (92M247). Their reaction with 1,4-bis(bromomagnesio)butane or pentane gave 1-(2'-amino-3'-pyridyl)cyclopentanol or cyclohexanol (87T663).

Selective acid hydrolysis of the derivatives (87) gave compound (89) in addition to the pyridine (90). On the other hand, hydrolysis of (88) gave (91) (86FES899).



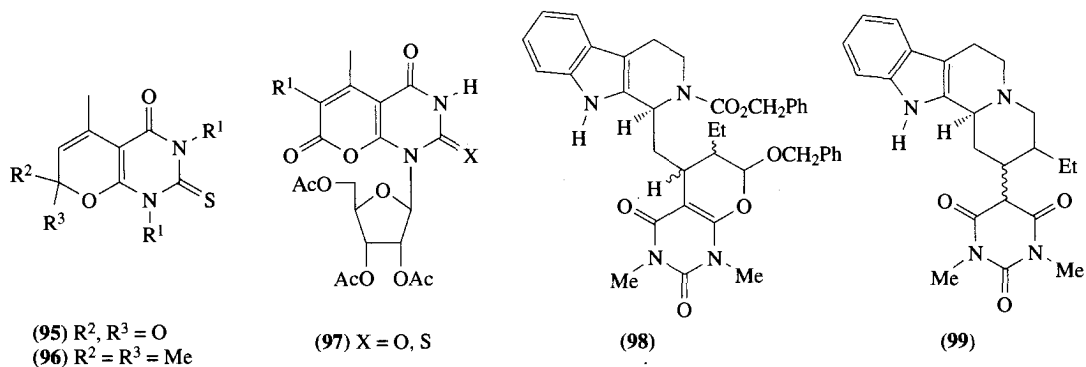
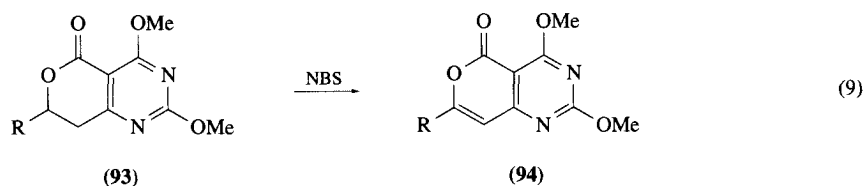
Pyridooxazines (**92**) react with NaOMe to give pyridine-3-alkylcarboxamide derivatives <85PJS297>. Reduction of pyrido[2,3-*b*]thiazinone with NaBH₄ gives the 2,3-dihydro derivative <89T4153>.



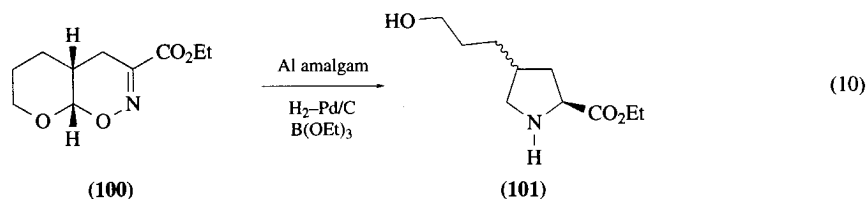
7.16.6.6 Pyrano[x,y-z][1,*n*]diazines, Oxazines, and Thiazines

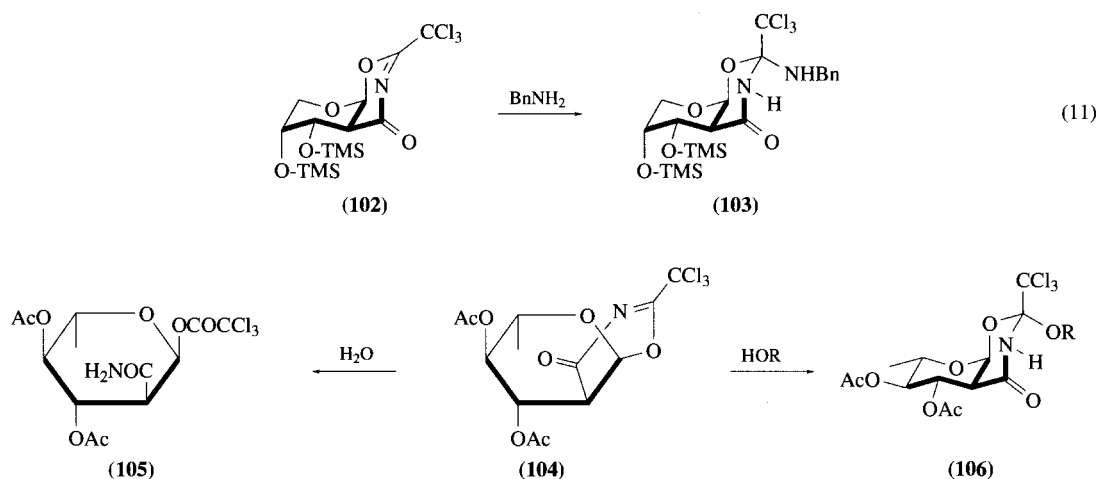
7.16.6.6.1 Electrophilic and nucleophilic attack at ring atoms

Reaction of tetrahydropyrano[3,2-*c*]pyridazin-8-one with benzaldehyde in the presence of an organic base gives the corresponding 7-benzylidene derivative <89IJC(B)167>. The aromatization (**93**) → (**94**) was achieved by NBS (Equation (9)) <89S316, 90JHC1899>. Reaction of compounds (**95**) with MeMgI gives the derivatives (**96**) <90T3953>. Coupling a ribofuranoyl acetate with the respective base gives the *N*-glycosides (**97**) <85BEP902232> and hydrogenolysis of the strictosidine analogue (**98**) gives the indole alkaloid (**99**) <88AG983>.



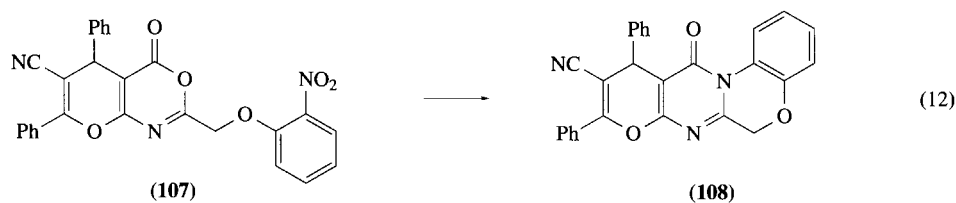
Reduction of compound (**100**) with aluminum amalgam or by hydrogenation in the presence of Pd/C and B(OEt)₃ gives compound (**101**) (Equation (10)) <87JCR(S)180>. Benzylamine can be added to the C=N bond of the adduct (**102**) to yield compound (**103**) (Equation (11)) <87CAR(167)143, 87T4555>. The oxazine ring in compound (**104**) undergoes rapid ring opening by water to give compound (**105**), whereas an excess of alcohol gives (**106**) (Scheme 4) <87T4555>.





Scheme 4

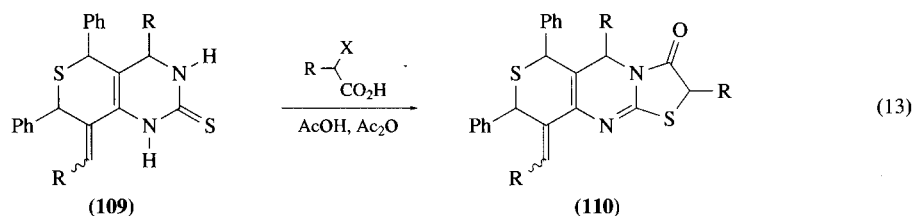
Amination of 2-thioalkylpyrano[3,4-*e*][1,3]oxazine with excess *n*-propylamine led to ring opening of the oxazine ring, while reaction with dialkylamines gave the 2-amino derivatives (85CB1371, 85CB4707). Reduction of the ether (107) gave cyclized product (108) (Equation (12)) (90IJC(B)1020). 1-*N*-[(*S*)-4-Amino-2-hydroxybutyryl]-2'-deoxykanamycin B has been prepared from an enamine derivative in several steps (82JAN905).



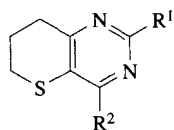
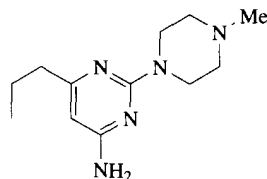
7.16.6.7 Thiopyrano[x,y-z][1,n]diazines, Oxazines, and Thiazines

7.16.6.7.1 Electrophilic and nucleophilic attack at ring atoms

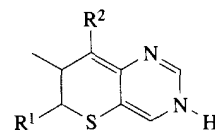
The reaction of α -halogenoacids with the derivatives (109) gave tricyclic products (110) (Equation (13)), which can be converted to the thiooxo analogue (85M1 716-01). Heating the pyrimidine (111) with AcOH gave compound (112), which was treated with POCl₃ to give the dichloro compound. Amination of the latter gave (113), which with piperazines gives (114). Desulfurization of the thiopyrano[3,2-*d*]pyrimidine (114) with Raney nickel afforded the pyrimidine (115) (86CPB4150). The desulfurization (116) $\rightarrow$ (117) was similarly achieved (87T3421).



The reaction of 4-hydroxythiopyrano[3,2-*d*]pyrimidine with POCl₃ gave the 4-chloro derivative, whose successive reaction with piperazine and hydrazine gave the 2-hydrazino-4-piperazino derivative (83BEP895995, 86JAP(K)61180788, 88EUP276057, 90JHC1159). The 2-piperazinothiopyrano[3,2-*d*]pyrimidine derivative was prepared similarly (92JAP(K)0409386). Photooxidation of thiopyrano[2,3-*d*][1,3]thiazinethione gives the respective thiopyranothiazinone (82AG800).

(111) $R^1 = \text{SMe}$, $R^2 = \text{OH}$ (112) $R^1 = R^2 = \text{OH}$ (113) $R^1 = \text{Cl}$, $R^2 = \text{NR}^3\text{R}^4$ (114) $R^1 = \text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N-R}^5$, $R^2 = \text{NR}^3\text{R}^4$ 

(115)

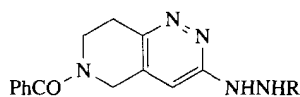
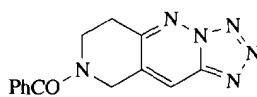
(116) $R^1 = \text{SMe}$ or $R^1 = R^2 = \text{SMe}$ (117) $R^1 = \text{H}$ or $R^1 = R^2 = \text{H}$

7.16.7 REACTIVITY OF SUBSTITUENTS

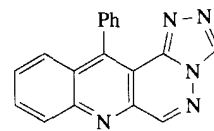
7.16.7.1 Pyrido[x,y-z]pyridazines

7.16.7.1.1 Electrophilic attack

Oxidation of the thioethers (**44**; $R^3 = \text{SR}^1$) by MCPBA gives the respective sulfones $\langle 90\text{CPB}3359 \rangle$. Condensation of 5-hydrazino-3,7-diphenylpyrido[3,4-*d*]pyridazin-4-one with benzaldehyde afforded the benzylidene derivative $\langle 92\text{CCC}1770 \rangle$. Acylation of endralazine (**118**) with acyl halides gave hydrazides (e.g., (**119**)) $\langle 82\text{SZP}628052 \rangle$ and nitrosation of compound (**118**) afforded the tetrazole (**120**) $\langle 92\text{AP}325621 \rangle$. The triazole (**121**) was formed by cyclization of the respective hydrazine with carboxylic acids $\langle 90\text{JHC}1099 \rangle$. Alkylation of the amino group in ethyl 2-methyl-4-(3-nitrophenyl)-5-oxo-6-(2-amino-2-methylpropyl)-1,4,5,6-tetrahydropyrido[2,3-*d*]pyridazine-3-carboxylate was achieved using 1,2-epoxy-3-(2-methoxyphenoxy)propane $\langle 90\text{JAP}(\text{K})0273084 \rangle$. Acetylation of the amino group of 5-aminopyrido[2,3-*c*]pyridazine was used to characterize it $\langle 91\text{JHC}1441 \rangle$.

(118) $R = \text{H}$ (119) $R = \text{CO}(\text{CH}_2)_{16}\text{Me}$ 

(120)



(121)

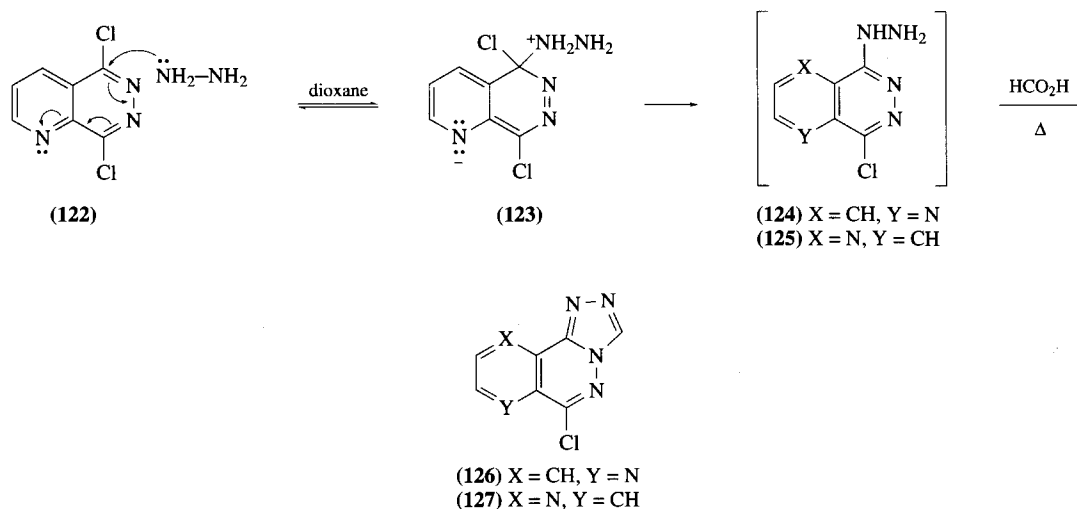
7.16.7.1.2 Nucleophilic substitution

The reaction of ones and diones with POCl_3 readily replaces the oxo function by chlorine which can be substituted by various nucleophiles. Reaction of compound (**122**) with hydrazine hydrate gives the intermediates (**124**) and (**125**), which react with formic acid to give (**126**) and (**127**) (Scheme 5) $\langle 88\text{AP}321943 \rangle$. The formation of the isomer (**126**) as the major product is due to the participation of the stabilized intermediate (**123**) $\langle 88\text{AP}321943 \rangle$.

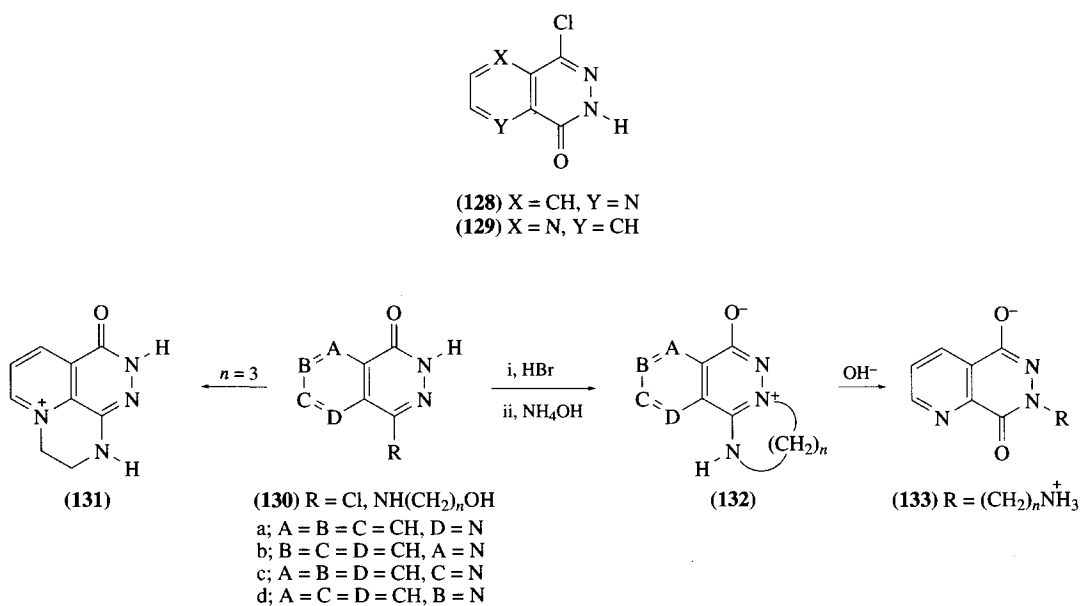
Alkaline hydrolysis of compound (**122**) gave the isomers (**128**) and (**129**) whereas on acid hydrolysis the isomer (**128**) predominates. Hydrazinolysis of the isomers (**128**) and (**129**) gave the respective hydrazino derivatives, which upon thermal decomposition gave the amines. Aminolysis of (**128**) and (**129**) with 2-hydroxyethylamine gave the corresponding 2-hydroxyethylaminopyridopyridazine $\langle 81\text{ACH}167 \rangle$. Reaction of compound (**122**) with diethylaminoethoxide gave the mono- and disubstituted derivatives $\langle 82\text{MI}716-02 \rangle$. Similarly, the dichloride in the pyrido[3,4-*d*]pyridazine series underwent hydrolysis by the action of acid or alkali $\langle 83\text{ACH}487 \rangle$.

Substitution of the chlorine in 1- and 5-chloropyrido[2,3-*d*]pyridazinones as well as 1- and 4-chloropyrido[3,4-*d*]pyridazinones with amino alcohols gave (**130**). Reacting the latter with HBr followed by NH_4OH afforded (**132**) (Scheme 6). In the case of compound (**130a**; $n = 3$) the coupling took place at the N-1 position leading to compound (**131**); this annelation was faster than with the five-membered ring system $\langle 85\text{ACH}177 \rangle$. Alkaline hydrolysis of compound (**132a**) afforded (**133**).

Although most substitution reactions have been carried out on chlorine substituents $\langle 88\text{JHC}879 \rangle$,



Scheme 5



Scheme 6

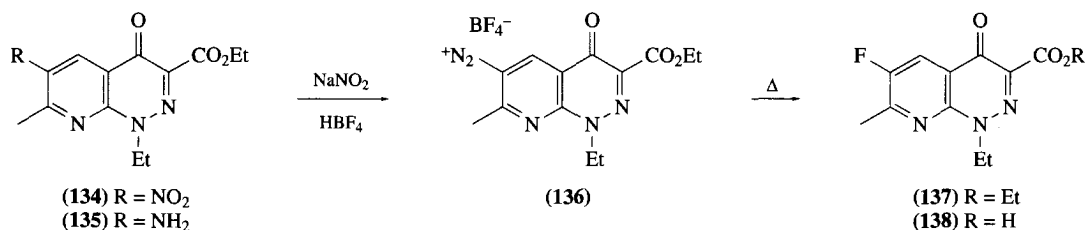
nucleophilic displacement of sulfonyl groups in the derivatives (**44**; R³ = SO₂R⁴) by amines can also be readily effected <85JAP(K)60185781, 90CPB3359>.

Hydrogenation of the nitro derivative (**134**) (H₂-Pd/C) gave the amine (**135**), which after diazotization gave (**136**) and thermal decomposition followed by acid hydrolysis of (**137**) afforded the fluoro derivative (**138**) (Scheme 7) <87JHC55>.

7.16.7.2 Pyrido[x,y-z]pyrimidines

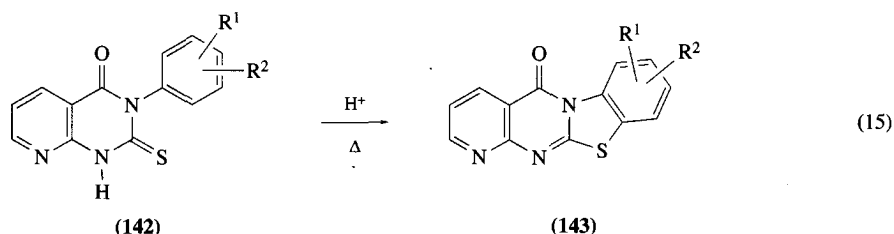
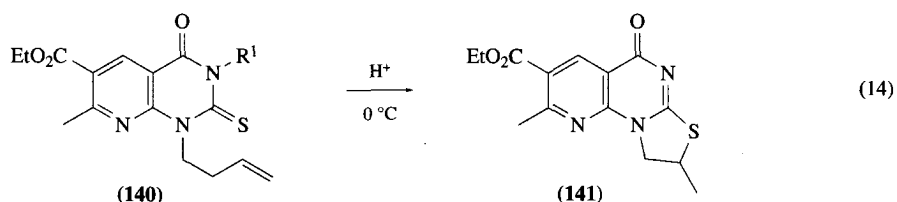
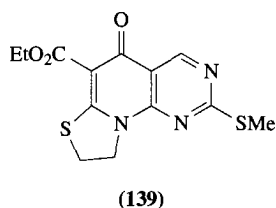
7.16.7.2.1 Electrophilic attack

Alkylation of pyrido[4,3-*d*]pyrimidin-5-one derivatives with isopropyl iodide gave the corresponding 5-alkoxy derivatives <86GEP3502590>. Also, alkylation of pyrido[2,3-*d*]pyrimidine-2,4,7-trione gave the corresponding 7-butyloxypyridopyrimidine <84H(22)513>. Alkylation of 2-thiooxo-



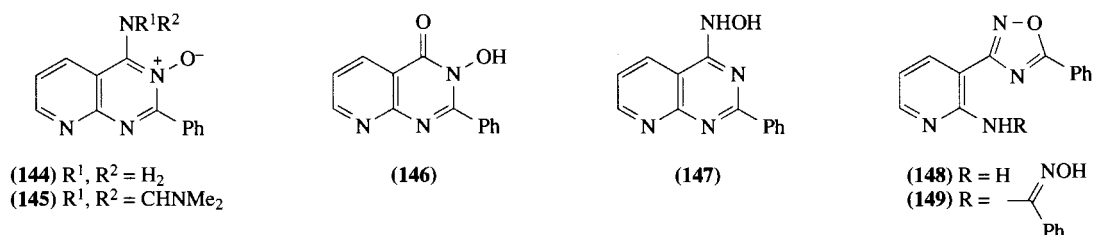
Scheme 7

1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine gave the 2-alkylthio derivative, whereas the 2-oxo analogue gave the *N*-alkyl derivative (88MIP144126, 88MIP144127, 90FES111, 93FES77). Reaction of the 7-thiooxo analogue with dibromoethane gave compound (139) (84JAP(K)59210093). A similar cyclocondensation took place using (140) to give compound (141) (Equation (14)) (82FES247, 82FES259, 82FES266). Similarly (142) gave (143) (84S586). The piperazine ring of pipemidic acid and its analogues can be alkylated (81JAP(K)81123981, 86EUP188094, 86JAP(K)61140568, 86MIP8601207). Benzoylation of pyrido[2,3-*d*]pyrimidine-2,4,6-trione gives a 7-benzoyloxy derivative which can be converted into the 6-benzoyl-7-hydroxy derivative by photo-Fries rearrangement (84LA1653). The amino derivatives reacted with arylsulfonyl isocyanate (86GEP3422824), triphenylphosphine oxide (83EUP75880), and 1,1'-carbonyldiimidazole-ROH or R¹R²NH to give urethane and urea derivatives. Alkylation took place with Ac₂O (83JMC403). Treatment of a 7-amino pyridopyrimidine-2,4-dione with NaNO₂-AcOH led to the 2,4,7-trione (85JHC345).

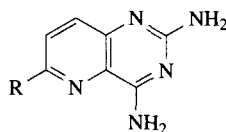


The *N*-oxide (144) was transformed by NaOH into the oxadiazole (148), accompanied by minor amounts of compounds (146) and (147), whereas the *N*-oxide (145) gave compound (146). Hydroxylamine hydrochloride converted (145) to compound (149). Treatment of the *N*-oxide (144) with nitrous acid yielded a substituted nicotinamide (87M399).

2-Methylpyridopyrimidines react with benzaldehyde to give 2-styryl derivatives (86MIP136568, 87MIP136565, 89MIP136566, 91KGS1397). Acylation of the methyl group with Ac₂O, aroyl chlorides or phenylisocyanate gave the corresponding 2-acylated products (91KGS1397, 92KFZ45, 92KGS535). The 6-hydroxymethyl group reacted with *p*-hydroxybenzamides in the presence of DEAD-Ph₃P to give



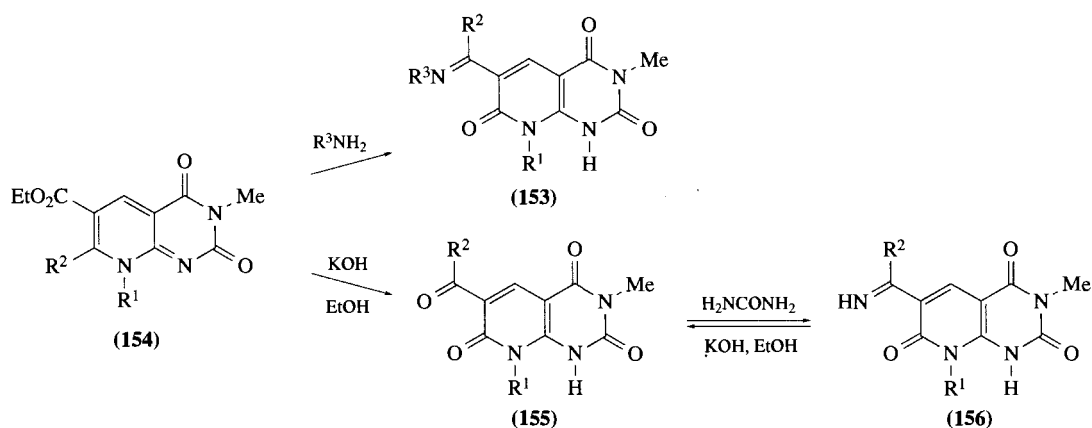
the respective ethers (92USP5159079). Oxidation of the thioethers (150) with Br_2 -dabco gave the sulfoxides (151), whereas H_2O_2 in AcOH gave the sulfones (152) which upon oxidation with peroxytrifluoroacetic acid give 1,5-dioxides (84JHC1521, 87JAP(K)62221686).



(150) $R = SAr$
 (151) $R = SOAr$
 (152) $R = SO_2Ar$

7.16.7.2.2 Nucleophilic attack

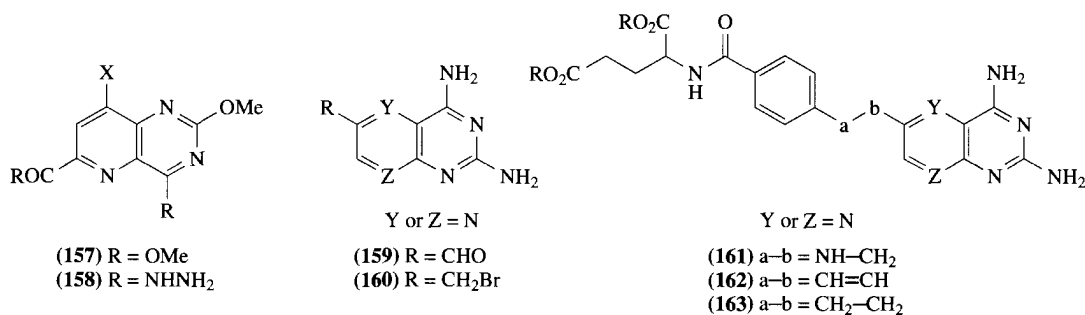
The pyrimidine ring in 6-carbethoxypyrido[2,3-*d*]- or [3,2-*d*]pyrimidine-2,4-dione is opened by NaOH, whereas reaction with HCl-AcOH hydrolyzes the ester group (82JHC805, 86FES899, 86FES954). Hydrolysis of the derivatives (154) using KOH resulted in a novel rearrangement involving the substituent at the 7-position to give products (155). Treatment of the ester (154) with amines gave the rearranged imino derivatives (153). Treatment of the derivatives (155) with urea gives the imines (156) which upon alkaline hydrolysis regenerate (155) (84CPB1699).



Scheme 8

Treatment of the esters (157; $X = H, Cl$) with hydrazine hydrate gave the hydrazides (158; $X = H, Cl$), which reacted with aldehydes to give the hydrazones and with nitrous acid to give tetrazolo derivatives (87H(26)457). Amide derivatives of piromidic acid (82JAP(K)8270897) and pipemidic acid have been prepared (90JAP(K)02300186). The carboxyl group at the 6-position of 4-amino-2-thiomethylpyrido[2,3-*d*]pyrimidine could be decarboxylated (84CPB122, 85JHC1735). The aldehyde functionality at the 6-position of compound (159; $Y = N, Z = CH$) could be generated by hydrolysis of the respective acetal (83JOC4852, 88JMC2164). Reductive amination of the aldehyde group gave the amines (161) (83JOC4852, 84USP4431805, 91JHC977, 92JMC1578, 92JMC2002), and a Wittig reaction afforded the alkenes (162) (85JMC914, 89EUP305667) which upon reduction gave (163) (85USP4532241).

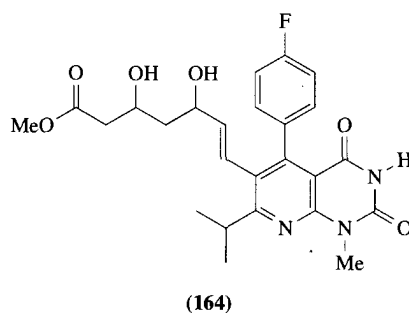
Reduction of aldehydes (**159**) gave the alcohols <91JHC977>, which upon reaction with PBr_3 -THF gave the bromides (**160**) <87JMC675, 90MIP9000172, 91JMC1447, 91MIP2001458, 92JMC332>. Reaction of bromides (**160**) with $\text{Bu}_3\text{P}-\text{NaH}$ gave a phosphorane derivative which is a key intermediate for the synthesis of 5,10-dideazaaminopterins <92JMC3002>, and 8,10-dideazaaminopterin (**163**) <84USP4460591>.



Alkylation of appropriate α -alkylhomoterephthalate esters with the bromide (**160**) afforded 10-alkyl-10-carboxy-4-amino-4-deoxy-8,10-dideazapteroic acid diesters, whose ester cleavage and decarboxylation were accomplished by heating with sodium cyanide in DMSO to afford the 2,4-diamino-10-alkyl-8,10-dideazapteroic acids. These acids were coupled with diethyl glutamate, followed by saponification, to give the products (**163**; R = H) <84JMC376>.

Alkynylation of 6-bromopyridopyrimidine could be achieved by reaction with propynyloxytetrahydropyran <89USP4883799>. Reaction of the 6-ethynyl derivative with dimethyl *N*-(2-fluoro-5-iodobenzoyl- or 5-bromothien-2-ylcarbonyl)-L-glutamate in the presence of $\text{PdCl}_2\text{-Et}_3\text{N-Ph}_3\text{P-CuI}$ in MeCN <89EUP327190, 89EUP343801> gave alkynyl derivatives linked to aromatic or heteroaromatic groups suitable as carriers for glutamic acid residues through their carboxyl groups. Carbon-carbon coupling of the 6-bromopyridopyrimidine with 3,4-dimethoxystyrene is catalyzed by palladium <91JHC1747>.

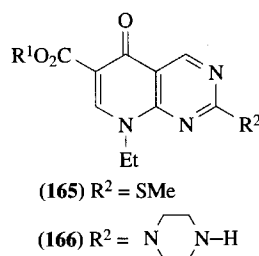
Condensation of pyridopyrimidinylpropenal with methyl acetoacetate followed by successive treatment with $\text{Et}_3\text{B-O}_2$ and NaBH_4 gave the HMG-CoA reductase inhibitor (**164**) <90EUP378850>, which could also be prepared from the respective 6-carboxylic acid ester <90GEP3900363>. Reaction of a β -ketoester at the 6-position in pyrido[2,3-*d*]pyrimidinone with hydrazine gave the 6-tetrahydropyridazinone derivative <88MIP8803025>. Reduction of a nitro group at the 6-position was effected by $\text{Fe(OH)}_2\text{-TAB-DMF}$ <92JHC1545>. The reactivity of a 2-methyl group in pyrido[2,3-*d*]pyrimidines has been established by acylation with Ac_2O or PhCOCl <92KGS1234>.



7.16.7.2.3 Nucleophilic substitution

Nucleophilic substitution of halogens at C-2 or C-4 of pyrido[2,3-*d*]pyrimidines occurs smoothly <88JHC245>. The 2-chloro- or the 2-thiomethylpyrido[2,3-*d*]pyrimidines and the respective 4-ones were readily substituted by amines <83AP(316)346, 89MIP2009145>. Substitution of the 2-methylthio group in compound (**165**) with piperazine hexahydrate followed by hydrolysis with HCl gave pipemidic acid (**166**; R¹ = H) <89JAP(K)01254683, 90JAP(K)0225485>. Substitution was also effected by 1,2-bis(1-piperazinyl)ethanedione and the product was hydrolyzed to give pipemidic acid <86JAP(K)61176578, 86JAP(K)61176579, 86JAP(K)61280494, 90JAP(K)0225484>. The 2-chloro or 2-imidazolyl

group can also be substituted with piperazine hexahydrate <81MIP477095, 91JAP(K)03106880>. The 2-oxo group of the 2,5-dioxypyridopyrimidine derivative could be displaced by heating with piperazine, PTSA·H₂O (PTSA, *p*-toluenesulfonic acid), or HMDS in pyridine to give pipemidic acid <86JAP(K)61282383, 88JAP(K)63183582>. The 4-chloro or 4-(1,2,4-triazolyl) derivatives of pyrido[2,3-*d*]pyrimidines could be substituted by a variety of amines <89MIP2009217, 90MIP152178, 90MIP152179, 90MIP152180, 91EUP414386, 91MIP9105784>. The 4-chloro substituent was also substituted by *p*-toluenesulfonylhydrazine, which can be decomposed by potassium carbonate to the dihydrooxo(piperazinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid <86JAP(K)61268682, 87JAP(K)62142177, 88JAP(K)63295574>.



Substitution of the 7-butoxy group in 7-butoxy-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-dione can take place with hydrazine <84LA1653> and 4-chloro or 5-chloro groups can be substituted by OH <87JAP(K)62263179, 91KGS1563>. Substitution of both chlorine atoms in 2,4-dichloropyridopyrimidine rings was achieved by phenylmethylamine <90EUP404355>.

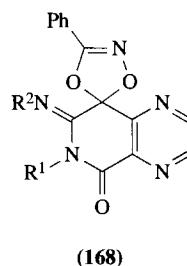
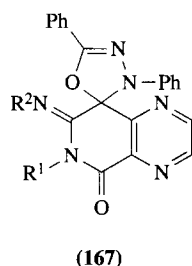
Hydrolysis or ethanolysis of a 2-trichloromethyl group on pyrido[2,3-*d*]pyrimidine gave the 2-hydroxy- and 2-ethoxypyridopyrimidine derivatives, respectively <84S970>. Treatment of pyrido[4,3-*d*]pyrimidin-5-one with POCl₃ followed by NaOEt gave the ethoxy derivative <86JAP(K)6176488>. Hydrolysis of the 4-amino group of 2,4-diamino-6-hydroxymethylpyrido[2,3-*d*]pyrimidine was achieved with NaOH, whereas the 2-amino group was hydrolyzed by 48% HBr with concomitant bromination of the side chain <91JHC977, 92EUP511792>.

7.16.7.2.4 Other reactions

The 5- or 7-chloro-pyrido[2,3-*d*]pyrimidines upon hydrogenation (Pd/C) gave the respective dechlorinated derivatives <85USP4512992, 87EUP243311, 88EUP279565>. The 7-position in tetrahydropyrido[2,3-*d*]pyrimidin-7-one is deoxygenated by borane-THF <92JAP(K)04235986>. Desulfurization of the 7-thiomethyl group with Raney nickel in ethanol affords 5-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)dione <84CPB122>.

7.16.7.3 Pyrido[x,y-z]pyrazines

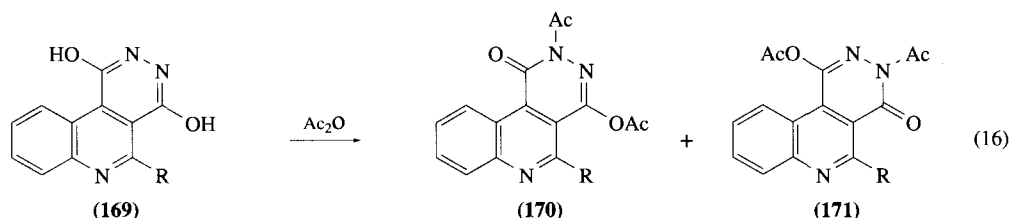
One example has been reported: 1,3-dipolar cycloaddition of *N*-phenylbenzonitrile imide or benzonitrile oxide to the carbonyl group of a 3-iminopyrido[3,4-*b*]pyrazine-1,4-dione gave (167; R¹ = cyclohexyl, R² = Ph) and (168; R¹ = cyclohexyl, R² = Ph), respectively <86LA938>.



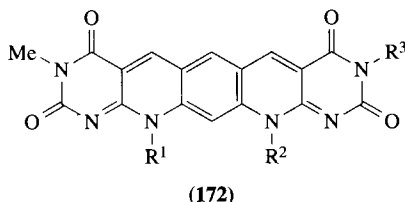
7.16.7.4 Benzo Fused Pyrido[x,y-z][1,n]diazines

7.16.7.4.1 Electrophilic and nucleophilic attack

Alkylation of the derivatives (169) afforded a mixture of the isomers (170) and (171) (Equation (16)) <84JHC27>. The methyl group at the 2-position of pyrimidoquinoline is reactive towards Ac_2O , BzCl , PhNCO , or PhCHO <88KGS1649>.



Condensation of 8-(substituted amino)-1,5-dihydro-5-deazaflavins with 6-chloro-5-formyluracil gave bis-dihydro-5-deazaflavins and 8-(5-formyluracil-6-yl)amino-1,5-dihydro-5-deazaflavins. The dehydrogenation of the former with DEAD or the dehydrative cyclization of the latter with Vilsmeier's reagent gave the pentacyclic derivatives (172) <84CC872, 88JCS(P1)1809>.

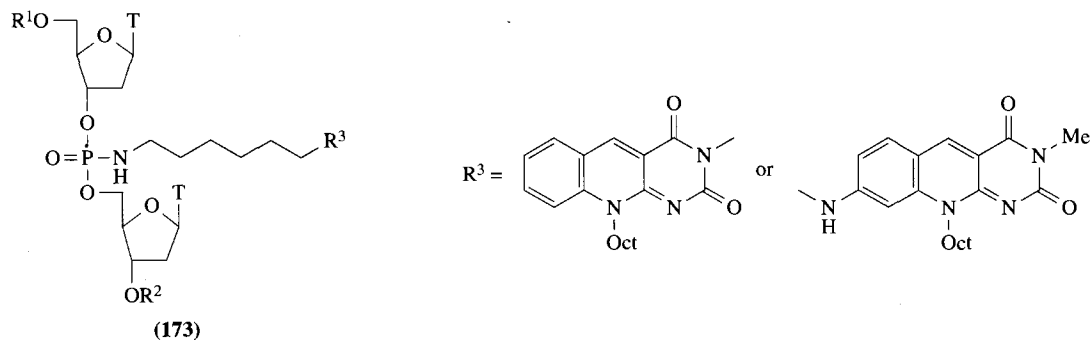


7.16.7.4.2 Nucleophilic substitution

Displacement of the chloro substituents in 1,4-dichloropyridazino[4,5-*c*]quinoline gave the dimethoxy derivative <84JHC27> and treatment of 10-phenylpyridazino[4,5-*b*]quinoline-1-thione with hydrazine gave the hydrazino derivative <90JHC1099>. Desulfurization of 5-thiomethyl on pyrimido[4,5-*b*]quinoline-2,4-dione with Raney nickel followed by reaction with H_2O_2 -AcOH gave the 5-hydroxy derivative. The methylthio group or the respective chloro group can be substituted by amines and active methylene compounds <91JHC1245, 92JHC763>.

8-Chloro(fluoro)-5-deazaflavins with amines give the 8-amino derivatives <84CC872, 85JHC873, 88JCS(P1)1809>. Dipolar cycloaddition of the 8-azido derivative gave the respective 1,2,3-triazole. Reaction of the amino derivative with nitrous acid followed by dimethylaminobenzene gave the respective azo derivative <82JHC945>.

Amination of a 6-aryloxypyrimido[4,5-*c*]isoquinoline derivative with butylamine gave the 6-butylamino derivative <89AJC1029>. The connection of 5-deazaflavin derivatives to the backbone of DNA oligomer is based on the replacement of the H-phosphonate linkage with the primary aminoalkylpyrimidoquinoline groups to give (173) <92CPB291>.

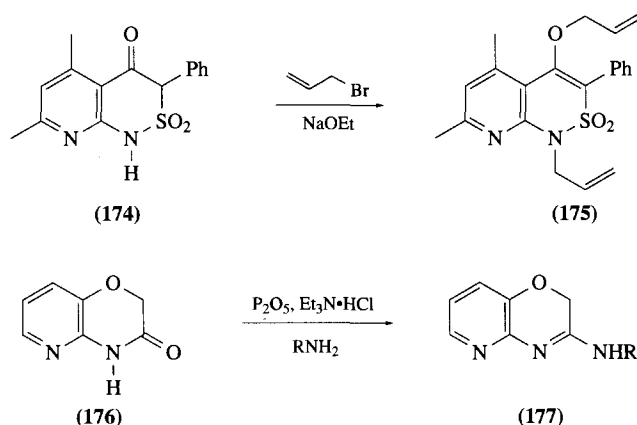


Oxidation of 6-methylpyrazino[2,3-*c*]isoquinoline with selenium dioxide gave the aldehyde, but oxidation of the 3,6-dimethyl derivative was not successful. Oxidation of a 6-carbaldehyde derivative by sodium chlorite afforded the acid <92AJC2083>.

7.16.7.5 Pyrido[x,y-z][1,*n*]oxazines and Thiazines

7.16.7.5.1 Electrophilic attack

Treatment of compound (174) with allyl bromide gave the derivative (175) (Scheme 9) <81MIP109777>.



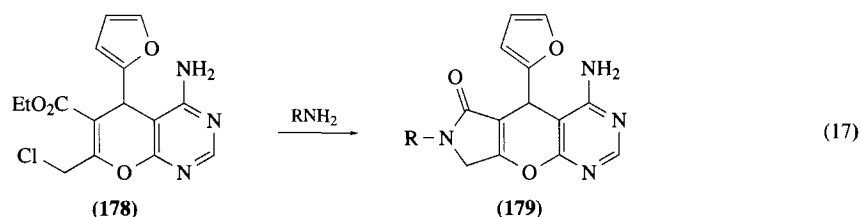
Scheme 9

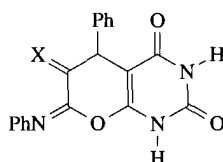
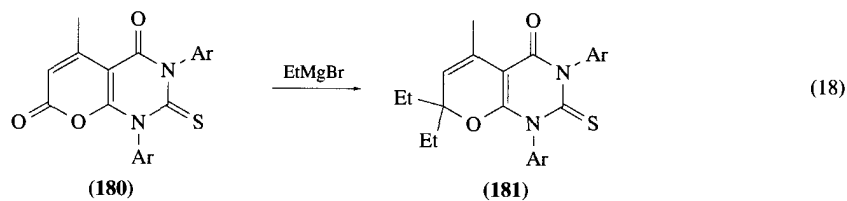
7.16.7.5.2 Nucleophilic substitution

Treatment of the oxazinone (176) with a mixture of P_2O_5 , $Et_3N \cdot HCl$ and an amine gave the derivatives (177) <86CS613>.

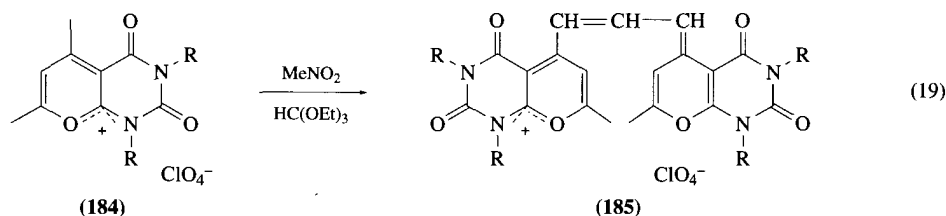
7.16.7.6 Pyrano[x,y-z][1,*n*]diazines and Oxazines

Reaction of compound (178) with alkyl(aryl)amines gave the tricyclic derivatives (179) (Equation (17)) <89CCC1336>. Reaction of the pyrones (180) with $EtMgBr$ furnished the diethyl derivatives (181) (Equation (18)) <90IJC(B)1141>. Wittig reaction of the ylide (182) afforded compound (183) <87PS(29)165>. Condensation of the salt (184) with $MeNO_2$ and $HC(OEt)_3$ gave the dye (185) (Equation (19)) <88MI 716-04>. Reaction of the 2-methyl group on pyrano[2,3-*d*][1,3]oxazine with benzaldehyde gave the styryl derivative <90IJC(B)1020>. Reaction of 7-chlorodihydro-4,5-dioxo-pyrano[3,4-*e*]oxazinethione with morpholine led to replacement of the 7-Cl substituent followed by opening of the pyrone and oxazine rings <88JPR859, 90MI 716-01>.





(182) X = PPh₃
 (183) X = CHC₆H₄NO₂-p



7.16.7.7 Thiopyrano[x,y-z][1,n]diazines

Reaction of 2-hydrazino-4-piperazinothiopyrano[3,2-d]pyrimidine with either RC(OEt)₃ or NaNO₂ gave the corresponding triazolo or tetrazolo derivatives <90JHC1159>.

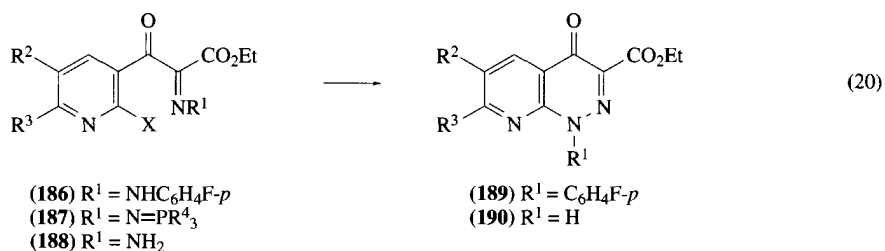
7.16.8 SYNTHESIS

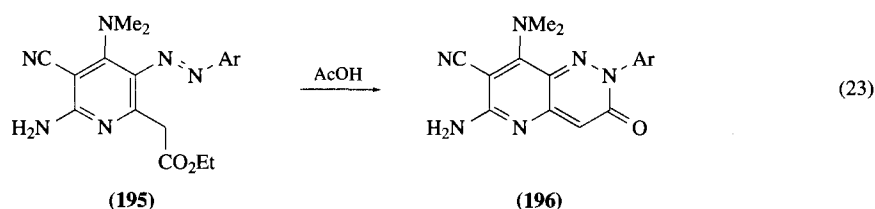
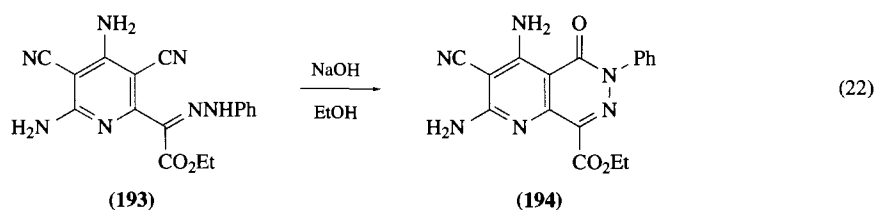
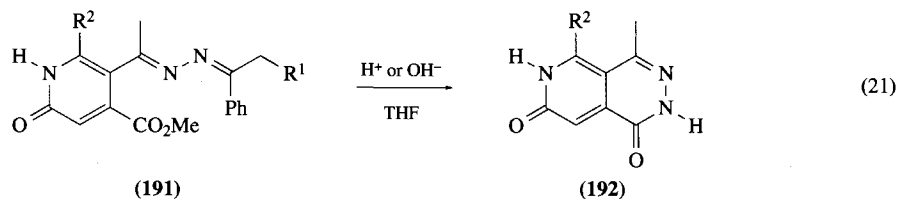
7.16.8.1 Synthesis of Pyrido[x,y-z]pyridazines

7.16.8.1.1 From pyridine intermediates

(i) Formation of the second ring from [6 + 0] atom fragments

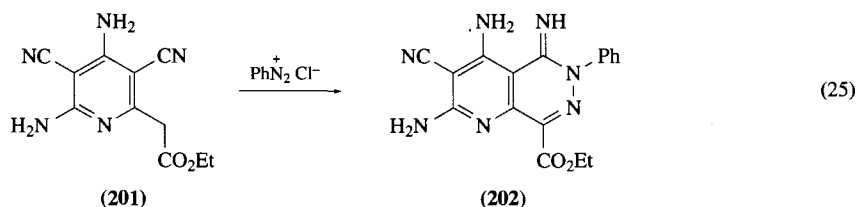
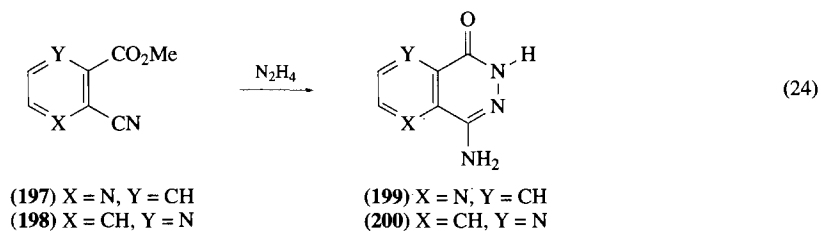
Cyclization of the derivatives (186; X = Cl, Br) to give compounds (189) was effected by base (K₂CO₃-MeCN/Δ or Bu^tOK at room temperature) (Equation (20)) <90CPB3359>. Reductive ring closure of α-diazo-β-oxo-3-pyridinepropionic acid ethyl ester with Ph₃P-Prⁱ₂O gave derivative (190) <87JHC55>. When the reaction was carried out on (187) it hydrolyzed to (188) and cyclized (190) <90CPB3211>. Hydrolysis of the azine (191) gave (192) (Equation (21)) <87S662>. Cyclization of (193) gave (194) (Equation (22)) <85ZN(B)1537>, and (195) gave (196) (Equation (23)) <91MI 716-01>.





(ii) Formation of the second ring from [4 + 2] atom fragments

This combination involves the use of either hydrazine or a diazonium salt as a two-atom fragment which cyclizes with a 2,3-disubstituted pyridine derivative to give the pyridazine ring. Thus, pyrido[2,3-*d*]pyridazine-5,8-diones were formed after heating quinolinic acid with hydrazines <83MI 716-01>. Heating compounds (197) and (198) with hydrazine gave the amines (199) and (200), respectively (Equation (24)) <81ACH167> and in a similar way pyrido[3,4-*d*]pyridazinones could be constructed <83ACH487>. 5-Aminopyrido[2,3-*d*]pyridazines have been prepared by the reaction of 2-acylnicotinonitriles with hydrazine hydrate <88S483>. Coupling of the ester (201) with $\text{PhN}_2^+\text{Cl}^-$ gave compound (202) (Equation (25)) <85LA1492, 88LA909>.

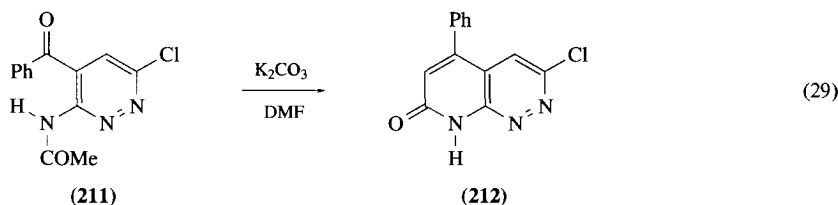
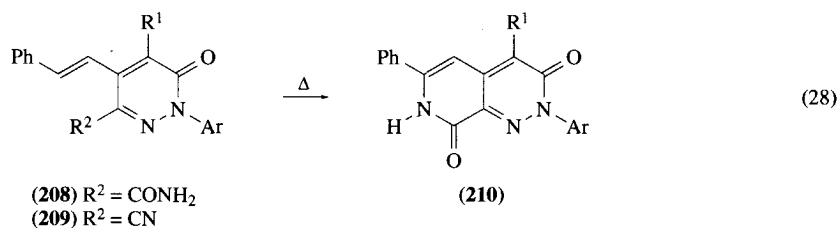
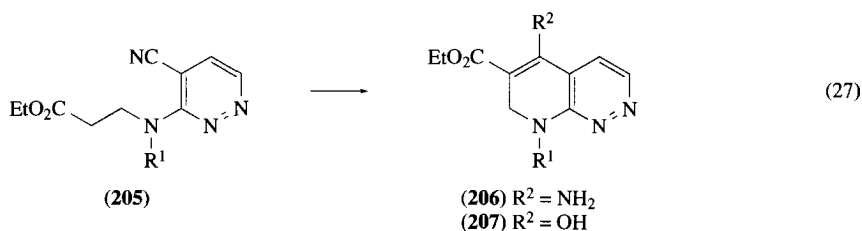
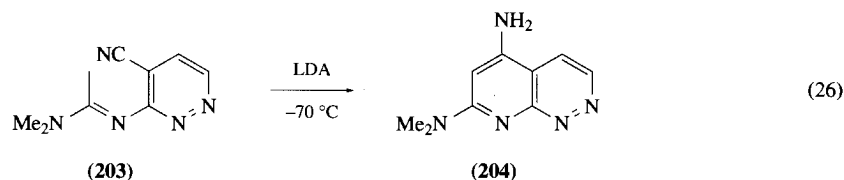


7.16.8.1.2 From pyridazine intermediates

(i) Formation of the second ring from [6 + 0] atom fragments

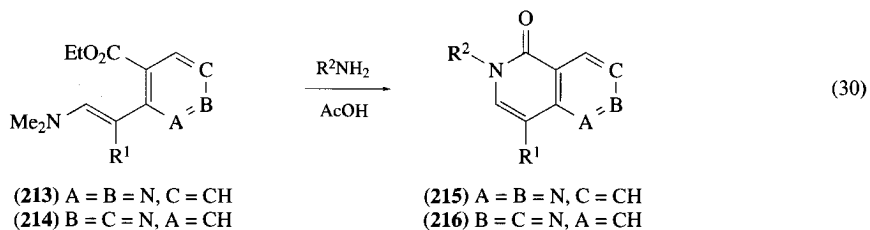
Intramolecular cyclization of the amidine (203) using a strong base (LDA) gives compound (204) (Equation (26)) <91JHC1441>. Cyclization of the esters (205) gives the derivatives (206) which upon

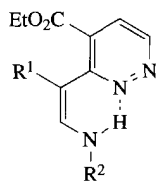
hydrolysis give the enols (**207**) (Equation (27)) <90AP(323)207>. Cyclization of the amides (**208**) to give derivatives (**210**) was achieved by heating <91MI 716-02>, whereas the nitriles (**209**) cyclized in acid or alkaline media (Equation (28)) <92CCC1770>. The amide (**211**) has been cyclized to compound (**212**) (Equation (29)) <92PHA679>.



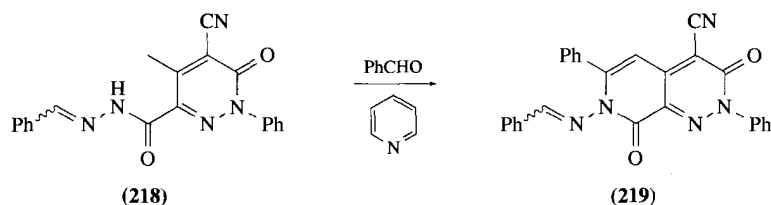
(ii) Formation of the second ring from [5 + 1] atom fragments

The pyridine ring can be constructed by condensation of the activated methyl or methylene group in pyridazinecarboxylate with DMF–DMA to give the enamines (**213**) and (**214**), which upon ring closure with amines in AcOH give derivatives (**215**) and (**216**) (Equation (30)). In some cases the enamine (**217**) can be isolated <89JHC933, 91JHC1043>. Stirring (**214**) in AcOEt–AcOH–H₂O gave a pyrano[3,4-*d*]pyridazine derivative that could be converted by amination to (**216**) <88JHC879>. Cyclization of (**218**) with benzaldehyde afforded compound (**219**) (Equation (31)) <92CCC1770>.





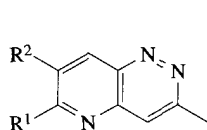
(217)



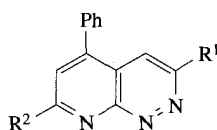
(31)

(iii) Formation of the second ring from [4 + 2] atom fragments

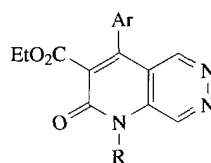
Cyclocondensation of 4-amino-6-methylpyridazine-3-carbaldehyde with aromatic methyl ketones, malononitrile, cyanoacetamide, or cyclohexanone affords the derivatives (220)–(223), respectively (83JHC101). A similar condensation of 3-amino-4-benzoylpyridazine with triethyl orthoacetate followed by base-catalyzed ring closure gave derivatives (224), whereas the amines (225) could be elaborated using the appropriate acetamide acetals as condensation reagents (92PHA679). The same strategy was used to synthesize the derivatives (226)–(228) (86S862, 88JHC879).



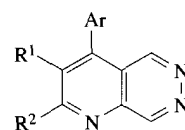
(220) $R^1 = \text{Me}$, $R^2 = \text{H}$
 (221) $R^1 = \text{NH}_2$, $R^2 = \text{CN}$
 (222) $R^1 = \text{NH}_2$, $R^2 = \text{CONH}_2$
 (223) $R^1, R^2 = -(\text{CH}_2)_4-$



(224) $R^2 = \text{OEt}$
 (225) $R^2 = \text{NR}^3\text{R}^4$

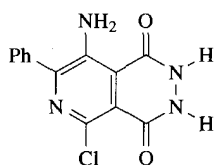


(226)

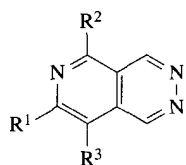


(227) $R^2 = \text{OEt}$
 (228) $R^2 = \text{NMe}_2$

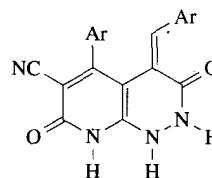
Cyclocondensation of 3-amino-6-chloro-4,5-diethoxycarbonyl-2-phenylpyridine with hydrazine hydrate gave compound (229) (92EUP491477). Condensation of 4,5-diacetylpyridazines with excess benzylamine in the presence of DBU gave the derivatives (230), whereas the reaction of compounds with two different acyl groups with ethyl glycinate–DBU gave a mixture of isomers (231) (89JHC933). Cyclization of 4,5-diarylidene-tetrahydropyridazine-3,6-dione with ethyl cyanoacetate or malononitrile in the presence of AcONH_4 gave the aryl derivatives (232) and (233), respectively (86JPR932, 87JPR525).



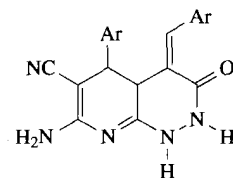
(229)



(230) $R^2 = R^3$, $R^1 = \text{Ph}$
 (231) $R^2 \neq R^3$, $R^1 = \text{CO}_2\text{Et}$



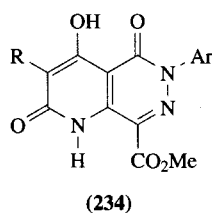
(232)



(233)

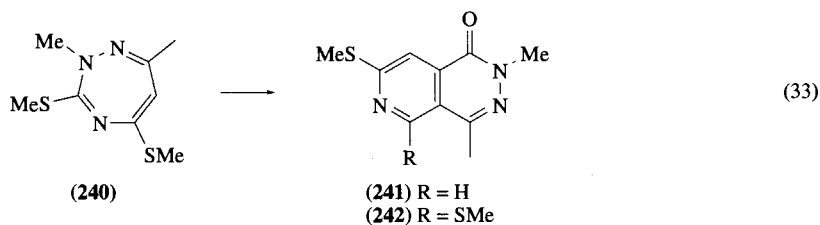
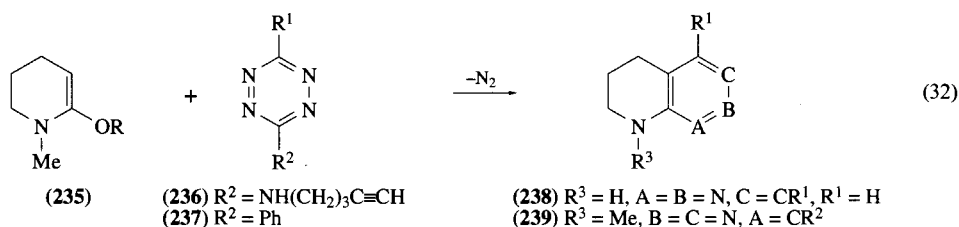
(iv) Formation of the second ring from [3 + 3] atom fragments

Reaction of 5-amino-2-arylpyridazin-3(2H)-ones with activated malonates gives the derivatives (234) (90JHC471).

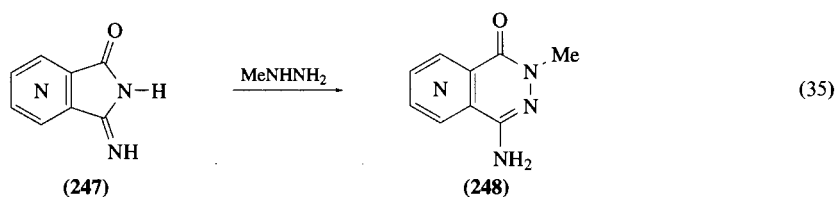
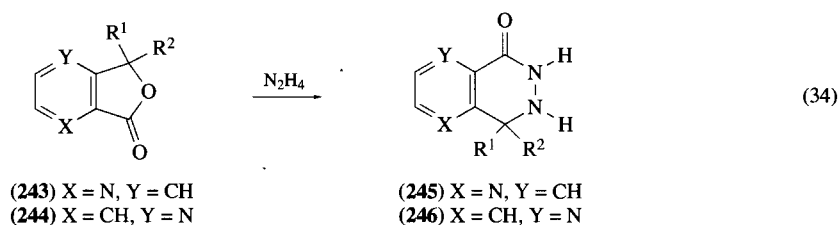


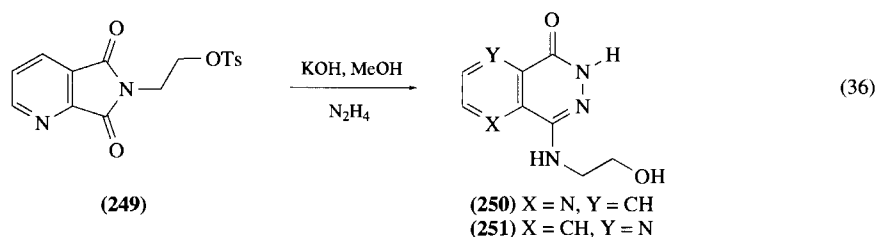
7.16.8.1.3 By transformation of other heterocycles

Inverse intramolecular cycloaddition reactions in the Carboni–Lindsery sense of the alkynes (**236**) gave the derivatives (**238**) (Equation (32)) <84CZ331>. An inverse electron-demand Diels–Alder reaction of the enamine (**235**) and compound (**237**) gave (**239**) (Equation (32)) <86CB3600>. The adduct of compound (**240**) with maleic anhydride underwent a [1,3]sigmatropic rearrangement to give products (**241**) and (**242**) (Equation (33)) <85JHC25>.



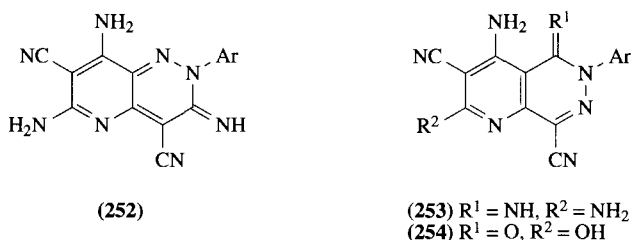
Mixtures of the isomers (**243**) and (**244**) react with hydrazine hydrate to give the products (**245**) and (**246**) (Equation (34)) <84EUP108382> and the aza derivatives (**247**). Methylhydrazine gave the amines (**248**) (Equation (35)) <84JHC965>. Alkaline cleavage of compound (**249**) followed by treatment with hydrazine gave compounds (**250**) and (**251**) (Equation (36)) <81ACH167>.





7.16.8.1.4 From acyclic precursors

Cyclocondensation of arylhydrazonomalononitriles with malononitrile, 2-amino-1,1,3-tricyanopropene, and 3-amino-2-cyanopent-2-ene-dicarboxylate <86H(24)2455, 89JPR878> gives the derivatives (252)–(254), respectively.

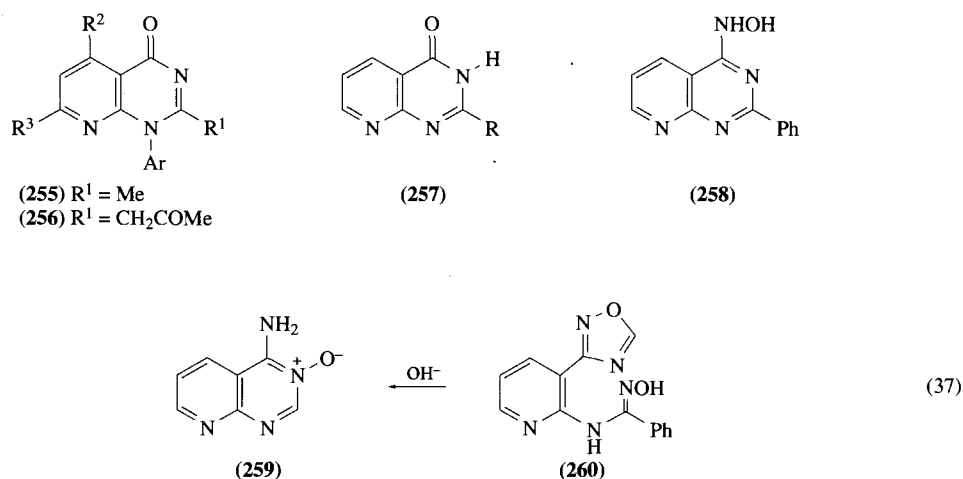


7.16.8.2 Synthesis of Pyrido[x,y-z]pyrimidines

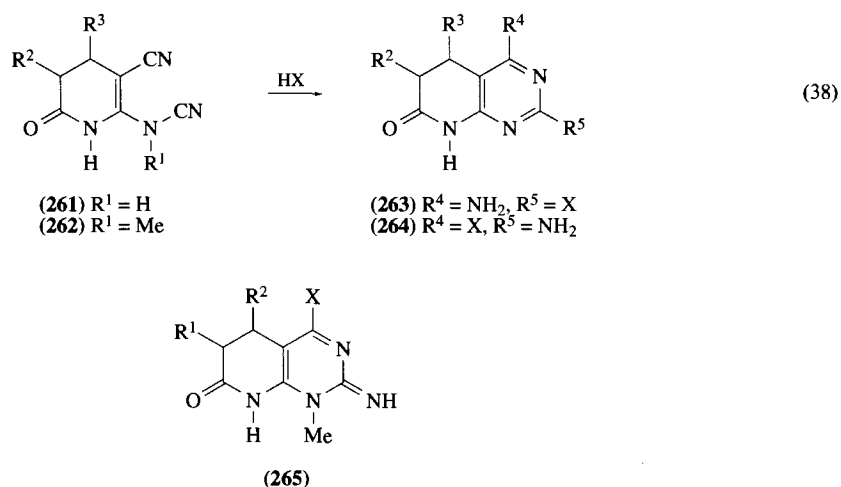
7.16.8.2.1 From pyridine intermediates

(i) Formation of the second ring from [6 + 0] atom fragments

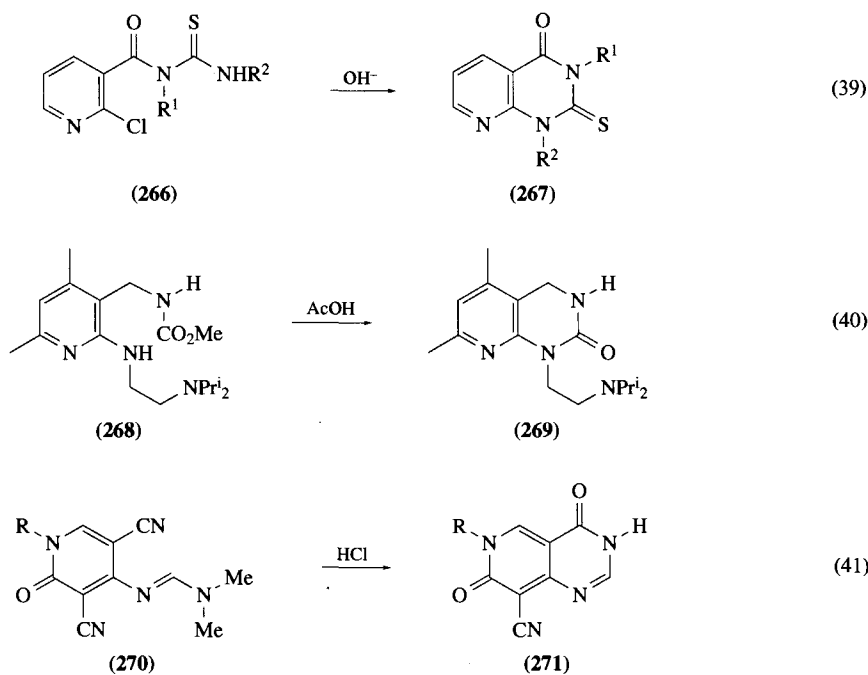
The usual starting materials are pyridine derivatives having a nitrile, amide, or amidoxime group at position 3 and an amino function at position 2. Thus, 2-*N*-acyl-*N*-arylamino nicotinonitriles upon treatment with HCl–EtOH or HIO₄ in Ac₂O–AcOH give (255) and 2-arylamino-6-methylnicotinamides with Ac₂O–AcONa give (255; R¹ = Me) and (256) <85KGS114>. The corresponding 2-acylamino nicotinamides cyclize thermally, or by alkali in pyridine, to give the derivatives (257) <87M399, 89EUP347146, 92KGS535, 92KGS1234>. The corresponding *N*-acylamino nicotinonitrile afforded compound (258) when reacted with hydroxylamine <87M399>. The 2-benzoylamino pyridine-3-carboxamide oxime can be transformed, in the presence of H₂SO₄ or PPA, to the *N*-oxide (259), which is also formed from the oxadiazole (260) by the action of aqueous alkali (Equation (37)).



Cyclization of (261) with HCl afforded (263), whereas HBr and HF led to (263) and (264) (Equation (38)). The similar reaction with (262) afforded only (265) <86H(24)3053>.



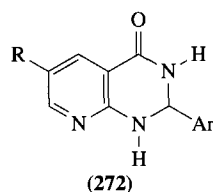
Alkali catalyzed reaction of 2-chloronicotinoylisocyanate with primary amines gave (267) via (266) (Equation (39)) <83CCC3315>. Acid-catalyzed cyclization of (268) and (270) gave (269) (Equation (40)) <83SAP8206106> and (271) (Equation (41)) <87M617>, respectively.



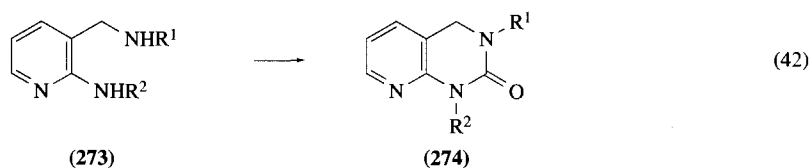
(ii) Formation of the second ring from [5 + 1] atom fragments

Most of the syntheses of pyrido[2,3-*d*]pyrimidines by this approach involve reaction of 2-aminonicotinamides with a one-carbon reagent. Thus, 2-aminonicotinamide with aryl- or 3-pyridine-carbaldehyde <82USP4361700, 92JHC1545>, carboxamides <84MIP126431, 86MIP136568>, valeryl chloride <92EUP481614>, diethyloxalate <91JPR637>, or *S*-methylpseudothiurea <92JHC1545> gave the products (272) and (257).

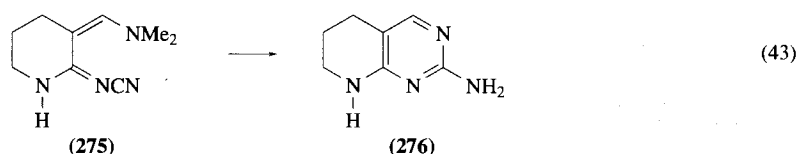
The reaction with ethyl chloroformate or CSCl_2 gave 1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione <83JAP5802950, 84JAP5903479> and the corresponding 2-thione (267) <81JAP(K)81164189>.



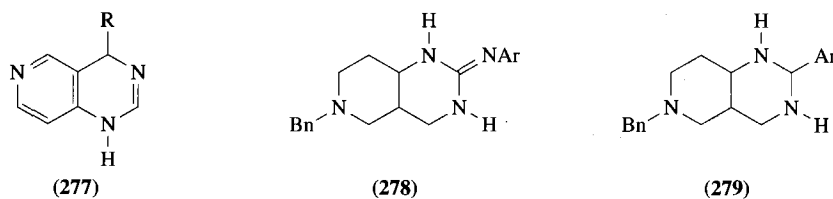
respectively. Cyclization of ethyl 2-(ethoxycarbonylamino)nicotinate with substituted amines gave 2,4-dioxypyrido[2,3-*d*]pyrimidine <87GEP3601731, 89GEP3738844>. Reaction of the diamines (273) with 1,1'-carbonyldiimidazole gave derivatives (274) (Equation (42)) <83JAP5800429, 88MIP8803025>.



Compound (275) with alcoholic ammonia gave the amino derivative (276) together with a pyridotriazine (Equation (43)) <85KFZ154>.

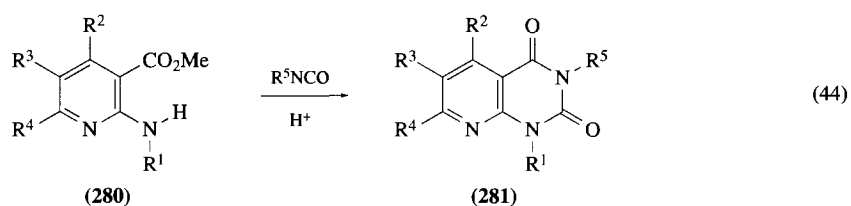


7-Chloro-3,4-dihydropyrido[2,3-*d*]pyrimidin-4-ones were prepared by heating 2-amino-5-substituted nicotinonitrile-1-oxides with POCl_3 in DMF <90EGP279019>. Cyclization of (4-amino-3-pyridinyl)cyclohexylmethanamine with $\text{HC}(\text{OEt})_3$ in AcOH gave compound (277; R = cyclohexyl) <91USP5059602>. Cyclocondensation of 4-amino-1-benzyl-3-piperidinemethylamine with either dichloroisocyanates or aromatic aldehydes gave the products (278) and (279), respectively <85PHA129>. Cyclization of 2-amino-3-cyanopyridine derivatives with formic acid and monochloroacetyl chloride affords pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones <91MI 716-03, 91PJC1265>.



(iii) Formation of the second ring from [4 + 2] atom fragments

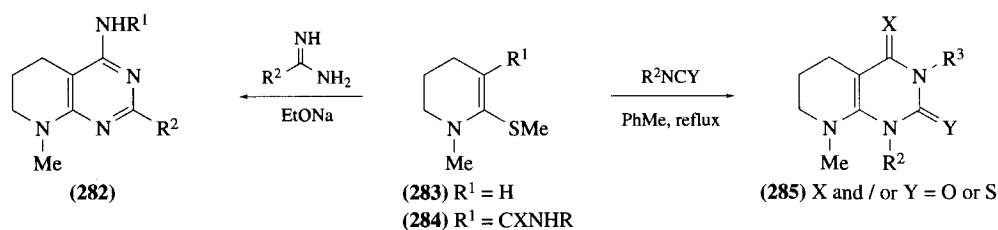
Reaction of the esters (280) with isocyanates gives ureas which cyclize to the derivatives (281) (Equation (44)) <88EUP260817, 89MIP388378, 90FES101, 91JMC624, 92MIP9212979>. The use of the respective iminophosphorane and isocyanates or isothiocyanates gave pyrido[2,3-*d*]pyrimidines having a 2-ethoxy <90LA995> or a 2-thione function <90FES111, 90MI 716-02>.



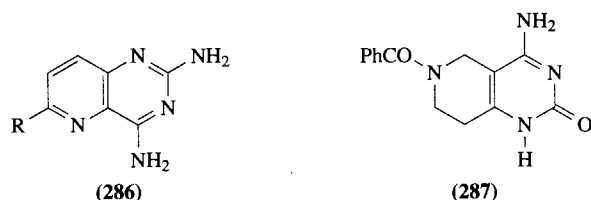
Pyridopyrimidinediones were prepared by reacting ethyl-2-(arylamino)-3-nicotinate with urethane in DMF–NaH <83JAP5802953> or by autoclaving 2-arylaminonicotinic acid with ethyl aminoformate and ZnCl_2 <81JAP(K)81164190>. Reaction of methyl or sodium 2-aminopyridine-3-carboxylates with *N*-aryldithiocarbamates gave the derivatives (267) or the 2,4-dioxo derivatives <84S586>. Cyclization by reaction of 2-aminonicotinonitrile with $\text{HC}(\text{OEt})_3$ followed by methylhydrazine gave the 4-methylhydrazinopyrido[2,3-*d*]pyrimidine <88JOC5309>. This cyclization has also been achieved using trichloroacetonitrile <84S970>, guanidine <82JHC1461, 88JMC2164, 88USP4725687, 92MIP9217478>, formamide, urea, thiourea, ammonium thiocyanate <91MI 716-04, 92FES979, 92IJC(B)719, 92KGS1384, 93PHA221>, and isothiocyanate <90JIC687>.

1,2-Dihydropyrido[2,3-*d*]pyrimidines can be synthesized by reaction of 2-amino-3-benzoylpyridines with amides <83AP(316)346>.

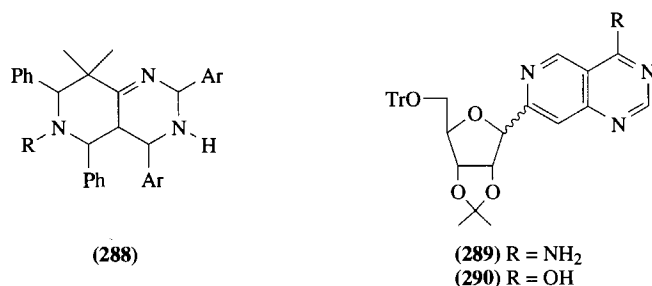
Octahydropyrido[2,3-*d*]pyrimidines (285) have been prepared by cyclization of the enamine (283) with aryl isocyanates or isothiocyanates (Scheme 10) <82S156, 83S225, 83S226>. When the reaction is done in acetone or ether at room temperature, the amide or thioamide derivatives (284) can be obtained, and cyclization with isocyanates or thioisocyanates gives (285) <82H(17)413, 84S703>. Amidines give (282) (Scheme 10) <83S225, 83S227>. 5-Hydroxymethyl-2-piperidone was converted to 2-*t*-butylcarbonylamino-4-hydroxy-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine <92USP5159079>. The pyrido[3,2-*d*]pyrimidines (286) were prepared by condensation of 3-amino-2-cyanopyridines with chloroformamidine hydrochloride <84JHC1521, 85JMC248>. The pyrido[4,3-*d*]pyrimidinone (287) was prepared by heating 1-benzoyl-4-amino-3-cyano-1,2,5,6-tetrahydropyridine with urea <92MIP9200296>.



Scheme 10

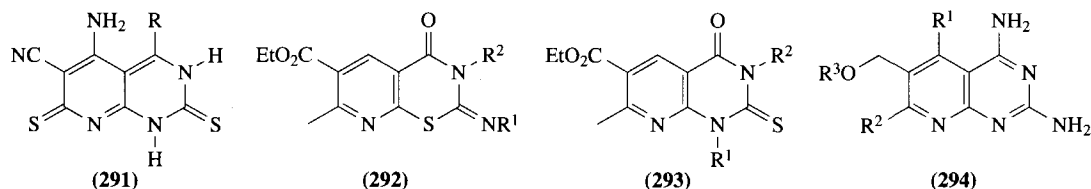


The pyridopyrimidines (288) have been prepared by reaction of *N,N'*-dibenzylidenephényl-methanediamines with 2,6-diaryl-4-piperidones <83S564>. The *C*-nucleoside analogue (289) was obtained by the cyclization of α - and β -5-ribose-4-amino-3-cyanopyridine with $\text{HC}(\text{OEt})_3$ – Ac_2O followed by treatment with saturated methanolic ammonia, whereas compound (290) was prepared by conversion to the amide before cyclization <92MI 716-01>.

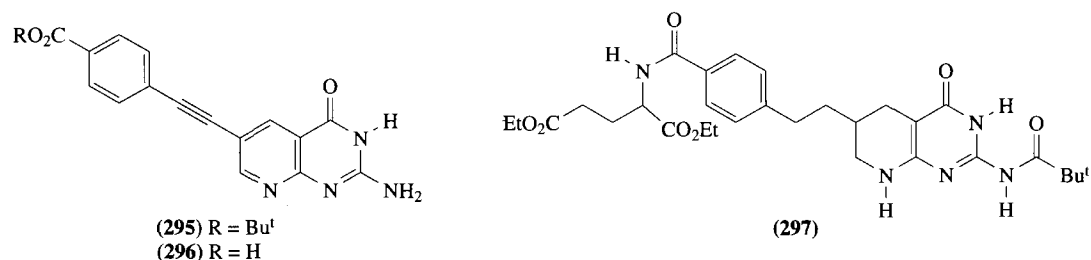


(iv) Formation of the second ring from [3 + 3] atom fragments

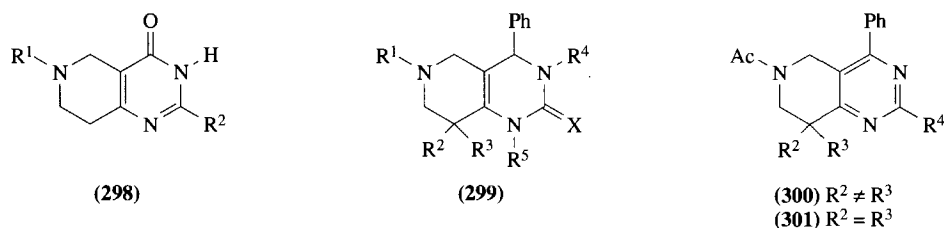
4,6-Diamino-3-cyanopyridine-2-thione was utilized in the synthesis of the derivatives (291) by reaction with isothiocyanates <86T687, 86ZN(B)105>. Condensation of ethyl 2-chloronicotinate with thioureas gave pyridothiazines (292) and pyridopyrimidines (293) <82FES247, 82FES259, 82FES266>. The use of *N*-alkyl(aryl)-*N'*-aminoalkylthioureas gave only pyridopyrimidine <86FES899>. Reaction of nicotinonitriles with guanidine carbonate gave the derivatives (294) <88JMC1209>.



Of particular interest is the synthesis of 5,10-dideaza-5,6,7,8-tetrahydrofolate. Thus, reaction of methyl 2-chloro-5-iodo 3-pyridinecarboxylate with *t*-butyl-4-ethynylbenzoate, followed by cyclization with guanidine gave the ester (295) which was hydrolyzed to the acid (296). Coupling the carboxylic group with diethyl L-glutamate followed by catalytic reduction gave the protected folic acid analogue (297) <88EUP265126, 89JOC3618>.



Reaction of 4-piperidone 3-carboxylic esters with amidines and guanidines gave the derivatives (298) <88PHA475, 90JHC1885, 92JCS(P1)157> and pyrido[3,4-*d*]pyrimidines were similarly prepared from 3-piperidone-4-carboxylic esters <92JAP(K)04224580>. Reaction of 3-benzylidene-4-piperidones with ureas or thioureas gave the derivatives (299) <85PHA536>, whereas reaction with amidines gave derivatives (300) <92EJM655>. The reaction of 3-aryl-4-piperidinones with morpholine followed by amidines gave (301) <92USP5137890>.

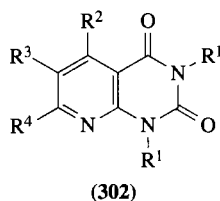


7.16.8.2.2 From pyrimidine intermediates

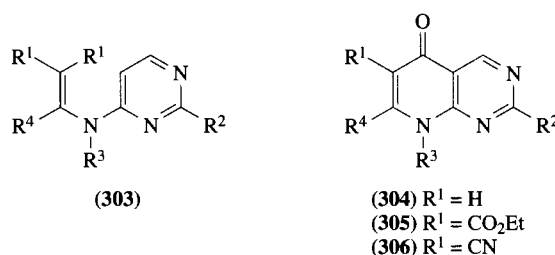
(i) Formation of the second ring from [6 + 0] atom fragments

The methods in this subsection utilize intramolecular cyclizations of 4-aminopyrimidine derivatives to give the pyrido[2,3-*d*]pyrimidines. The functional group may exist on the 4-amino group or at the 5-position of the pyrimidine.

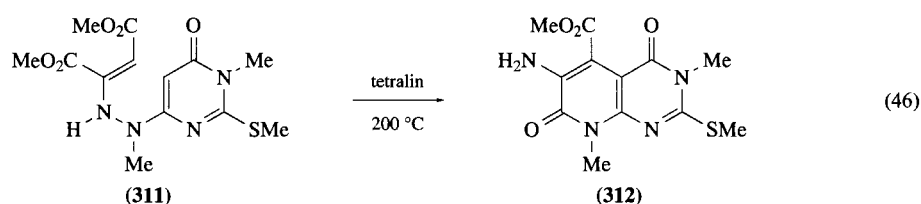
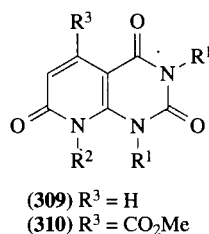
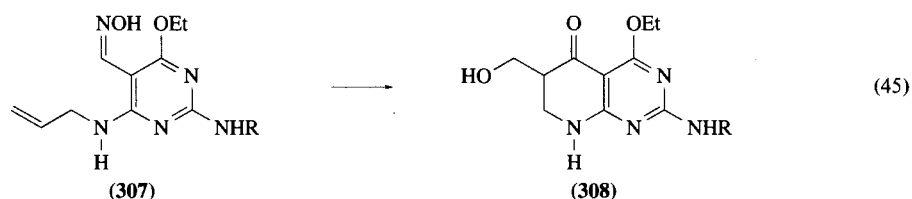
Pyridopyrimidinedione has been prepared by catalyzed oxidative cyclization of 6-allylaminouracil using Pd(AcO)₂ or PdCl₂-CuCl-O₂. Thermal cyclization of the respective 1,3-dimethyl derivative gave a mixture of the derivative (302) and 5-allyl-6-amino-1,3-dimethyluracil <85CPB1375>. Thermal cyclization of the corresponding 6-propargylamino-1,3-dimethyluracil also gave (302) <85CPB4740>.

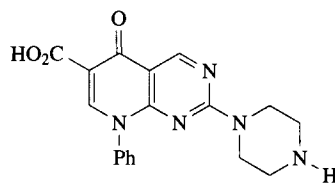


Thermolysis of the pyrimidinylaminomethylene derivative of Meldrum's acid (**303**) produced (**304**) <84USP4432981, 90SL549>, whereas cyclization in presence of trimethylsilyltrifluoromethanesulfonate in toluene or PPA and P_2O_5 gave (**305**) <83JAP(K)5823692, 83JAP(K)5846085, 83JAP(K)5872583, 83JAP(K)5885887>. Intramolecular cyclocondensation of the diesters (**303**; $R = CO_2Et$), by heating in Ph_2O or PPA, gave the esters (**305**) <81JAP(K)81135485, 82JAP(K)8248984, 86JAP(K)61289089>. Similarly, (**303**; $R^1 = CN$) gave the 5-imino derivative of nitriles (**306**) <81JAP(K)81125386>.



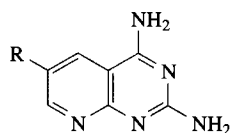
An intramolecular cycloaddition of the oximes (**307**) gave a cycloadduct, via a nitrile oxide intermediate, and reductive cleavage of the isoxazoline ring (Raney nickel- H_2) provided the products (**308**) (Equation (45)) <91H(32)1327>. The cyclization of 6-aminopyrimidine-5-acrylate derivatives could also be effected by Et_3N -DBN to give the derivatives (**309**) <84H(22)513, 85H(23)2057>. Reaction of 6-aminouracils with DMAD gave mixtures of the esters (**310**) and addition products which upon heating cyclized to give (**310**) as the major products and also pyrrolopyrimidines as minor products <86H(24)927>. Cyclization of the Michael adduct (**311**) provided compound (**312**) and a pyrrolo[2,3-*d*]pyrimidine (Equation (46)) <92JCS(P1)1287>. A 6-aminopyrimidine-5-carboxylate having a propionate group at N^6 underwent cyclization, dehydrogenation, and saponification to give the acid (**313**) <85EUP153580>.



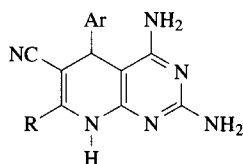


(313)

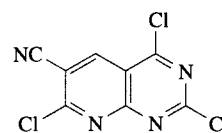
Acid-catalyzed cyclocondensation of 6-aminopyrimidines having an acetal group on position 5 gives the derivatives (314) and the 5,6-dihydro derivative <83JOC4852, 89EUP340905, 92JAP(K)04235986>. Reaction of 2,4,6-triaminopyrimidine with 3,4,5-trimethoxybenzylidene cyanocarbons gave Michael adducts which cyclize in acid giving derivatives (315) <84AP(317)709>. 1-(2,4,6-Trichloro-5-pyrimidinyl)-2,2-dicyanoethylene was heated to give compound (316) <88GEP3643456>. Heating 5-arylideneamino-1,3,6-trimethyluracils with DMF-DMA afforded the aryl derivatives (317) <82JHC805> and 5-formyl-1,3-dimethyl-6-(2-dimethylaminovinyl)uracil and ammonia gave compound (318) <87EUP244352>.



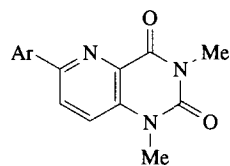
(314)



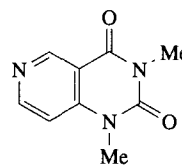
(315)



(316)

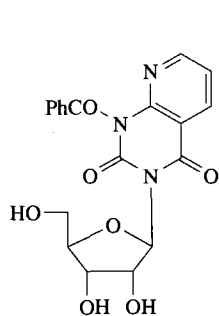


(317)

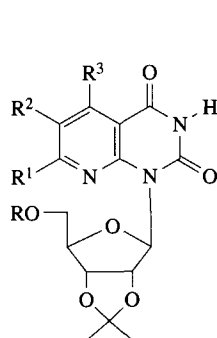


(318)

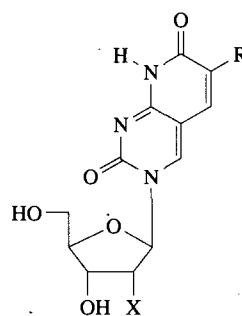
Cyclization of 6-(allylamino)isouridine took place with PdCl_2 -dioxan- O_2 to give the ribonucleoside (319) after debenzoylation <89JAP(K)01143895> and the derivatives (320) were synthesized similarly <90H(30)231>. The formation of the pyridine ring in the derivatives (321) and (322) has been effected by irradiation ($h\nu$, 300 nm) of the respective pyrimidine derivatives having a 2-methoxycarbonylalkenyl group at C-5 and an amino group at C-4 <82JOC2174>.



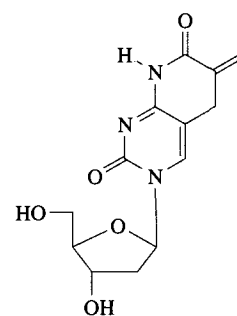
(319)



(320) R = H, Ac



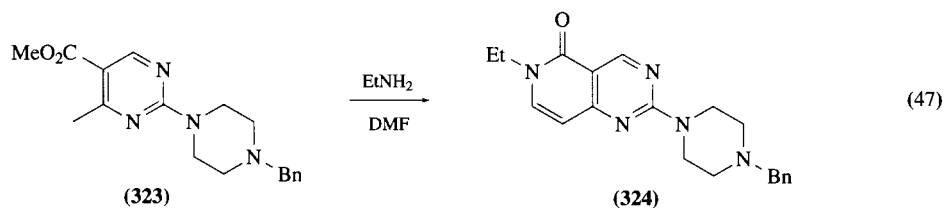
(321)



(322)

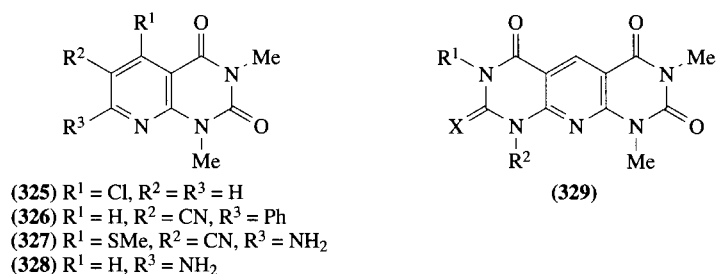
(ii) Formation of the second ring from [5 + 1] atom fragments

The pyrimidine ester (323) was amidated with ethylamine and cyclocondensed with DMF to give compound (324) (Equation (47)) <86EUP188094>. 5-Acetyl-6-amino-1,3-dimethyluracil was cyclized using POCl_3 -DMF to give compound (325) <87EUP243311>.



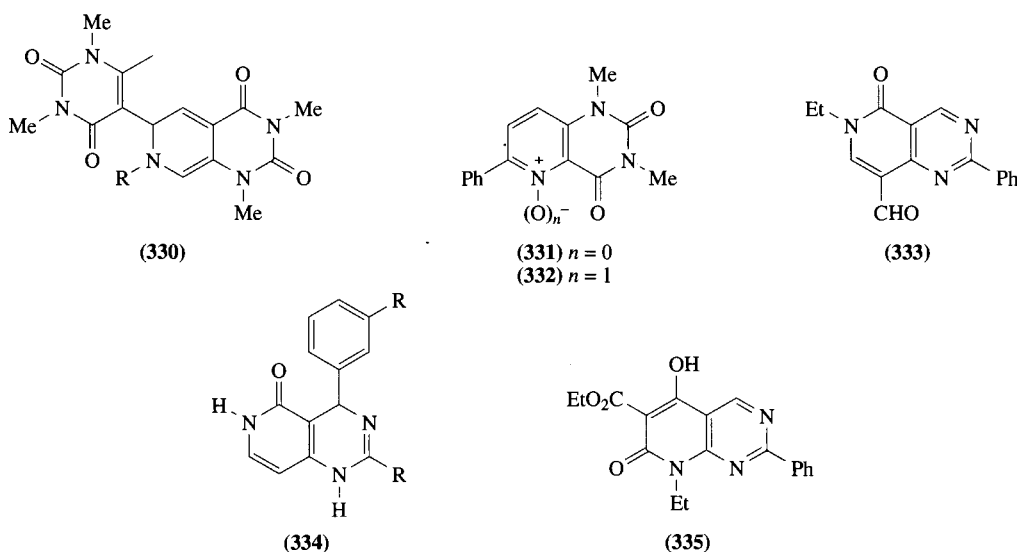
(iii) Formation of the second ring from [4 + 2] atom fragments

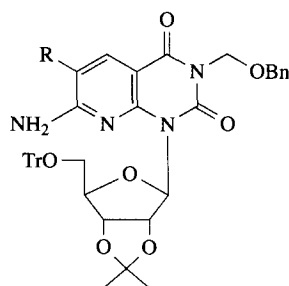
Condensation of 6-amino-5-formylpyrimidines with benzoyl acetonitrile gave compound (326) <84LA1653>. The cyclization of a 6-aminopyrimidine-5-dithiocarboxylate with Me_2SO_4 followed by reaction with $\text{CH}_2(\text{CN})_2$ in the presence of K_2CO_3 -DMSO gave compound (327) <84CPB122>. Reaction of 5-dimethylaminomethylene-6-imino-1,3-dimethyluracil hydrochloride with active methylene compounds or barbituric acid derivatives yielded the derivatives (328) and (329), respectively <85JHC345, 88JHC217>.



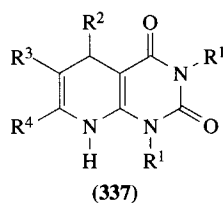
The pyrido[3,4-*d*]pyrimidines (330) have been obtained by reaction of 5-formyl-1,3,6-trimethylpyrimidine-2,4(1*H*,3*H*)-dione with primary amines <88JHC205>. Reaction of 1,3,6-trimethyl-5-nitrouracil with phenylacetaldehyde in the presence of piperidine yielded compound (331) and its *N*-oxide (332) <82JHC805>. Heating 4-methyl-2-phenylpyrimidine-5-carboxylic acid with diethylformamide- POCl_3 gave compound (333) <86JAP(K)6150982> and reaction of 4-methyl ($\pm$)-1,4-dihydropyrimidine-5-carboxylates with 1,3,5-triazine in DMF- NaH gave the derivatives (334) <86GEP3502590, 86GEP3502742>. Reaction of ethylchloromalonate with ethyl 4-ethylaminopyrimidine-5-carboxylate gave compound (335) <81USP4301281>.

A number of protected nucleosides (336) have been prepared by cyclization of pyrimidine nucleosides <84H(21)289, 84MI 716-02>.

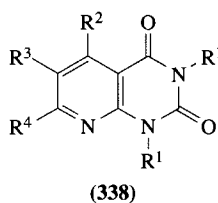


(336) R = CN, CONH₂, CO₂Et*(iv) Formation of the second ring from [3 + 3] atom fragments*

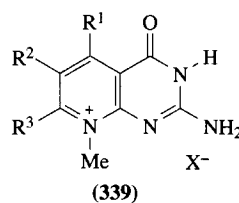
Various pyrido[2,3-*d*]pyrimidines (337) have been prepared by cyclization of 4-aminopyrimidines with α,β -unsaturated ketones <84JAP(K)59225188, 86GEP3501696, 90GEP3900363, 92AP(325)341> in hot DMF (argon atmosphere); in air oxidation to the fully aromatic derivatives (338) occurs <92JHC1045>. Similarly, cyclocondensation of 2,4,6-triaminopyrimidines with 3-amino-2-methylacrolein gave 2,4-diamino-6-methylpyrido[2,3-*d*]pyrimidine <86JHC523>. This reaction was also done with 4-methylaminopyrimidine derivatives to give the salts (339) <93JOC1104>. α,β -Unsaturated esters have been reacted with 4,6-diamino-2-methylthiopyrimidine to afford derivatives (340) <85JHC1735>.



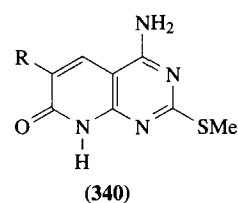
(337)



(338)

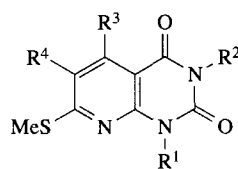


(339)



(340)

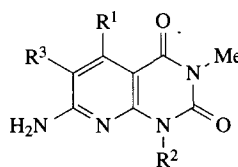
Reaction of ketenethioacetals having nitrile or ester substituents with 6-aminouracils gave the derivatives (341); in some cases the intermediates could be isolated <84CPB122>.



(341)

R³ = NH₂, OH
R⁴ = CN, CO₂R

Arylidenemalonitriles react with 6-amino- and 6-hydroxyamino-1,3-dimethyl and 3-methylpyrimidinedione to give the derivatives (342; R³ = CN) <84CC1549>. This ring was also constructed by the reaction of β,γ -unsaturated nitriles with 2,4-diamino-6(1*H*)-pyrimidinone <89EUP314280>.

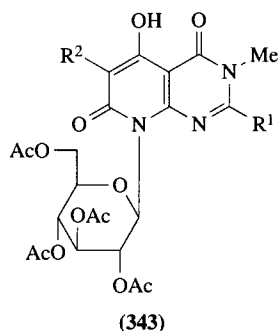


(342)

4-Aminopyrimidine derivatives can also be cyclized with 1,3-dicarbonyl compounds <82UKZ1112, 83JOC4852, 93JOC1104> such as triformylmethane to give 2-amino-7-formylpyrido[2,3-*d*]pyrimidin-4-one, whereas its *N*-methyl derivative gave the respective derivative of (339). Malonaldehyde bis(dimethyl acetal) and diethyl 2-formylglutarate <84JCS(P1)959, 86GEP3422824> have been used to

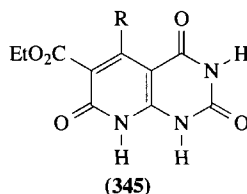
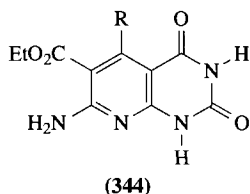
prepare pyridopyrimidines and 7-pyridopyrimidinones, respectively. The use of bromomalon-aldehyde led to the respective 6-bromopyridopyrimidine <89JOC3618, 91JHC1747>.

Reaction of ethyl α -(arylmethyl)acetoacetate with 2,4,6-triaminopyrimidine gave 7-pyrido[2,3-*d*]pyrimidinones <85USP4512992, 88EUP279565>. Reactions of glycopyranosylaminopyrimidinones with malonic acids in Ac_2O afforded the derivatives (343) <91M255>.

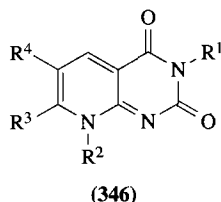


4-Oxo-4*H*-chromene-3-carbaldehydes have been used as a source of the 3-carbon fragment: reaction with 2-aminopyrimidinediones gave 6-salicyl-2,4-pyrido[2,3-*d*]pyrimidinediones <83AP(316)55>.

The reagent $\text{CH}(\text{CH}=\text{N}^+\text{Me}_2)_3 \cdot 3\text{Cl}^-$ (prepared from DMF, POCl_3 , $\text{BrCH}_2\text{CO}_2\text{H}$) has been used to prepare 2,4-diamino-6-formylpyrido[2,3-*d*]pyrimidine <83EUP75880, 84USP4431805>. Pyrido[2,3-*d*]pyrimidine derivatives (344) and (345) have been obtained by the condensation of furfurylidenebarbituric acid with ethyl cyanoacetate and diethylmalonoate in presence of NH_4OAc , respectively <90MI 716-03>.

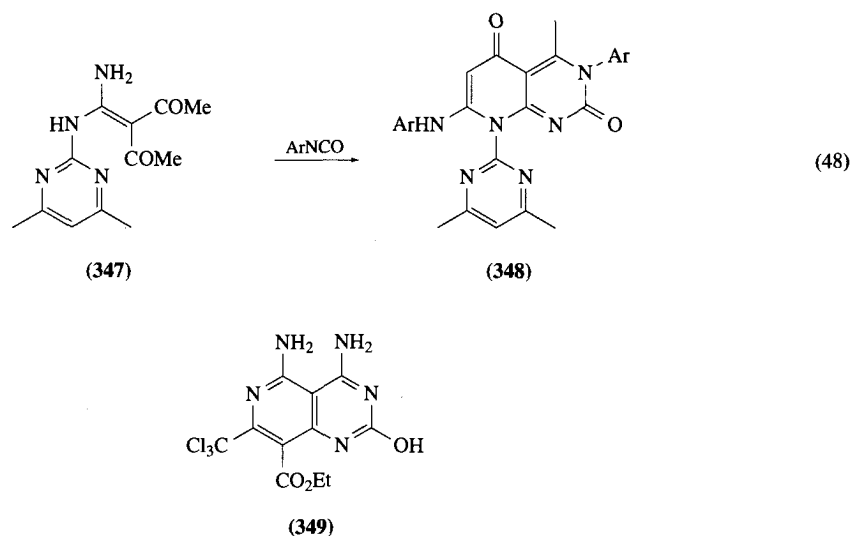


β -Haloketones or aldehydes have also been used as three-carbon fragments in the cyclization of 4-aminopyrimidines. Thus, 2-(β -bromoethyl)-2-methyl-1,3-dioxolane was used to obtain the derivatives (339) <93JOC1104> and 3-chloro-2-alkenals gave the derivatives (346) <83S75, 84CPB1699, 92GEP4035479>. The 1-chloroalkenal fragment in 6-chloro-5-formyl-3-methyl-2,4-pyrimidinedione led upon its reaction with *N,N'*-dialkyl-*p*-phenylenediamine to the respective pyridopyrimidine in low yield, whereas the use of two equivalents gave derivatives (70) <86CPB2653>.

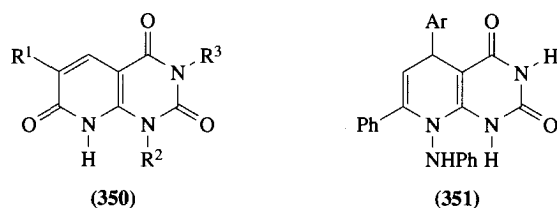


7.16.8.2.3 From acyclic precursors and by transformation of other heterocycles

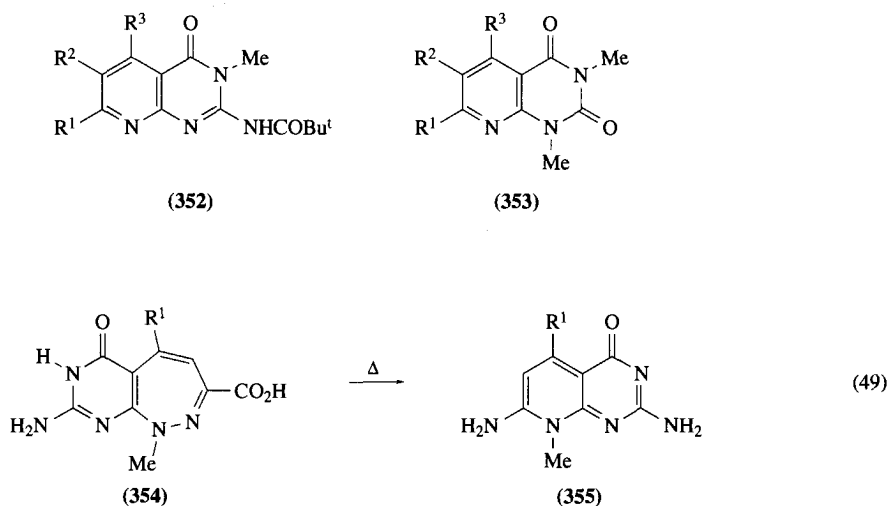
Cyclocondensation of compound (347) with aryl isocyanates affords the derivatives (348) (Equation (48)) <91IZV2593> and reaction of ethyl 3-amino-4,4-dicyano-3-butenate with trichloroacetonitrile gave compound (349) <91MI 716-05>. 6-Amino-1,3-dimethyluracil was reacted with aromatic aldehydes and β -ketoesters to give derivatives (337) <86USP4596805, 90MIP9012015>. Reaction of 5-cyano-1,3-dimethyluracil with ethyl cyanoacetate or malononitrile gave the amines (342; $\text{R}^3 = \text{CO}_2\text{Et}$ and CN); the use of ketones gave low yields <84H(21)289, 84JHC1543>.



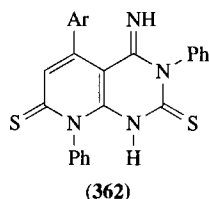
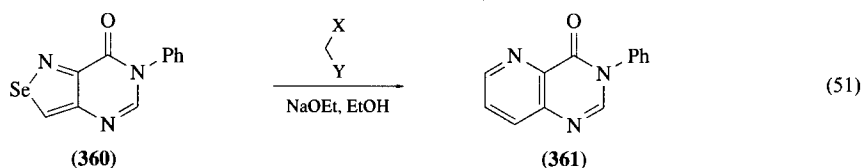
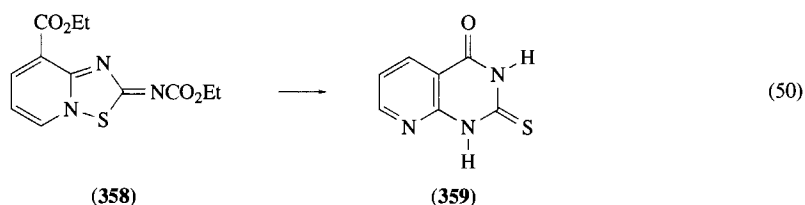
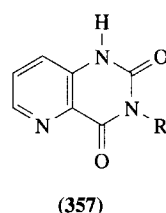
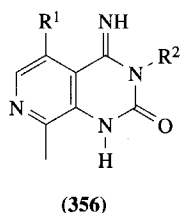
The synthesis of bicyclic compounds by exploitation of ring transformation reactions has been achieved using 6-imino-1,3-dialkyl-2,4-pyrimidinediones as cyclic 1,3-ambident reagents which upon reaction with 1,3-dialkyluracils give the derivatives (350) <84H(21)289>. Reaction of 2-methyl-5,7-diphenylpyrido[2,3-*d*][1,3]oxazin-4-(3*H*)-one with amines or aldimines gave the respective pyrido-pyrimidine derivative <84IJC(B)977, 90MI 716-01>. Replacement of the oxygen atom in pyranopyrimidines using phenylhydrazine gave the derivatives (351) <90MI 716-04>.



Diels–Alder cycloaddition of pyrimido[4,5-*e*]-1,2,4-triazines with electron-rich dienophiles resulted in the formation of the pyridine ring as in derivatives (352) and (353) <87TL1977>. Pyrimidodiazepines (354) are susceptible to ring-opening/ring-closure rearrangement reactions leading to the pyridopyrimidines (355) (Equation (49)) <82JOC667>.



Reaction of oxazolyl ureas with acrylonitrile or fumaronitrile gave (356) <92CCA599>. *N*-(Phenylsulfonyloxy)quinolinimide with dry ammonia gave a mixture of compounds (357) and 2-carbamoyl-3-pyridylurea, and similar reactions took place with hydrazine, hydroxylamine hydrochloride, and aromatic amines <86H(24)2201>. Ring expansion of 1,2,4-thiadiazolopyridine (358) gave compound (359) (Equation (50)) <87H(26)689>. The isoselenazolo[4,3-*d*]pyrimidine (360) was transformed into compound (361) using active methylene compounds (Equation (51)) <85CPB3065>. The dithione (362; Ar = *p*-ClC₆H₄) was prepared from (1-*p*-chlorophenylethylidene)malonitrile by reaction with phenyl isothiocyanate <92PHA418>.

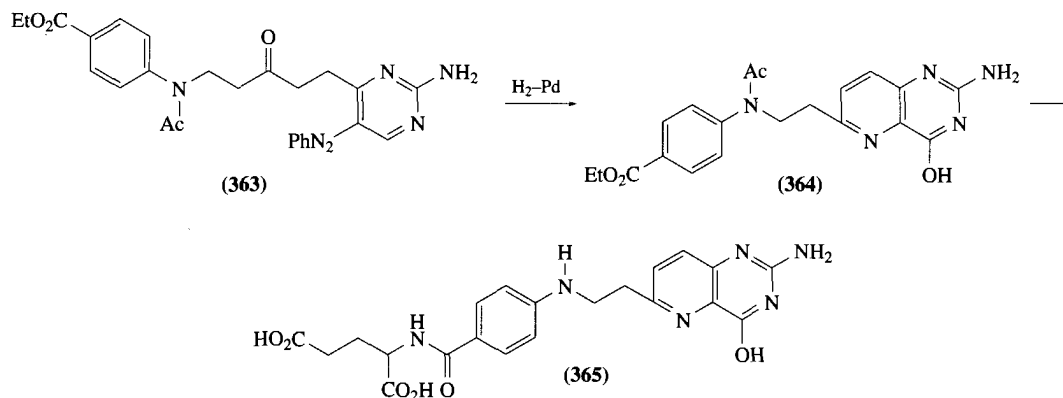


7.16.8.2.4 Special compounds

This section discusses selected syntheses for some important compounds for which much synthetic effort has been reported. One of the methods of synthesis of pipemidic acid (166; R¹ = H) was done by treating 2-piperazino-4-ethylaminopyrimidine-5-carboxylate with 3-butenal, followed by potassium permanganate oxidation <81MIP498856>. Alternatively, the piperazine ring was introduced on a pre-built pyridopyrimidine ring <81JAP8125234>. Pipemidic acid trihydrate was also prepared <83JAP(K)5835187, 85JAP(K)60239486, 86JAP(K)61249983, 86JAP(K)61268683>.

The synthesis of 8-deazahomofolic acid (365) was accomplished by the catalytic hydrogenation of (363) to give (364) whose hydrolysis, trifluoroacetylation, coupling with diethyl L-glutamate, via activation of the carboxyl group with isobutyl chloroformate, and then hydrolysis gave (365) (Scheme 11). Hydrogenation over PtO₂-EtOH-TFA followed by hydrolysis gave the 5,6,7,8-tetra-

hydro derivative of (365) <88JMC150>. An enantioselective synthesis of (6*R*)- and (6*S*)- 5,10-dideaza-5,6,7,8-tetrahydrofolic acid derivatives in 13 steps has been patented <91EUP407212>.



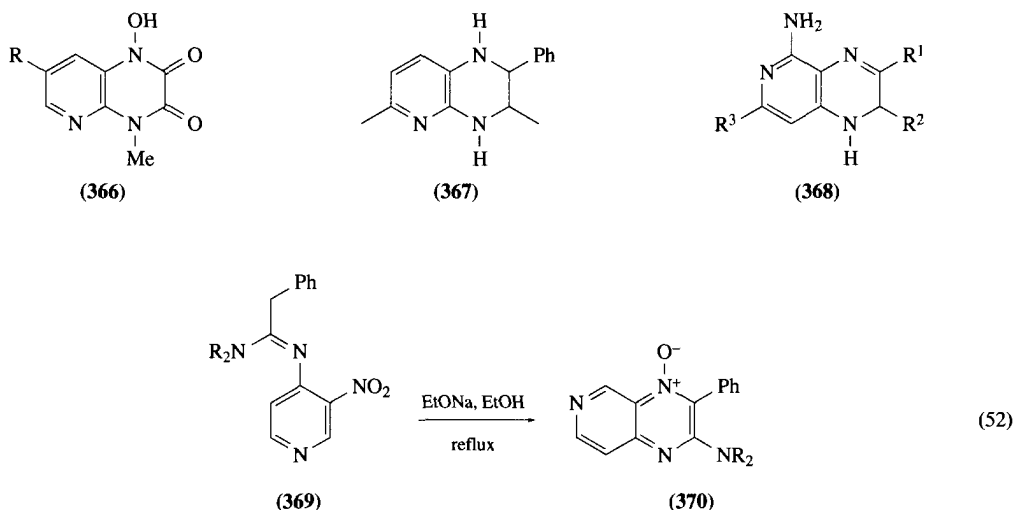
Scheme 11

7.16.8.3 Synthesis of Pyrido[x,y-z]pyrazines

7.16.8.3.1 From pyridine intermediates

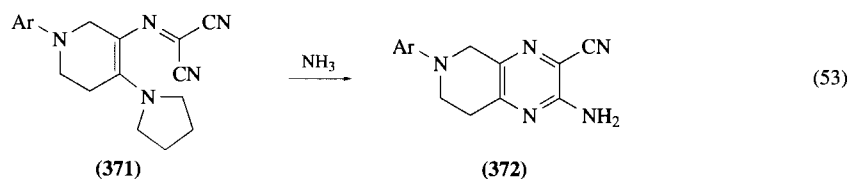
(i) Formation of the second ring from [6 + 0] atom fragments

This strategy is of little use for the synthesis of pyrido[2,3-*b*]pyrazines but has been widely used for preparing pyrido[3,4-*b*]pyrazines. Reactions of *N*-(3-nitro-2-pyridyl)sarcosine esters with base give the derivatives (366) <87TL6363, 92T7887>. Oxidation and catalytic reduction of 2-(6-methyl-3-nitro-2-pyridyl)amino-1-phenylpropan-1-ol gave compound (367) <87AP(320)1143>. A similar approach has been used for the synthesis of the derivatives (368) <89EUP336345, 89JMC2089, 91JMC3176, 92JMC4809>. Alternatively, hydrogenation of the respective α -aminoketone oximes (Raney nickel) gives (368) <82EUP61178, 82JMC1045, 83EUP90681, 84USP4450160, 86USP4600716, 89JMC2363, 91JMC3176, 92USP5095017>. Cyclization of the amidines (369) gives the *N*-oxides (370) (Equation (52)) <92SI206>.



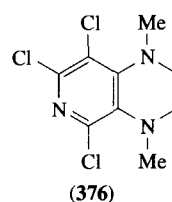
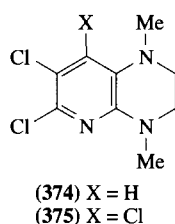
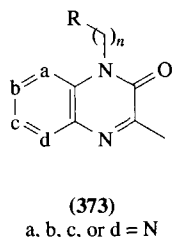
(ii) Formation of the second ring from [5 + 1] atom fragments

This strategy is rarely useful. Treatment of the enamines (371) with NH_3 -MeOH gave the aryl derivatives (372) (Equation (53)) <85H(23)1703>.



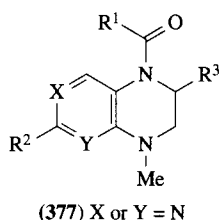
(iii) Formation of the second ring from [4 + 2] atom fragments

The starting material frequently used for this approach is 2,3-diaminopyridine, which upon reaction with symmetrical 1,2-dialdehydes or ketones gives pyrido[2,3-*b*]pyrazines <82KFZ1329, 86JCS(P1)1043, 91JAP(K)0374386>. This diaminopyridine was also condensed with oxalic acid to give the 2,3-dihydroxy derivative <92JAP(K)04178385>. The reaction proceeded similarly with a substituent on the amino group and ethyl oxalate <81USP4296114>. The above condensation was also done with 3,4-diaminopyridine to give pyrido[3,4-*b*]pyrazines <86JCS(P1)1043>. When the reaction of diamines is carried out with unsymmetrical dicarbonyl compounds, the possibility exists for the formation of isomeric products. The kinetics and regioselectivity of the reaction of 2,3- or 3,4-diaminopyridines with bifunctional carbonyl compounds such as glyoxalic, pyruvic, and benzoylformic acids under different experimental conditions have been studied <90JHC157>. The reaction of trifluoropyruvaldehyde with 2,3- and 3,4-diaminopyridines started with the reaction of the most reactive amino group with the aldehyde <88JOC5088>. A small amount of the other isomer was formed. Cyclocondensation of diaminopyridine derivatives with pyruvic acids gave derivatives (373) <83FES330, 88FES613, 90JMC3044>. Reaction of 2,3,5,6-tetrachloropyridine with TMEDA gave (374) together with 3,5,6-trichloro-2-dimethylaminopyridine. When the pentachloropyridine was reacted with DMEDA a mixture of compounds (375) and (376) was obtained <82JCS(P1)2897, 92H(34)1539>.



(iv) Formation of the second ring from [3 + 3] atom fragments

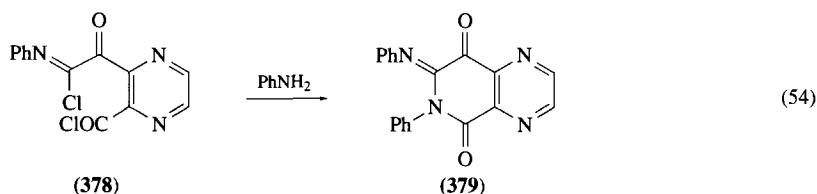
The 1,2,3,4-tetrahydropyrido[2,3-*b*] or [3,4-*b*]pyrazines (377) were prepared by the condensation of the respective (acetylamino)chloropyridines with 2-chloro-*N,N*-dialkylamines hydrochloride <91S982>.



7.16.8.3.2 From pyrazine intermediates

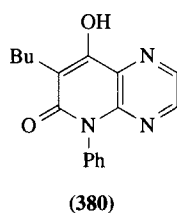
(i) Formation of the second ring from [5 + 1] atom fragments

Cyclization of compound (378) with aniline afforded compound (379) (Equation (54)) <86LA132>.



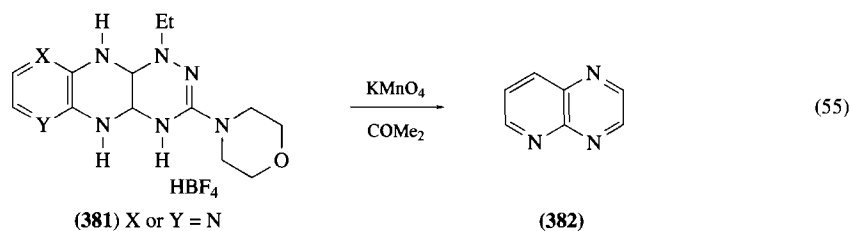
(ii) Formation of the second ring from [4 + 2] atom fragments

Methyl 2-anilino-3-pyrazinecarboxylate has been reacted with butylacetate in the presence of alkoxide to give compound (380) <85USP4492702>.



7.16.8.3.3 By transformation of other heterocycles

Reaction of 2,3-diaminopyridine with 1-ethyl-3-morpholino-1,2,4-triazinium tetrafluoroborate gave a mixture of the cyclic adducts (381), which upon treatment with KMnO_4 -acetone afforded pyrido[2,3-*b*]pyrazine (382) (Equation (55)) <87KGS280>.

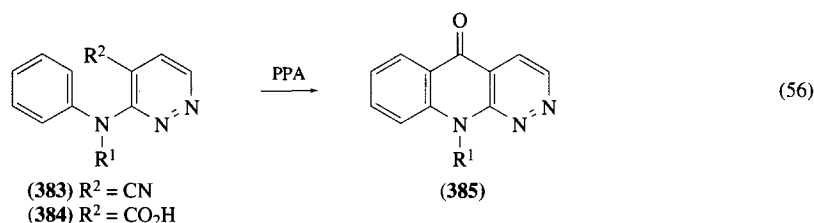


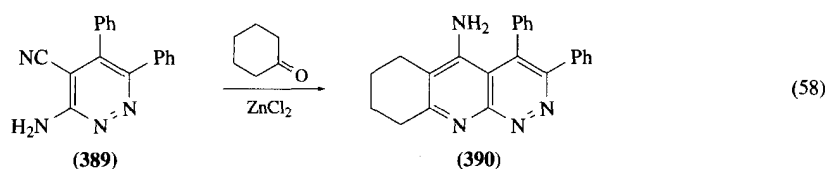
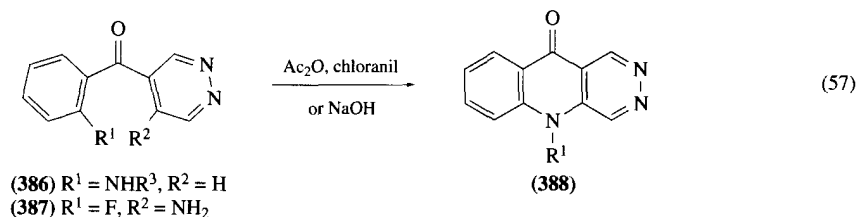
7.16.8.4 Synthesis of [1,*n*]Diazino[*x,y-z*]quinolines and Isoquinolines

7.16.8.4.1 Synthesis of pyridazino[*x,y-z*]quinolines

(i) From pyridazine intermediates

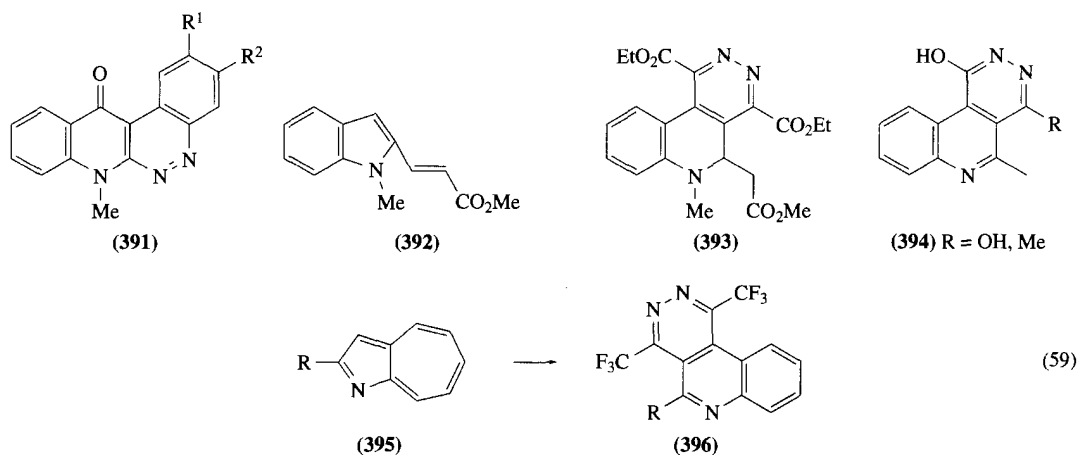
Cyclization of the nitriles (383) or the acids (384) with PPA gave the derivatives (385) (Equation (56)) <87AP(320)1222>. The amino ketones (386) upon treatment with Ac_2O followed by oxidation (chloranil) or directly using NaOH give the derivatives (388) (Equation (57)) <89LA481>. Cyclization of the fluoro derivative (387) in boiling DMF with K_2CO_3 gave compound (388; $\text{R}^1 = \text{H}$) <88JCS(P1)401, 89H(29)1309>. Reaction of compound (389) with cyclohexanone gave compound (390) (Equation (58)) <91ZN(B)835>.





(ii) From quinoline intermediates

Examples synthesized by this approach are few. Thus, cyclization of 2-amino-3-arylquinolin-4-ones using NaNO_2 -AcOH gave the quinocinnolines **(391)** <85MI 716-01>. Reaction of the indole **(392)** with dimethyl-1,2,4,5-tetrazinedicarboxylate gave compound **(393)** via a [4 + 2] cycloaddition/[4 + 2] cycloreversion followed by oxidative heterolysis at the N—C-4a bond and cyclization via Michael-type addition <89HCA65>. *N*-Substituted pyrrolo[3,4-*c*]quinolines were transformed upon reaction with hydrazine to **(394)** <84JHC27>. [4 + 2] Cycloaddition of azaazulenes **(395)** to 3,6-bis(trifluoromethyl)tetrazine gave adducts which, via N_2 -elimination and rearrangement, gave the derivatives **(396)** <93CB441>.



Cyclization of 4-oxo-1,2,3,4-tetrahydroquinoline-3-acetic acid with 4-chlorophenylhydrazine gave 2-(4-chlorophenyl)-4,4a,5,6-tetrahydropyridazino[4,3-*c*]quinolin-3(2*H*)-one <89JAP(K)01216991>. Cyclization of 3-aryl-2-carbethoxy-4-quinolones with hydrazine or phenylhydrazine gave the respective tetrahydropyridazino[4,5-*b*]quinolinediones <89ZOR1045>.

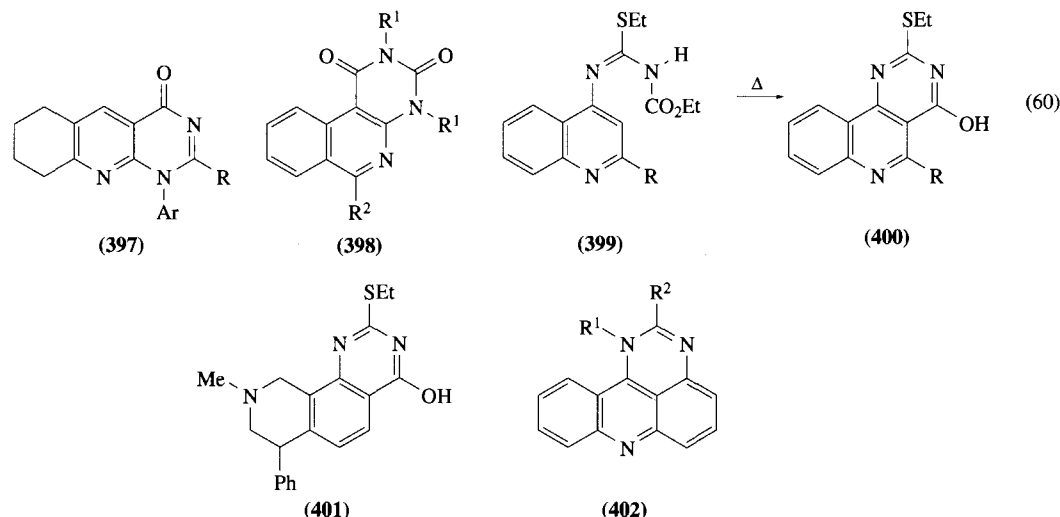
Reduction of quinoline-3,4-dicarboxylate with LAH gave the diformyl derivative, which with hydrazine gave the pyridazinoquinoline. Condensation of the diester with hydrazine afforded a mixture of pyridazinoquinolinediones and a pyrroloquinoline derivative <84JHC27>. Cyclization of 3-carbethoxy-2-dichloromethyl-4-phenylquinoline with hydrazine gave 10-phenylpyridazino[4,5-*b*]quinolin-1-one, which in turn was transformed into the corresponding thione <90JHC1099>.

7.16.8.4.2 Synthesis of pyrimidino[*x,y-z*]quinolines and isoquinolines

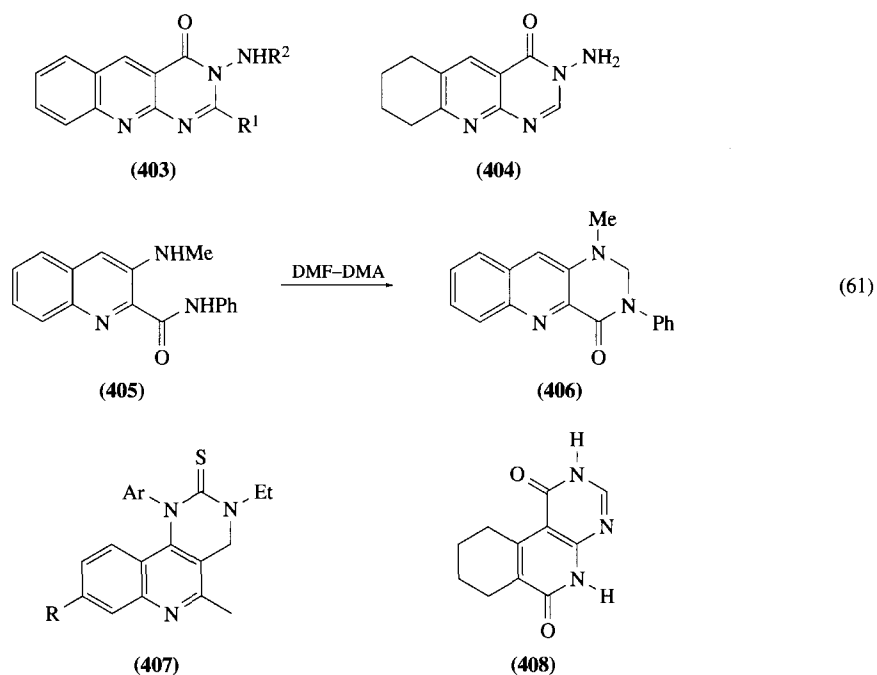
(i) From quinoline and isoquinoline intermediates

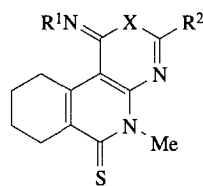
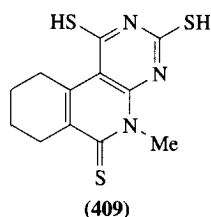
(a) Formation from [6 + 0] atom fragments. Intramolecular cyclocondensation of 2-acylaryl-amino-3-cyanotetrahydroquinolines by HCl-EtOH gave the derivatives **(397)** <88KGS85>. Thermal

cyclization of ethyl 3-ureidoisoquinoline 4-carboxylate gave **(398)**, <89AJC1029> and thermal cyclization of **(399)** afforded **(400)** (Equation (60)). A similar type of cyclization was used for the synthesis of compound **(401)** <81JHC1417>. Cyclization of the acyldiaminoacridines using HCl-MeOH gave the derivatives **(402)** <87TL5029>.

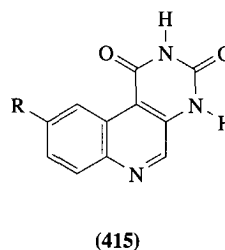
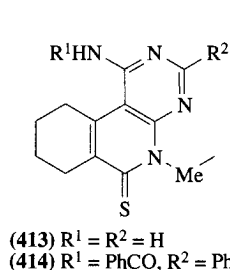


(b) *Formation from [5 + 1] atom fragments.* Reaction of ethyl 2-aminoquinoline-3-carboxylate or its tetrahydro derivative with ethoxymethylene cyanoacetate followed by hydrazine gave compounds **(403)** and their tetrahydro derivatives, respectively <82JHC1425>. Cyclocondensation of 5,6,7,8-tetrahydro-2-arylamino-3-quinolinecarboxamide with $\text{Ac}_2\text{O}-\text{AcONa}$ gave 2-acetonyltetrahydro-4-pyrimidoquinolinone <88KGS1649> and with ethyl chloroformate gave 1,3-diaryloctahydro-2,4-pyrimidoquinolinedione <89ZOR182>. Reaction of 2-amino-5,6,7,8-tetrahydroquinoline-3-carbohydrazide with $\text{HC}(\text{OEt})_3$ gave compound **(404)** and a triazepinoquinoline <82JHC1425>. Reaction of the amine **(405)** with DMF-DMA gave compound **(406)** (Equation (61)) <84CPB1604>. Condensation of 4-anilino-3-ethylaminomethylquinaldines with CS_2 gave the derivatives **(407)** <84MI 716-01>. The reaction of oxoisoquinolines having *o*-aminocarboxamide functions with $\text{HC}(\text{OEt})_3$ gave compound **(408)** <87EGP252189, 87ZC69>. The cyclization of *o*-aminocarbonitrile on tetrahydrothioxoisoquinoline with CS_2 gave **(409)** <90PS(48)211>. Reaction of *o*-aminoisoquinoline-carbonitrile with $\text{HC}(\text{OEt})_3$ followed by hydrazine gave the derivative **(410)** <90PS(48)211>.

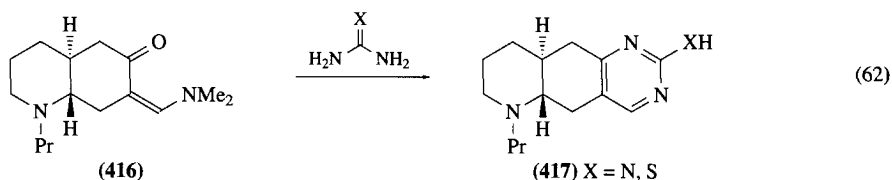




(c) *Formation from [4 + 2] atom fragments.* The reaction of *o*-aminoisoquinolinecarbonitrile with formamide gave the amine (413), and with excess benzoyl chloride afforded compound (411); aminolysis gave (412) and reaction with ammonium acetate gave (414) <91PS(56)197>. Reaction of 3-amino-4-quinoline carboxylic acid with urea gave compound (415; R = H) <86AP(319)382>.

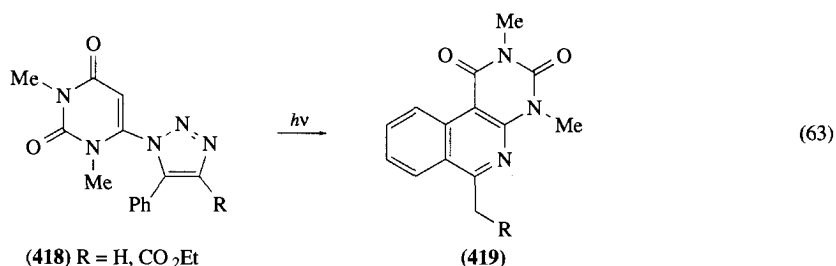


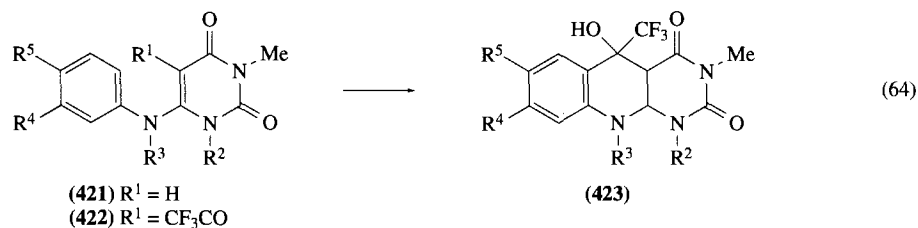
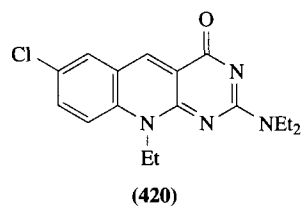
(d) *Formation from [3 + 3] atom fragments.* Cyclization of compound (416) with guanidine carbonate or thiourea gave the derivatives (417) (Equation (62)) <85USP4507478>.



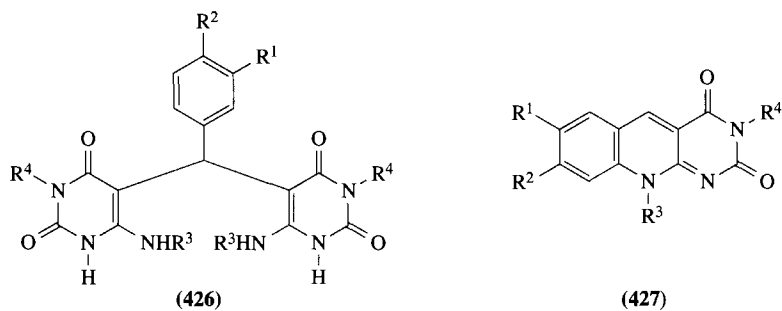
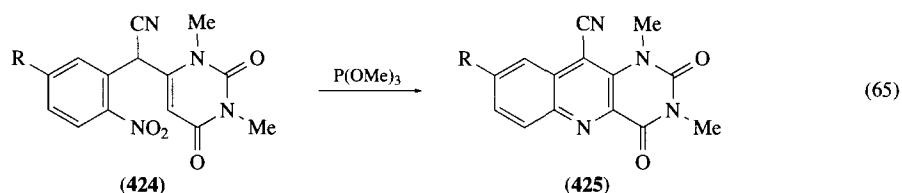
(ii) From pyrimidine intermediates

(a) *Formation from [6 + 0] atom fragments.* Photolysis of the triazoles (418) generated the derivatives (419) (Equation (63)) <91TL323>. Cyclization of 4-chloro-2-diethylamino-6-(*N*-ethylanilino)-5-pyrimidinecarbaldehyde with sulfuric acid, PPA or DMF-POCl₃ gave compound (420) <84GEP3233604, 85JHC841, 85JHC873>. Reaction of the amines (421) with activated trifluoroacetic anhydride gave (422) which cyclized to the derivatives (423) (Equation (64)) <84AP(317)42>.

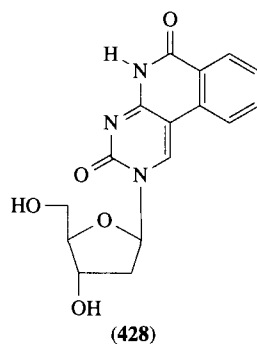




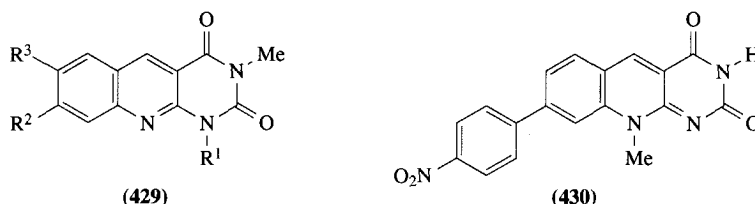
Cyclization of the nitro derivatives (424) with trimethyl phosphite gave the compounds (425) (Equation (65)) <86AP(319)379>. 5-Deazaflavins were synthesized by oxidative cyclization of the amines (426) with DEAD to give compounds (427) <85JHC159, 85JHC841, 85JHC873, 93JCS(P1)547>.



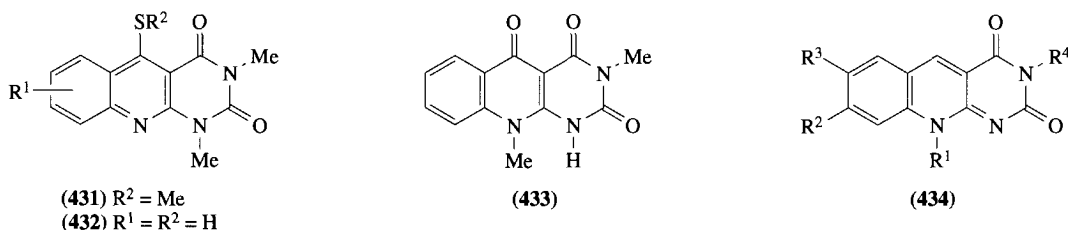
Cyclization of 3',5'-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-yl)-N⁴-benzoyldeoxycytidine in methanol containing iodine and under mercury lamp irradiation gave compound (428) after desilylation <87JAP(K)6259293, 87MIP8701373>.



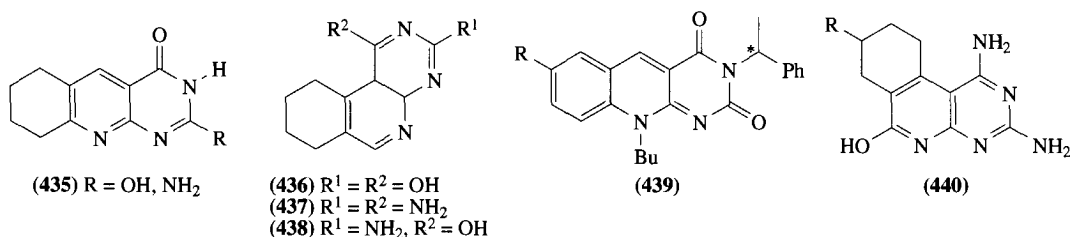
(b) *Formation from [5 + 1] atom fragments.* Treatment of the donor-substituted 6-anilinouracils (**421**; $R^3 = H$) with Vilsmeier's reagent results in three reactions, depending on substitution: (1) donors in the *meta* position cause regiospecific cyclizations yielding compounds (**429**); (2) donors in the *para* position yield 5-formylanilinouracils, which can be cyclized by PPA to compounds (**429**); (3) *meta* dimethylamino substituents result in additional formylation and *in situ* cyclization to derivatives (**7**) which compete with the formation of compounds (**429**). These reactions are explained by postulating a vinylogous amidine as intermediate <82AP(315)949>. During the formation of compound (**430**) a demethylation was noticed <85JHC841, 85JHC873>.



The source for one carbon atom in the [5 + 1] cyclization can be CS_2 , as in the reaction of the derivatives (**421**; $R^3 = H$) to give derivatives (**431**) and (**432**) after methylation <91JHC1245>. Reaction of 3-methyl-6-*N*-(methylanilino)uracil with carbonyldiimidazole gave compound (**433**) as the major product in addition to a 5-imidazolyl derivative (**434**) <83AP(316)476>.

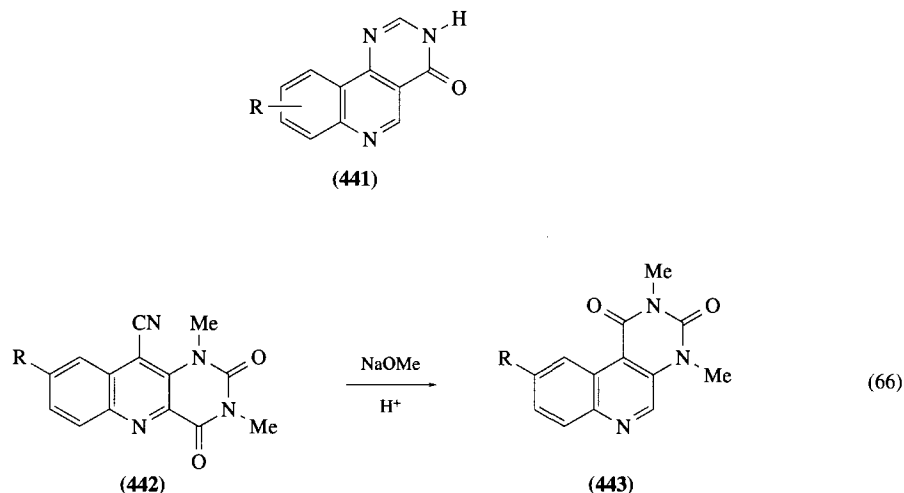


(c) *Formation from [3 + 3] atom fragments.* Cyclocondensation of either *o*-halogeno-benzaldehydes with substituted aminouracils or 6-chloro-5-formylpyrimidine with aniline derivatives gives derivatives (**434**) <82CC1085, 82JHC929, 84JCS(P1)561, 89JA4928, 89JA4935, 90JCS(P1)253, 91JAP(K)0381276, 91JHC1537>. Alternatively, condensation of 6-chlorouracils with *o*-substituted aminobenzyl alcohols gives (**434**) <89CC44>. The separation of the enantiomers from the racemic 5-deazaflavin products depends on the bulkiness of the substituent on the phenyl group at N-3 <92TL3169>. Synthesis of (5-carba)isoalloxazines with restricted rotation about the C(1')—N(10) single bond has been achieved <88JCS(P1)313>. Similarly, compounds (**435**) were obtained by the condensation of 6-aminopyrimidinone derivatives with 2-chloro-1-cyclohexenecarboxaldehyde <85JHC1149>; the use of 2,4,6-triaminopyrimidine afforded (**437**) regiospecifically <86JHC523>. 2,6-Diamino-4-oxopyrimidine with 1-cyclohexenecarbaldehyde afforded a mixture of derivatives (**435**) and (**438**) <86JHC523>, whereas 6-amino-2,4-dioxypyrimidine or 2,4,6-triaminopyrimidine regiospecifically afforded compounds (**436**) and (**438**), respectively. The same strategy has been used for the synthesis of the optically active derivatives (**439**) <87CPB1397>. Condensation of 2,4,6-triaminopyrimidine with 4-aryl-2-carbomethoxycyclohexanone in Ph_2O gave the derivatives (**440**) <91USP5077404, 92JMC320>. Reaction of 6-ribityl or 6-*n*-octylaminouracil with salicylaldehyde derivatives gave the derivatives (**434**) <91JHC439>.

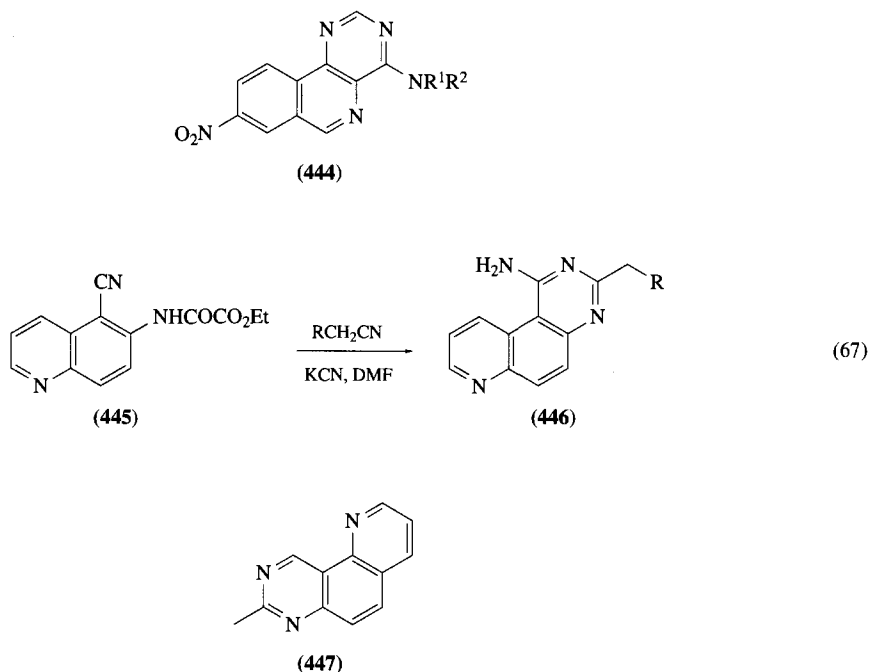


(iii) From acyclic precursors and by transformation of other heterocycles

Cyclocondensation of α -cyano- β -phenylamino-*N*-[(dimethylamino)methylene]acrylamide in the presence of $\text{Me}_2\text{NH}_2^+\text{OAc}^-/\text{AcOH}$ gave derivatives (**441**) <84KGS538, 88KGS88>. Cyanopyrimido[5,4-*b*]quinolines (**442**) rearrange to the pyrimido[4,5-*c*]quinolines (**443**) (Equation (66)) <86AP(319)382>.



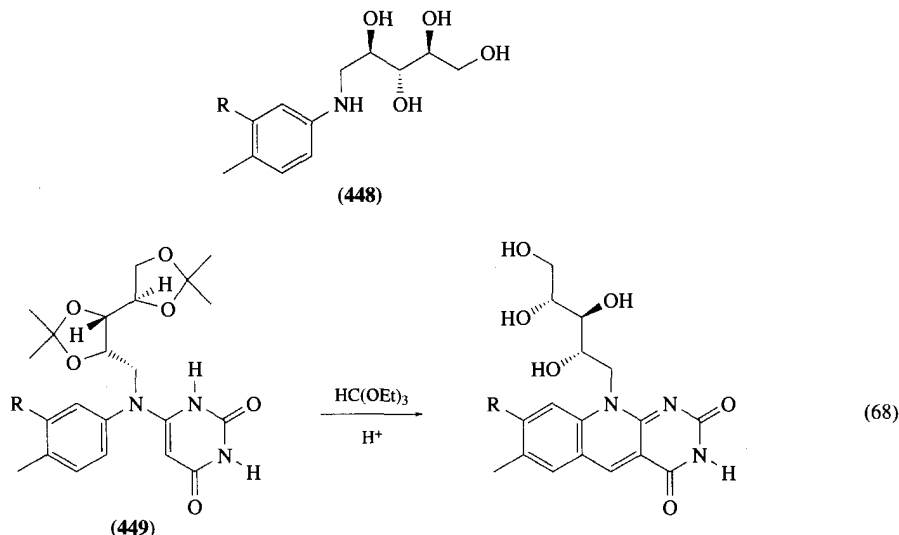
Rearrangement of 4-amino-8-nitropyrimido[4,5-*b*][1,5]benzothiazepine using H_2O_2 in AcOH gave compounds (**444**) <83URP725427> and cyclocondensation of compound (**445**) using RCH_2CN in the presence of KCN–DMF afforded the derivatives (**446**) (Equation (67)) <81H(16)2115>. Reaction of 8-bromopyrido[2,3-*f*]quinoline with KNH_2 in liquid ammonia gave compound (**447**) and a trace of the respective 4-amino derivative together with some 8-aminopyridoquinoline <83JHC447>.



(iv) Synthesis of particular classes of compound

5-Deazariboflavin (**434**) has been prepared by condensation of 6-chloro-5-formyluracil with *N*-D-ribityl-3,4-xylydine <84JAP(K)5905186>, or by acetylation of 6-[*N*-D-ribityl-3,4-xylydino]uracil followed by cyclization (POCl_3 –DMF) and deacetylation <86RTC538>. Alternatively, the ribitol deriva-

tive (**448**) was transketalized with 2,2-dimethoxypropane and treated with 2,4,6-trichloropyrimidine to afford a mixture of phenylpyrimidylamines. The required component was transformed to the benzyloxy derivative and hydrogenation gave intermediate (**449**) which was cyclized ($\text{HC}(\text{OEt})_3$) and deprotected to afford 5-deazariboflavin (Equation (68)) $\langle 90\text{AP}(323)873 \rangle$.

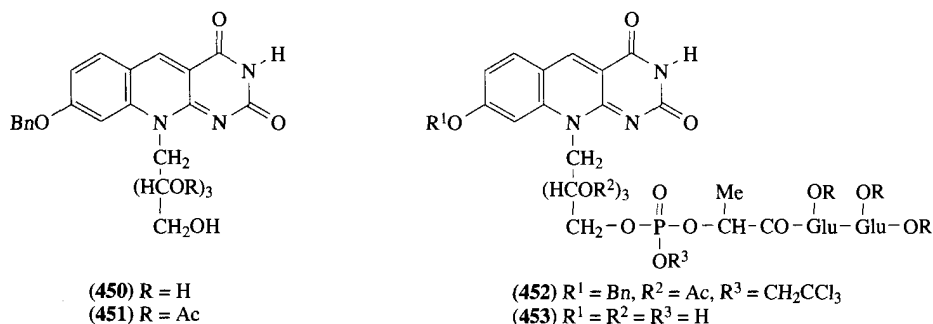


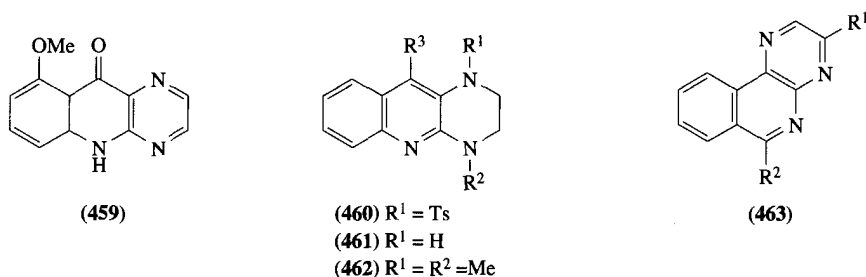
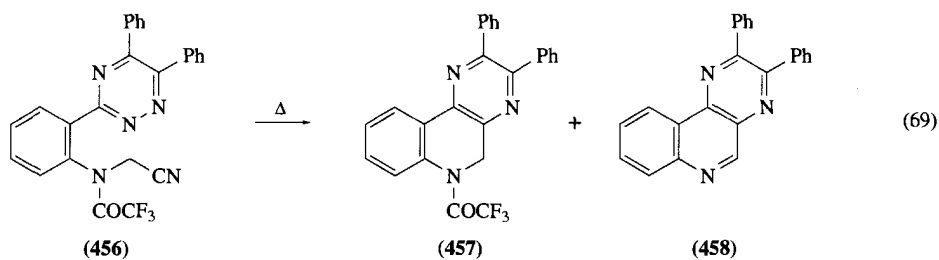
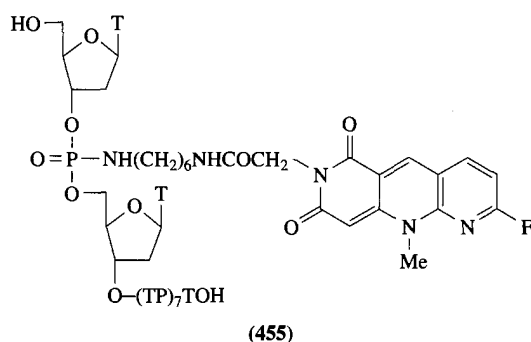
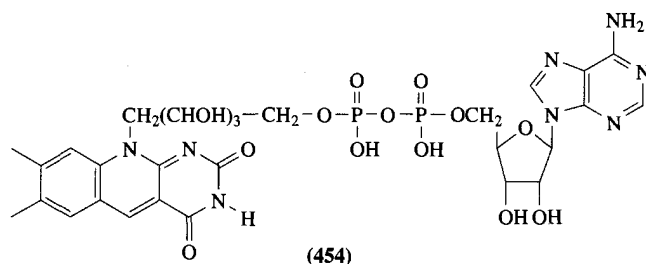
The first total synthesis of redox coenzyme factor 420 (F_{420}) (**453**) was achieved by the reaction of 4-benzoyloxy-2-chlorobenzaldehyde with 6-ribitylamino-uracil to give compound (**450**) $\langle 88\text{CC}524, 90\text{JCS}(P1)253, 91\text{JHC}439 \rangle$. The ribityl residue was partially acetylated via tritylation, acetylation and detritylation to give (**451**). The reaction between (**451**) and the peptide moiety, (L-lactoyl- γ -L-glutamyl)-L-glutamic acid tribenzyl ester, by the phosphite triester approach using β, β, β -trichloroethyl phosphorodichloridite gave (**452**), followed by deprotection to give F_{420} (**453**). The synthesis of 5-deazaflavin adenine dinucleotide (5-dFAD) (**454**) involves 5-deazariboflavin (**434**) as a key intermediate $\langle 86\text{RTC}538 \rangle$. Oligodeoxynucleotide (**455**) was also synthesized $\langle 93\text{CPB}778 \rangle$.

Biosynthesis of 7,8-didemethyl-8-hydroxy-5-deazaflavin starts from guanosine-5'-triphosphate (GTP), which leads through several steps to 5-amino(6-ribitylamino)-2,4(1*H*,3*H*)-pyrimidinedione 5'-phosphate, whose addition to 4-hydroxybenzoic acid which comes from shikimate gave the target compound $\langle 85\text{JA}8300 \rangle$. The biosynthesis of riboflavin and deazaflavins has been studied in *Methanobacterium thermoautotrophicum* $\langle 91\text{JBC}9622 \rangle$.

7.16.8.4.3 Synthesis of Pyrazino[*x,y-z*]quinolines and isoquinolines

The first reported synthesis of the pyrazino[2,3-*c*]quinoline system was by an intramolecular Diels–Alder cycloaddition of (**456**) to give (**457**) and (**458**) (Equation (69)) $\langle 89\text{JOC}1245 \rangle$. 1,4-Dipolar cycloaddition of methyl 3-(aminotrimethylsilyl)pyrazine-2-carboxylate with aryne afforded compound (**459**) $\langle 91\text{H}(32)1773 \rangle$. Cyclization of 2-amino-3-(2-bromoethyltosylamino)quinoline using K_2CO_3 -BuOH gave (**460**; $\text{R}^2 = \text{R}^3 = \text{H}$), whose tosyl group was removed to give compound (**461**; $\text{R}^2 = \text{R}^3 = \text{H}$) $\langle 92\text{H}(34)1055 \rangle$. Reaction of 3-bromo-4-nitroquinoline-1-oxide with *N,N'*-dimethylethylenediamine gave compound (**462**; $\text{R}^3 = \text{NO}_2$) $\langle 87\text{JOC}2285 \rangle$. Condensation of 1-methyl-isoquinoline 3,4-diamine with glyoxal and methylglyoxal gave derivative (**463**) $\langle 92\text{AJC}2083 \rangle$, and with ethyl pyruvate afforded the respective pyrazinoisoquinolinone $\langle 90\text{AJC}179 \rangle$.

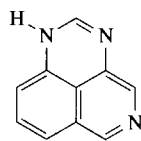




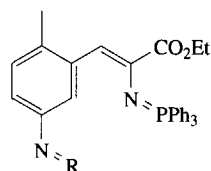
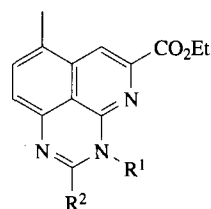
7.16.8.5 Synthesis of Other Benzopyrido[x,y-z][1,n]diazines

7.16.8.5.1 Pyrido[x,y-z]quinazolines

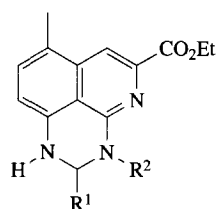
Cyclization of 4,5-diamino-isoquinoline in formic acid afforded compound (464); carbon disulfide gave the corresponding thione derivative (87H(26)1029). Aza-Wittig reaction of the ylide (465) with isocyanates led to the derivative (467) (Equation (70)) and reaction with diphenylketone gave compound (466) which with isocyanate gave the derivative (468) (91TL5379, 92JOC6703). On the other hand, compound (465) reacted with aromatic aldehydes followed by treatment with isocyanate to give the derivatives (470) as major products together with (469). The reaction of 1-amino-isoquinoline-8-iminophosphorane with CS_2 gave the respective pyrido[2,3-*de*]quinazoline (92JOC6703).



(464)

(465) R = PPh₃(466) R = C=CPh₂

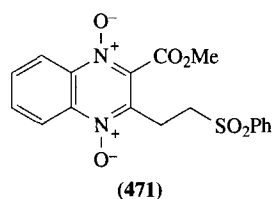
(70)

(467) R² = NHR¹(468) R² = CHPh₂(469) R² = R¹

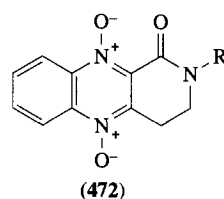
(470)

7.16.8.5.2 Pyrido[x,y-z]quinoxalines

Reaction of 2,3-diaminopyridine with 4,5-dimethylcyclohexa-3,5-dien-1,2-dione dimer gave a pyrido[2,3-*b*]quinoxaline <88CJC1500>. Reaction of tetrachloro-4-cyanopyridine with *o*-phenylenediamine gave the corresponding dihydropyridoquinoxaline <82JCS(P1)2897>. Reaction of compound (471) with alkylamines gave the tricyclic derivatives (472) (Equation (71)) <82JMC868>. Amination of quinoxaline-2-acrylonitrile-1,4-dioxide gave the dioxides (473) <82JMC868>. Reaction of 3-aminoquinoxaline-2-carbaldehyde with aliphatic ketones or esters yielded pyrido[2,3-*b*]quinoxaline and its 2-one analogue, respectively <82ZC256>. Cyclocondensation of methacroleine *N,N*-dimethylhydrazone with 2,3-dimethylquinoxaline-5,8-dione gave compound (474) after spontaneous oxidation <87JOC2285>. A polymer containing this ring system was also prepared <87MI 716-01>. Condensation of *o*-quinone with ethylenediamine gave products of the type (475) <86KGS959>. Condensation of iminoisoquinoline-1,4-dione with *o*-phenylenediamine gave (476) <86LA938>.



(471)

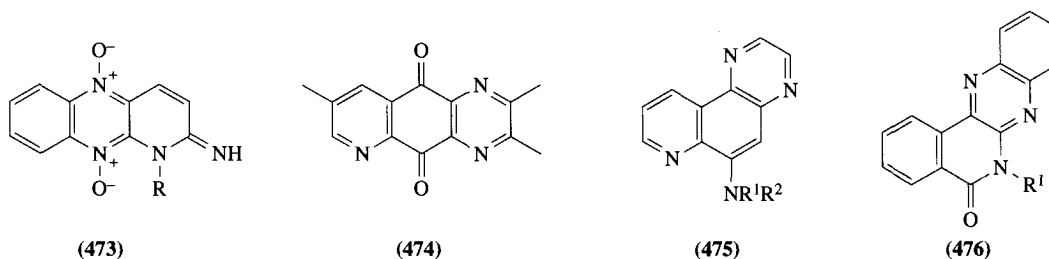


(472)

(71)

7.16.8.6 Synthesis of Pyrido[x,y-z][1,n]oxazines and Thiazines

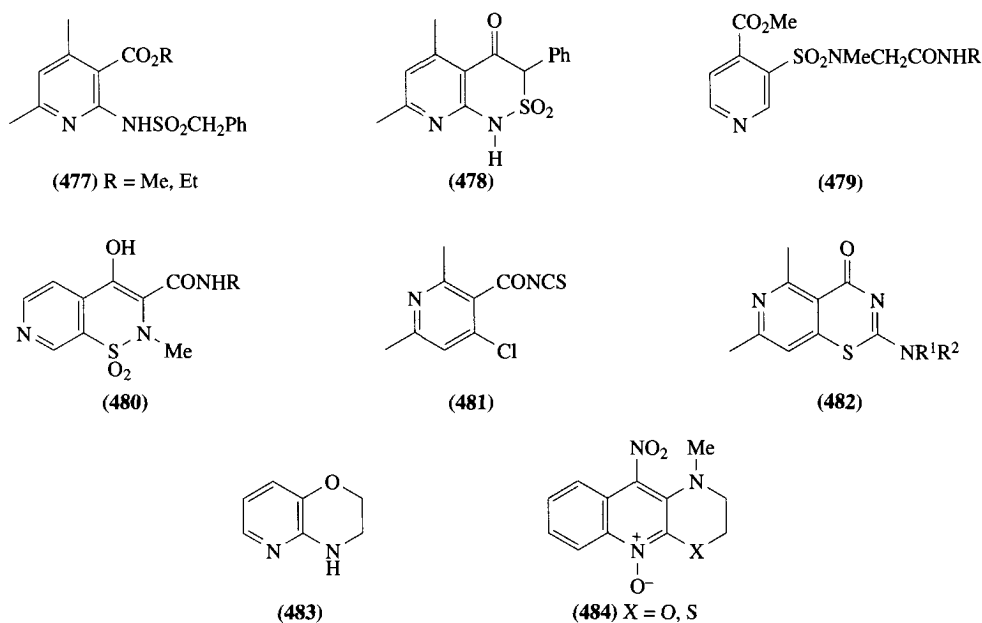
Most of the methods described during the period covered by this chapter use pyridine intermediates and the skeletons of the oxazine and thiazine rings are built onto the pyridine ring.



7.16.8.6.1 From pyridine intermediates

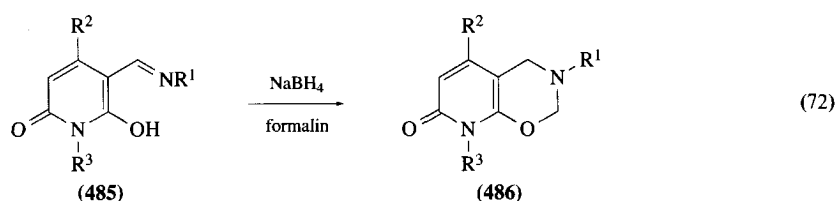
(i) Formation of the second ring from [6 + 0] atom fragments

Cyclocondensation of the esters (477) with base gives compound (478) <81MIP109777> and the derivatives (479) similarly give (480) <84JAP(K)5936685, 86YZ1008>. Cyclization of the thioisocyanate (481) with amines gives the amino derivatives (482) <83CCC3426>. Etherification of 2-amino-3-hydroxypyridine with 2-chloroethanol followed by cyclization gave compound (483) <83ACH487>. The same strategy has been used for the synthesis of the tricyclic derivatives (484) <90JAP(K)0296580, 93H(36)1005>.



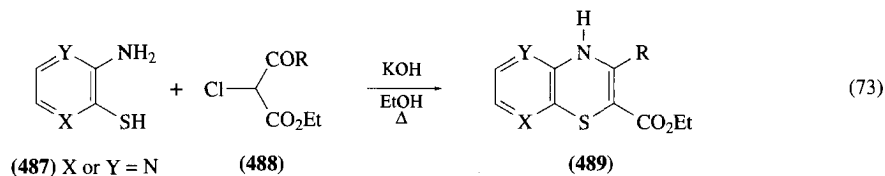
(ii) Formation of the second ring from [5 + 1] atom fragments

2*H*-Pyrido[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione can be prepared by the cyclization of methyl 2-anilinonicotinate with trichloromethyl chloroformate or by treating the respective acid with phosgene, <91JHC2029>. 4*H*-1,2-Dihydropyrido[2,3-*d*][1,3]oxazine-4-ones have been prepared by treatment of 2-arylamino nicotinic acid with paraformaldehyde, orthoformate, 1,1-dialkyl or 1,1,1-trialkylalkoxyalkanes in the presence of ZnCl₂ <91AP(324)821>. Reduction (NaBH₄) of the Schiff bases (485) followed by condensation with formalin affords the derivatives (486) (Equation (72)) <92IJC(B)729>.

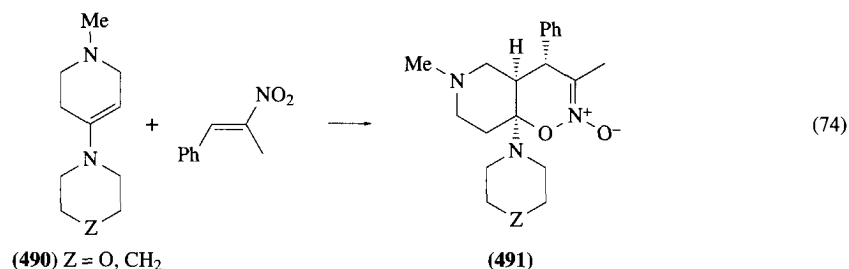


(iii) Formation of the second ring from [4 + 2] atom fragments

Thioloaminopyridines (**487**) were heated with the α -chloroesters (**488**) to give the pyridothiazines (**489**) (Equation (73)) <87GEP3540702, 87GEP3545097>. A similar condensation using α -haloketones has been used to prepare pyrido[4,3-*b*][1,4-]oxa(thia)zines <83JMC1614, 84EUP107130>. Cyclocondensation of 3-aminoquinoline-4-thiol with α -haloacids similarly gave the respective thiazinoquinolines <92S656>.

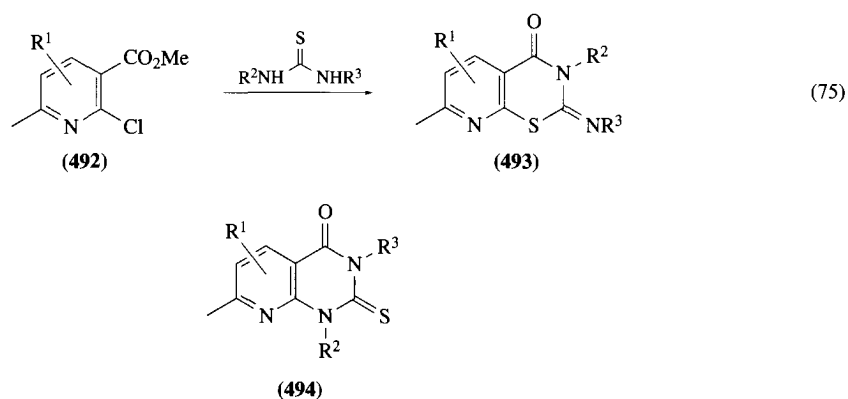


Reaction of (*E*)-1-phenyl-2-nitropropene and the enamines (**490**) gave the derivatives (**491**) (Equation (74)), which are stable in the solid state but in solution are in equilibrium with open-chain isomers <86CCA165>. Treatment of the 2-chloronicotinamide with thioesters and NaH afforded 2-aryl or alkyl pyrido[3,2-*e*][1,3]thiazine-4(*H*)-ones <89T4153>.



(iv) Formation of the second ring from [3 + 3] atom fragments

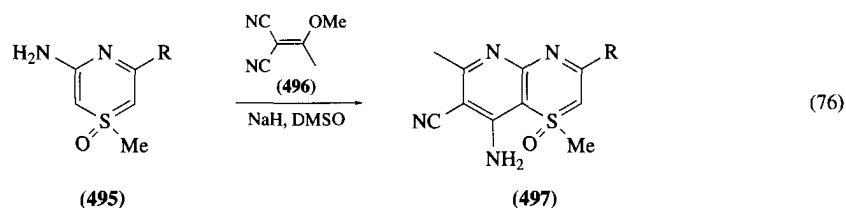
Condensation of the esters (**492**) with thiourea or its *N*-substituted derivatives (Equation (75)) gave either the pyridothiazines (**493**) or the isomers (**494**) depending on the thiourea substituents <82FES266, 83MIP122833, 86FES899>.



7.16.8.6.2 From thiazine intermediates

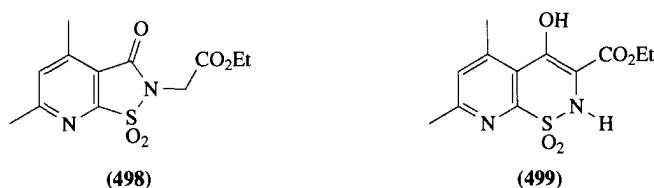
(i) Formation of the second ring from [3 + 3] atom fragments

Condensation of the amines (**495**) with 1,3-bis-electrophiles, such as the reagent (**496**), followed by cyclization with NaH-DMSO gives the compounds (**497**) (Equation (76)) <87LA551>.



7.16.8.6.3 By transformation of other heterocycles

The pyrido[3,2-*e*][1,2]thiazine (499) has been prepared by rearrangement of the ester (498) using NaOEt–DMF <86FES819, 86FES892>.

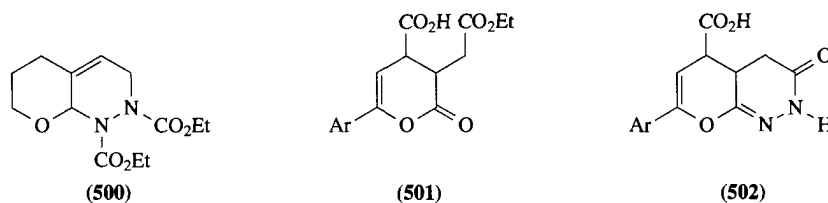


7.16.8.7 Synthesis of Pyrano and Thiopyrano[*x,y-z*][1,*n*]diazines

7.16.8.7.1 Synthesis of pyrano and thiopyrano[*x,y-z*]pyridazines

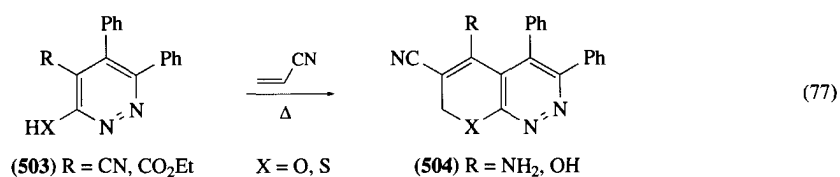
(i) From pyran intermediates

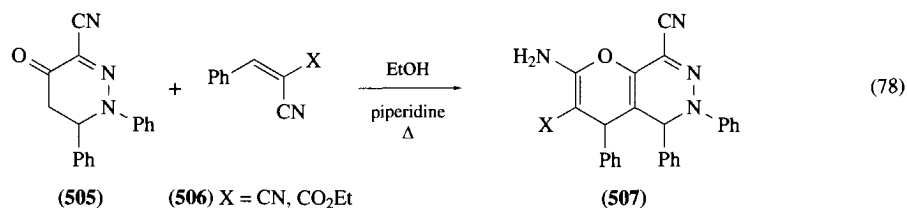
The use of pyran intermediates for the synthesis of these ring systems has presented few examples. The [4 + 2] cycloaddition of 5-ethenyl-3,4-dihydro-2*H*-pyrans with DEAD yields compounds (500) <86CB3204>. Reaction of the esters (501) with hydrazine hydrate gave the pyranodiazines (502) <86MI 716-01>.



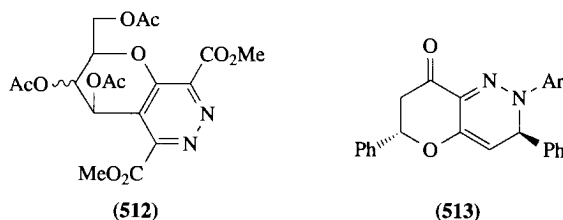
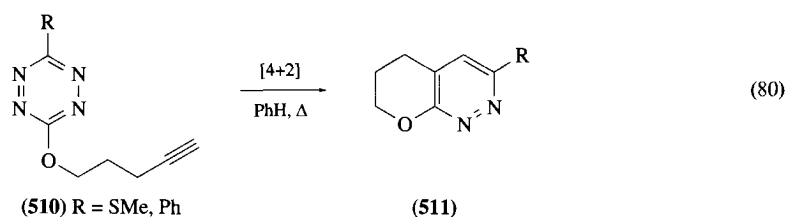
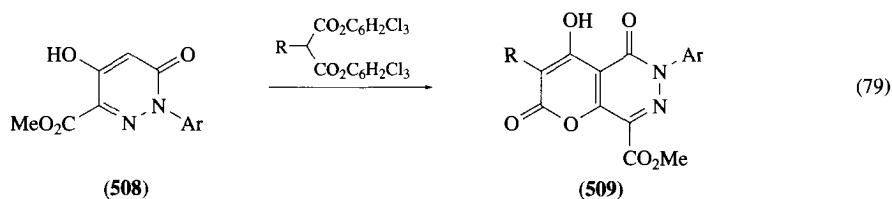
(ii) From pyridazine intermediates

Pyridazine intermediates (e.g., (503)) have been used more frequently for the synthesis of pyranodiazines (e.g., (504)) (Equation (77)) <89JPR757>. Reacting the nitrile (505) with the reagents (506) gave the derivatives (507) (Equation (78)) <86JHC93>.





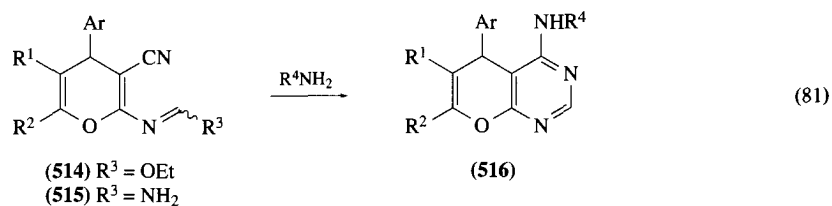
Condensation of the esters (508) with active malonates produced the derivatives (509) (Equation (79)) <89JHC169>. Intramolecular Diels–Alder cycloaddition of tetrazines carrying an alkyne side chain, such as in compounds (510), gives the products (511) <85TL4355, 87CZ16>. Diels–Alder reaction of dimethyl tetrazine-3,6-dicarboxylate with 3,4,6-triacetoxyanhydrohexenitroles gave compound (512) <85LA628>. Reaction of arylazoacetylacetones with benzaldehyde gave the diphenyl-trioxoheptadiene arylhydrazones, whose cyclization with AcOH gave the *N*-aryl derivatives (513) <89IJC(B)167>.

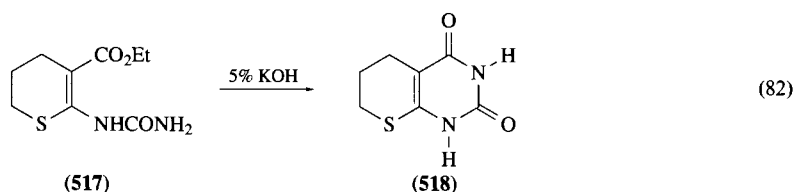


7.16.8.7.2 Synthesis of pyrano and thiopyrano[*x,y-z*]pyrimidines

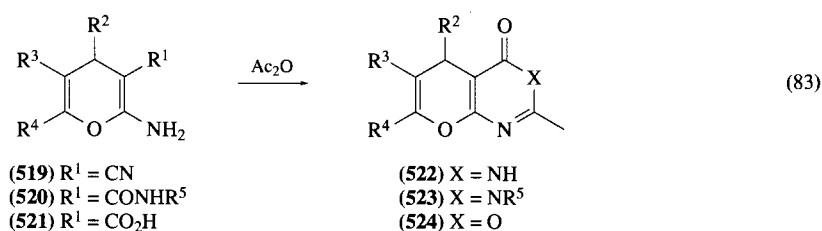
(i) From pyran and thiopyran intermediates

(a) *Formation from [6 + 0] atom fragments.* Cyclization of the imines (514) with amines gives the pyranopyrimidines (516) (Equation (81)) <84CCC2309, 89M1101>. Alternatively, the amidines (515) cyclized to the derivatives (516; R⁴ = H) in boiling ethanol <89CCC1336>. Cyclization of the urea (517) with alkali gives compound (518) (Equation (82)) <85S190>.

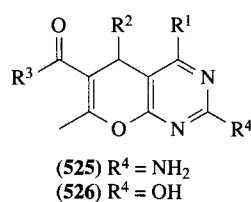




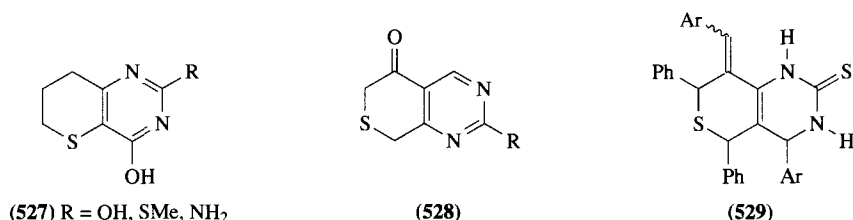
(b) *Formation from [5 + 1] atom fragments.* The derivatives (519) serve as good precursors of the derivatives (522) (Equation (83)) <82MI 716-03, 89LA585, 90CCC718>. The cyclization can be effected with formic acid <89MI 716-03> or other one-carbon-inserting reagents <86ZN(B)925>. Similar cyclizations are (520) → (523) and (521) → (524); the transformation (524) → (523) is achieved by reaction with amines <90IJC(B)1020>.



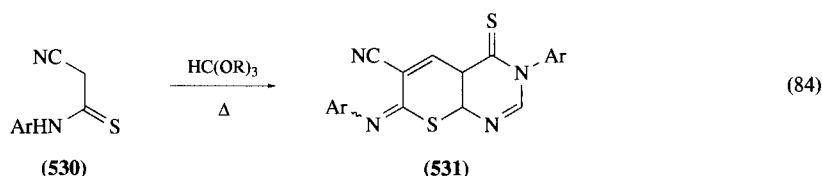
(c) *Formation from [4 + 2] atom fragments.* The cyclization of 2-amino-3-cyano- or 2-amino-3-carbomethoxypyran with trichloroacetonitriles, ethylcyanoacetate, malononitrile, or benzoylthiocyanate gives the derivatives (525) and (526), respectively <87JHC1677, 88AP(321)131, 91IJC(B)25, 92MI 716-02>.



(d) *Formation from [3 + 3] atom fragments.* Cyclization of ethyl 3-oxotetrahydrothiopyran-2-carboxylate with urea, *S*-methylisothiourea, or guanidine yielded the derivatives (527) <83BEP895995, 86CPB4150>. 4-Dimethylaminomethylene-2*H*-thiopyran-3,5-dione afforded the thiopyranopyrimidines (528) with amidines or guanidines <84JHC1437> and 2,6-diphenyl-3,5-diarylidene-thiopyran-4-ones gave compounds (529) with thiourea <85MI 716-02>.

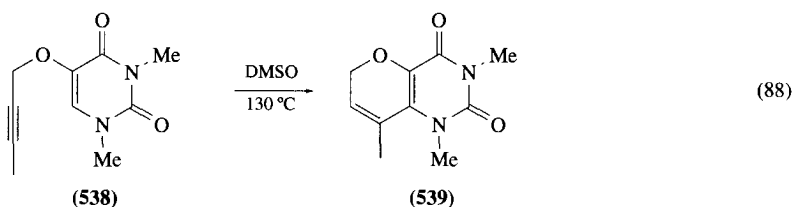
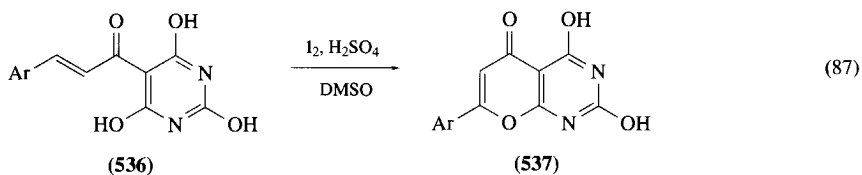
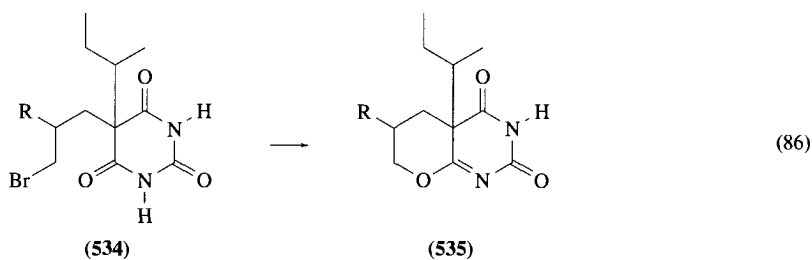
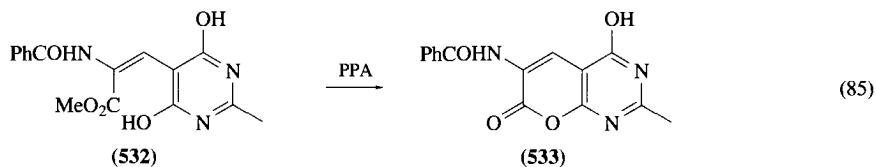


(e) *From acyclic precursors.* Heating the thioamides (530) with orthoformates gives the diaryl derivatives (531) (Equation (84)) <85URP1110146, 87IZV2033>.

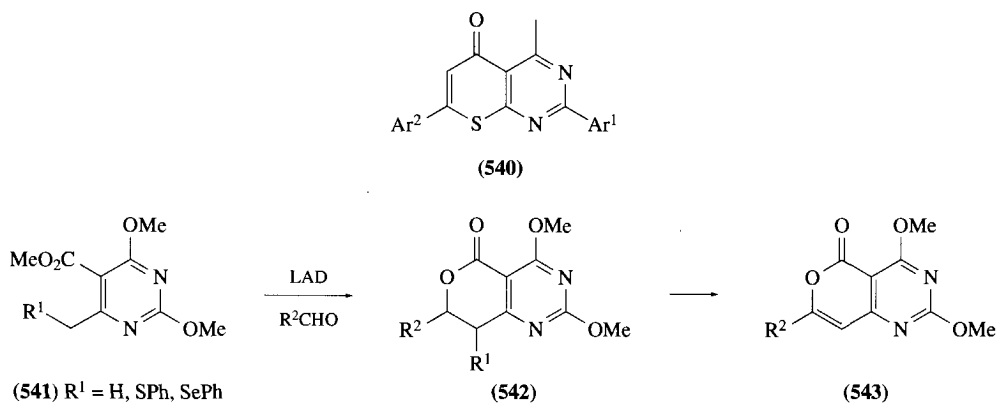


(ii) From pyrimidine intermediates

(a) *Formation from [6 + 0] atom fragments.* Cyclization of the pyrimidine (532) using PPA gave compound (533) (Equation (85)) <90JHC1021>. Dehydrobromination of the bromides (534) gives derivatives (535) (Equation (86)) <92AP(325)291> and reaction of the chalcones (536) with $I_2-H_2SO_4$ in DMSO gave the compounds (537) (Equation (87)) <88MI 716-03>. Pyrolysis of the alkyne (538) afforded compound (539) (Equation (88)) <89JHC1851>.

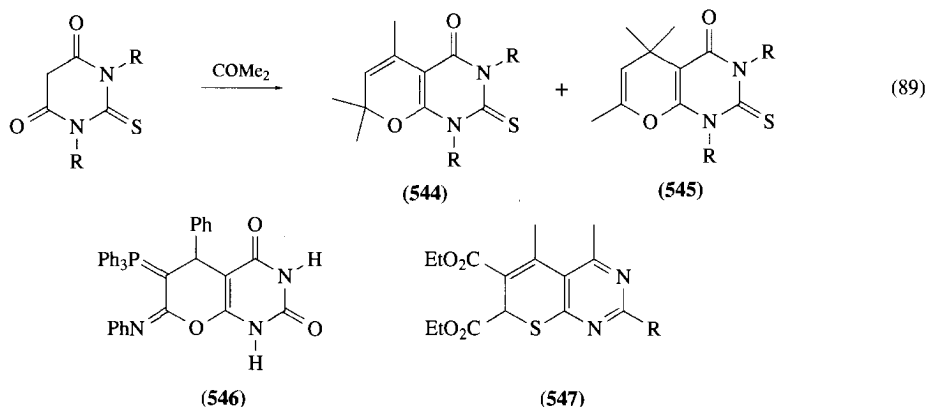


(b) *Formation from [5 + 1] atom fragments.* Condensation of 5-acetyl-4-thiopyrimidines with aromatic aldehydes provided the derivatives (540) <90MI 716-04>. Lithiation of the pyrimidines (541) with LDA, followed by reaction with aldehydes, gave compounds (542) (Scheme 12) <89S316>. Bromination and dehydrobromination of compound (542; $R^1 = H$) gave (543) (Scheme 12) <90JHC1899>.

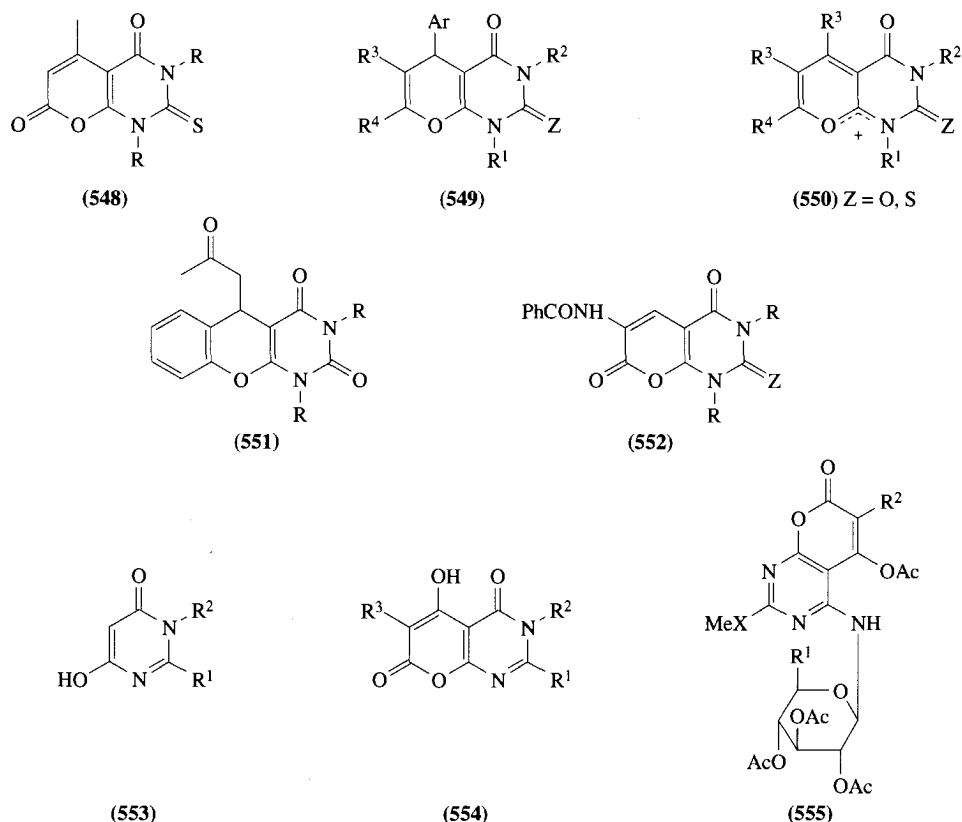


Scheme 12

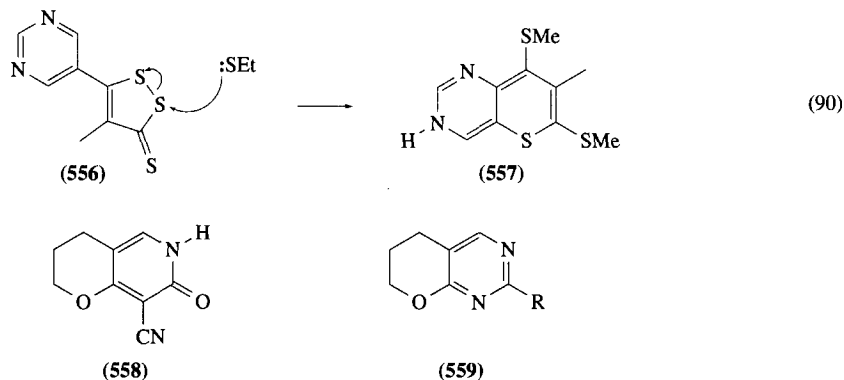
(c) *Formation from [4 + 2] atom fragments.* The isomeric pyrano[2,3-*d*]pyrimidines (**544**) and (**545**) were obtained by reaction of 1,3-diaryl thiobarbituric acids with acetone (Equation (89)) <86T4045, 90T3953>. Similarly, the cyclocondensation of uracil with acetone gave pyrano[2,3-*d*]pyrimidine <87SC1435>. Reaction of 5-benzylidenebarbituric acid with *N*-phenyliminoketenylidene-triphenylphosphorane gave compound (**546**) <87PS(29)165>. Cyclocondensation of 5-acetyl-6-thiopyrimidines with diethyl maleate and maleic anhydride gave compound (**547**) <90JIC436, 92MI 716-03>.



(d) *Formation from [3 + 3] atom fragments.* Pechmann condensation of 1,3-diarylthiobarbituric acids with ethyl acetoacetate (EAA) afforded (**548**) <90IJC(B)1141, 90T3953> and 2-thiobarbituric acids with alkenylketones in the presence of P_2O_5 gave (**549**) <90H(31)129, 90SC1265>. The use of $HClO_4$ or H_3PO_4 led to the salts (**550**) <88MI 716-04>. When the chalcone possesses a salicylidene residue, the benzopyranopyrimidines (**551**) are obtained <88MI 716-04, 92OPP675>. The cyclization of barbituric and 2-thiobarbituric acids was also effected by reaction with cinnamionitrile derivatives to give (**549**; $R^4 = NH_2$) <83KGS277, 84ZOR2448, 87IJC(B)216, 91IJC(B)363>, and with methyl 2-benzoylamino-3-dimethylaminopropenoate or hippuric acid and triethyl orthoformate to give (**552**) <89JHC1273, 91IJC(B)978, 92IJC(B)688>. Cyclocondensation of (**553**) with a variety of active methylene compounds gave (**554**) <84M1459> and (**555**) were similarly prepared <89M1119>.

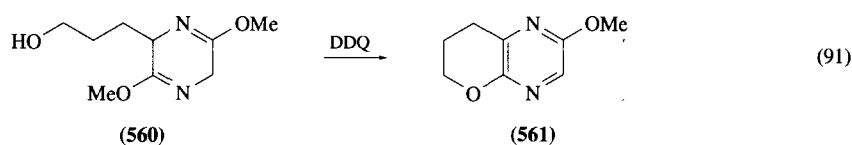


(e) *Other methods.* The strictosidine analogue (**98**) <88AG983> was prepared from a pyrido-indoleacetaldehyde tandem-Knoevenagel–Diels–Alder reaction using *N,N*-dimethylbarbituric acid and 1-benzyloxypropene. Reaction of compound (**556**) with sodium ethanethiolate gave the thio-pyranopyrimidine (**557**) (Equation (90)) <87T3421>. Condensation of valerolactone and the nitrile (**558**) followed by treatment with $\text{Et}_3\text{O}^+ \text{BF}_4^-$ gave a complex which with amidines gave the pyrano[2,3-*d*]pyrimidines (**559**) <83KGS1321>.



7.16.8.7.3 Synthesis of pyrano[*x,y-z*]pyrazines

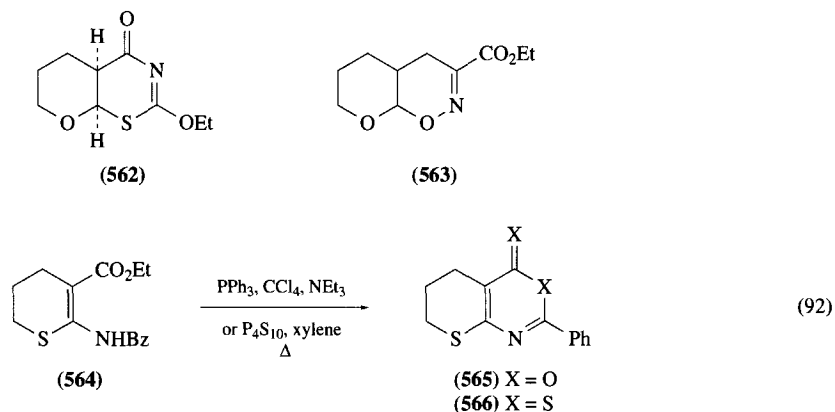
Only one example is relevant to this section. Oxidation of the alcohol (**560**) using DDQ gives the pyrano[2,3-*b*]pyrazine (**561**) (Equation (91)) <88JCS(P1)2585>.



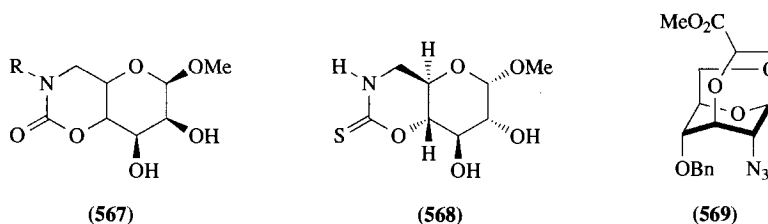
7.16.8.8 Synthesis of Pyrano[*x,y-z*][1,*n*]oxazines and Thiazines

7.16.8.8.1 From pyran intermediates

Cycloaddition of 3,4-dihydropyran to ethoxy(thiocarbonyl)isocyanate gave compound (**562**) <82CB1259> and ethyl α -nitrosoacrylate gave compound (**563**). Cyclization of the ester (**564**) using $\text{PPh}_3\text{--CCl}_4\text{--NEt}_3$ gave compound (**565**) <81CB3188> and use of P_4S_{10} gave the thio analogue (**566**) <82AG800>.

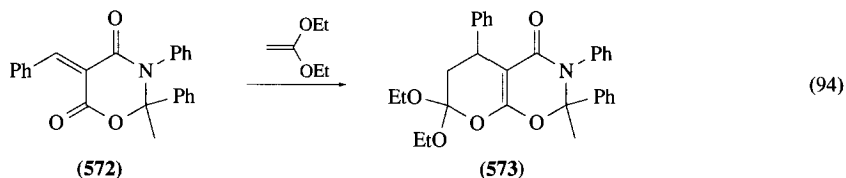
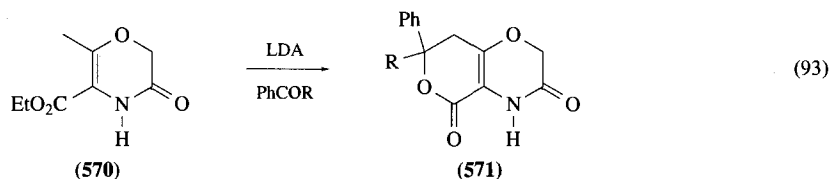


3-Substituted 1-(2-chloroethyl)-3-(methyl- α -D-glucopyranosid-6-yl)-1-nitrosoureas readily decompose on treatment with aqueous sodium bicarbonate to give the pyrano[2,3-*e*]oxazines (**567**) <83CPB3924>. Triethylamine-induced intramolecular cyclization of methyl 6-deoxy-6-isothiocyanato- α -D-glucopyranoside regioselectively yielded compound (**568**) <92TL3931, 93JOC5192>. Reduction of the azide (**569**) ($\text{NiCl}_2\text{-H}_3\text{BO}_3\text{-NaBH}_4$) gives the corresponding 2-amino-2-deoxy sugar, which spontaneously undergoes intramolecular cyclization to give compound (**2**). Catalytic hydrogenation of this product (**2**) followed by hydrolysis (10% TFA- Ac_2O) gave a mixture ($\sim 3:1$ α,β) of (**3**) <93CAR(241)131>. Cycloaddition of trichloroacetyl isocyanates to 1,5-anhydro-2-deoxyarabino-hex-1-enitols and dihydropyrans gave products having the pyranooxazine ring system as a result of [4 + 2] cycloaddition, along with products resulting from [2 + 2] cycloaddition <87T4555>.



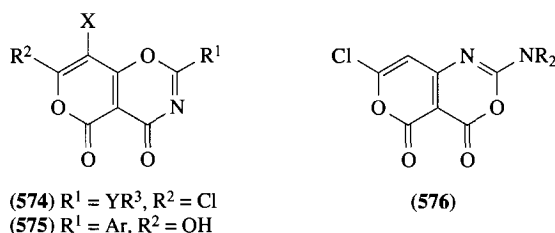
7.16.8.8.2 From oxazine intermediates

Lithiation of compound (**570**) (LAD) followed by reaction with carbonyl compounds yields the derivatives (**571**) (Equation (93)) <89AP(322)291>. Diels-Alder reaction of compound (**572**) with ketene diethylacetal gave compound (**573**) (Equation (94)) <92CL485>.



7.16.8.8.3 From acyclic precursors

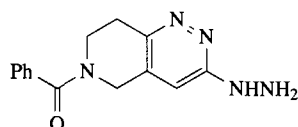
Reaction of malonyl(bromomalonyl) chloride with thiocyanates and selenocyanates gave the derivatives (**574**) <82JCS(P1)1575, 82JCS(P1)2499, 83CB3725, 85CB1371, 91MI 716-06>. The reaction product of malonyl chloride and an aromatic cyanate is strongly dependent on the reaction conditions <85CB1371>. Condensation of malonyl chloride with nitriles without an α -methylene group gave pyrano[3,4-*e*][1,3]oxazines <81MI 716-01, 83PJS7> and with cyanimides gave derivatives (**576**) <85CB4707>. The reaction of arylamides with malononitrile in dichloroethane yielded (**575**) and the malonic acid diamide <87KGS382>.



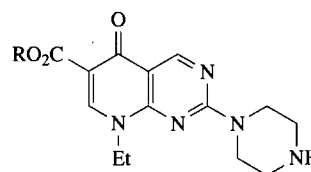
7.16.9 IMPORTANT COMPOUNDS AND APPLICATIONS

A wide range of biological properties have been claimed in the patent literature for molecules falling within the scope of this chapter. However, little has emerged in the form of commercial products. The greatest number of claims has been made for derivatives of the pyrido[2,3-*d*]pyrimidine ring system.

Endralazine (**118**), which is similar in structure to hydralazine, is an antihypertensive agent which has a direct effect on vascular smooth muscle. It is believed to produce selective arteriodilation by preventing the release of bound calcium ions from intracellular storage sites <82MI 716-04, 82SZP628052>. Pipemidic acid (**166**; R = H) has a close structural relationship to nalidixic acid and, like nalidixic acid, has useful antibacterial properties <91JAP(K)03106880>, especially for urinary tract infections <86JAP(K)61249983>. Piromidic acid is the pyrrolidine analogue.



(118) Endralazine



(166) Pipemidic acid (R = H)

5-Deazaaminopterin derivatives (folate analogues) are potent antineoplastics <88USP4725687, 91USP5077404> particularly in treating tumors resistant to methotrexate or aminopterin <90MIP9000172>. Some derivatives are equipotent with methotrexate, both as inhibitors of bovine liver dihydrofolate reductase and of L1210 murine leukemia cells.

Pyrido[3,4-*b*]pyrazines containing the bisazo or tetrakisazo chromophores are useful as high-sensitivity electrophotographic photoconductors <89JAP(K)0128648>.

ACKNOWLEDGMENTS

The authors thank Professor R. R. Schmidt, University of Konstanz, and Professor D. C. Baker, University of Tennessee, for making available library facilities. Thanks also go to the Alexander von Humboldt and Fulbright Foundations for supporting Professor E. S. H. El Ashry.

7.17

Bicyclic 6-6 Systems: Four Heteroatoms 1 : 3

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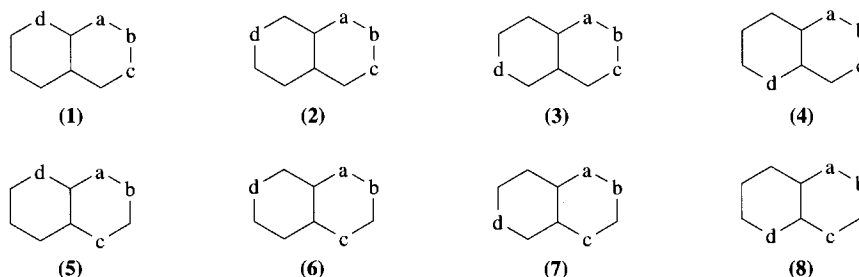
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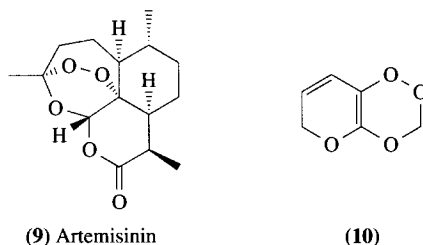
7.17.1 INTRODUCTION

No single chapter in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) was devoted to 6,6-fused heterocycles containing four heteroatoms arranged 1 : 3 with no heteroatoms occupying the bridgehead position. Indeed, the ring index of that edition only contained one example and subsequent reviews have referred to just one other <93PHC256>. This chapter describes such 6,6-

fused heterocyclic systems; that is, general structures (1)–(8). Both aromatic and nonaromatic structures will be examined with the emphasis being on those systems which contain N, O, and S as heteroatoms. Many examples exist in which the heterocyclic system contains B, P, and Se, some serving as part of protected or derivatised glycosides; these compounds are not surveyed here. This chapter concentrates on work published since the appearance of CHEC-I but earlier work is also included.



A compound which falls within the remit of this chapter is the natural product artemisinin (9), the traditional Chinese medicine known as qinghaosu. Artemisinin, which was first isolated in 1972, and its analogues are of particular interest due to their potent antimalarial properties. Indeed, at the time of writing, the author found over four hundred references to the isolation, synthesis, structure and function of artemisinin and analogues, not including the numerous patents taken out on these compounds. This chapter will not attempt to provide a current account of artemisinin research; several papers and reviews provide a chronological progress report on research in the area <92CSR85, 93MI 717-01, 93MI 717-02, 93MI 717-03, 93MI 717-04, 93MI 717-05, 93MI 717-06, 94MI 717-01, 94MI 717-02, 94MI 717-03, 94MI 717-04>. However, chemistry pertaining to the synthesis and properties of the 3*H*,6*H*-pyrano[2,3-*e*]-1,2,4-trioxine ring system (10), the nucleus of the artemisinin molecule, will be reported.



7.17.2 THEORETICAL METHODS

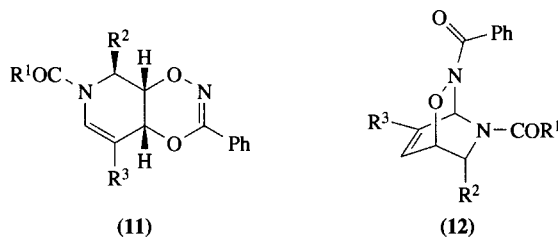
HMO calculations for a variety of pyrido-1,2,4-triazines and pyridopyrazines indicate that the most basic nitrogen atom is in the pyridine ring <66JSP(19)25>. Subsequent calculations on pyrido-1,2,4-triazines using the CNDO method have suggested otherwise. The most basic nitrogen atom in pyrido[2,3-*e*]-1,2,4-triazines and pyrido[3,2-*e*]-1,2,4-triazines is indeed situated in the pyridine ring. However, for pyrido[3,4-*e*]-1,2,4-triazines and pyrido[4,3-*e*]-1,2,4-triazines the largest negative charge resides on N-4 of the triazine moiety <78ACH61>.

7.17.3 EXPERIMENTAL STRUCTURAL AND SPECTROSCOPIC METHODS

7.17.3.1 X-ray Diffraction

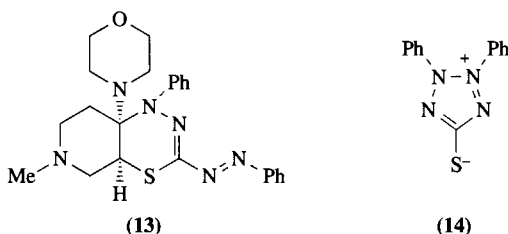
The cycloaddition of methyl 1,2-dihydro-1-pyridine carboxylate and *N*-benzoyl hydroxylamine in the presence of an oxidant ($\text{Et}_4\text{N}^+\text{IO}_4^-$) can lead to two possible regioisomeric cycloadducts. On standing, the cycloadduct rearranges to yield a new compound, shown by x-ray crystallography to be the pyrido[4,3-*e*]-1,4,2-dioxazine (11a). This compound can only have arisen from the rearrange-

ment of a cycloadduct with the structure (12a), thus elucidating the course of this cycloaddition reaction <85AX(C)456, 85JOC2080>.

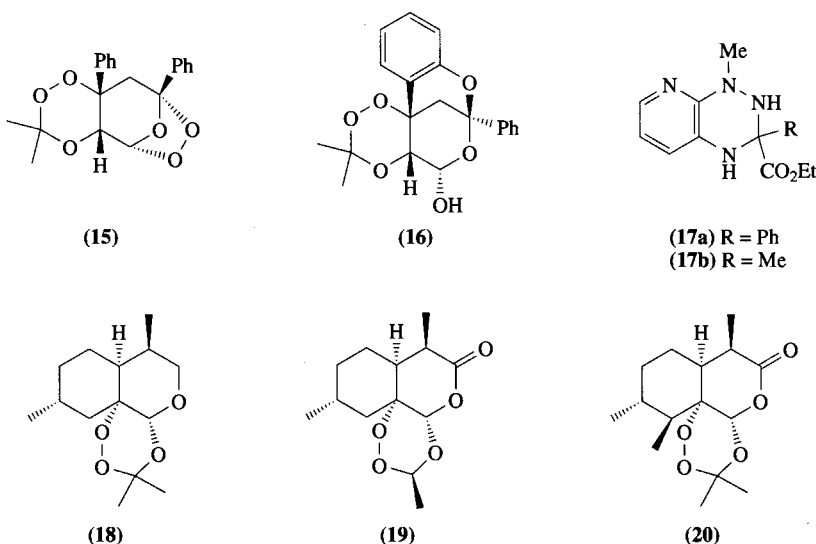


- (a) $R^1 = \text{OMe}, R^2 = R^3 = \text{H}$
 (b) $R^1 = \text{Me}, R^2 = \text{Bu}^n, R^3 = \text{H}$
 (c) $R^1 = \text{Me}, R^2 = \text{Ph}, R^3 = \text{H}$
 (d) $R^1 = \text{OMe}, R^2 = \text{Bu}^n, R^3 = \text{CO}_2\text{Me}$

The structure of the pyrido[1,3,4]thiadiazine (13) was solved using x-ray crystallography during a reinvestigation of the reactions of dehydridithione (14). A detailed treatment of the data is presented <76JCS(P1)1673>.



The structures of the following compounds have been determined using x-ray crystallography: (15) and (16) <86HCA941>; (17a) <87CPB80>; (18) <88HCA2042>; (19) <88CC372>; (20) <90CC1487, 94T957>.

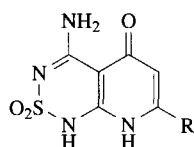


7.17.3.2 Molecular Spectra

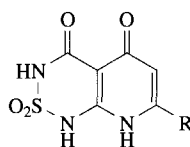
7.17.3.2.1 NMR spectroscopy (^1H , ^{13}C)

The pyridothiadiazine dioxides (21a,b) and (22a,b) were characterized primarily by ^{13}C NMR spectroscopy <88AQ89>. A study of the ^{13}C NMR spectra of a series of pyrano[4,3-*e*]-1,2,4-triazines

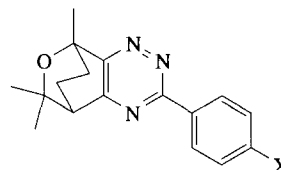
(23a–f) revealed a good correlation between the substituent on the pendant phenyl moiety and the expected chemical shifts for the triazine system <79JHC1389>.



(21a) R = Me
(21b) R = Ph

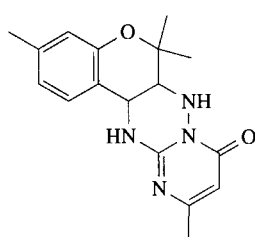


(22a) R = Me
(22b) R = Ph

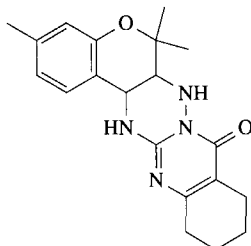


(23a) X = H
(23b) X = 4-Br
(23c) X = 4-CF₃
(23d) X = 4-Me
(23e) X = 4-F
(23f) X = 4-OMe

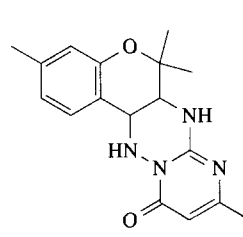
The stereochemistry about the reduced pyrano[4,3-*e*]-1,2,4-triazine ring junction in compounds (24) and (25) was shown to be *cis* by ¹H NMR (*J* = 3.5 Hz). The stereochemistry of the corresponding pyrano[3,4-*e*]-1,2,4-triazines (26) and (27) was also assumed to be *cis* though this is not clear from ¹H NMR (*J* = 5 Hz); the large coupling constant is due to a distorted triazine ring <90JHC1917>.



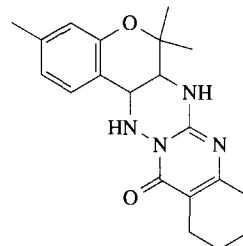
(24)



(25)

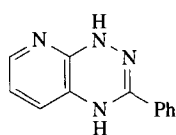


(26)

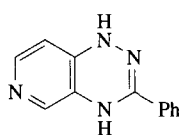


(27)

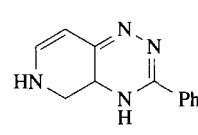
The structures of the reduced pyrido-1,2,4-triazines (28), (29), and (30) were established unequivocally using a combination of ¹H and ¹³C NMR spectroscopy, and particularly by the use of NOE techniques <81JOC4754>.



(28)



(29)



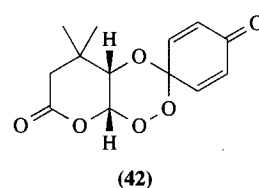
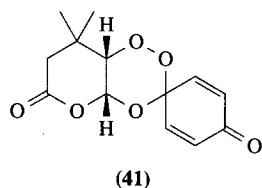
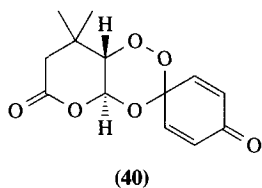
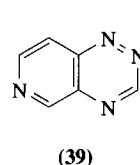
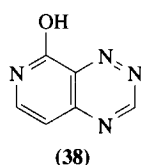
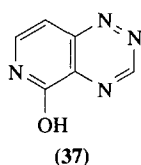
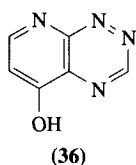
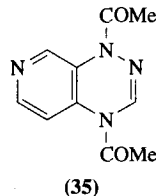
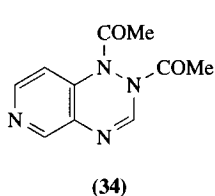
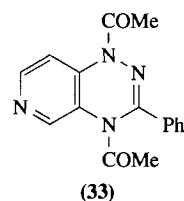
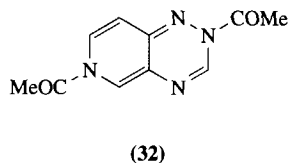
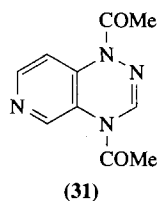
(30)

Low temperature NMR studies, particularly NOE data, were used to determine the preferred conformations of the *N,N'*-diacetyl pyrido-1,2,4-triazines (31), (32), (33), (34), and (35). In most cases one of the acetyl groups adopted a single favored conformation; the acetyl group in question was usually located on a nitrogen atom adjacent to an *sp*² hybridized nitrogen. The methyl group of the acetyl moiety was also pointing towards the *sp*² hybridized nitrogen <85CJC3210>.

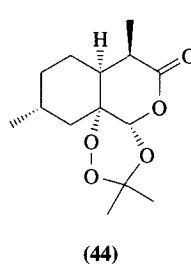
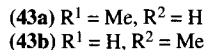
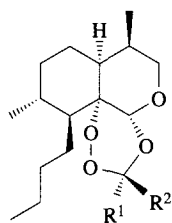
The structures of compounds (36), (37), and (38) and other products from nucleophilic additions to pyrido[3,4-*e*]-1,2,4-triazine (39) were deduced by ¹H and ¹³C NMR studies, in some cases by comparison to related heterocyclic systems <92CJC2828>.

The stereochemistry of the trioxanes (40), (41), and (42) was determined using variable temperature NMR experiments. The presence of characteristic line broadening effects in the spectrum of the *cis* isomers (41) and (42), due to ring inversion, distinguished them from the rigid *trans* isomer (40) <88JOC4986>.

The structures of compounds (43a,b) were established by a combination of NOE experiments and comparison with the spectra of other examples of this type of ring system <90H(31)2125>. A conformational study of compounds (19), (20), and (44) was carried out using NOESY and ROESY



experiments to determine the preferred conformation of the pyrano-1,2,4-trioxane ring system present in these potential chemotherapeutic agents <94T957>.



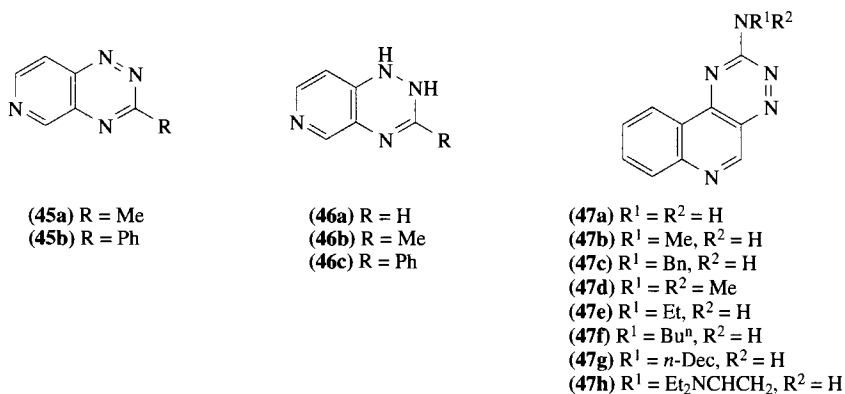
7.17.3.2.2 Mass spectrometry

The mass spectra of triazines (39) and (45a,b) each showed a characteristic loss of N_2 whereas the fragmentation of the dihydro analogues (46a-c) depended on their tautomerism <83MI 717-01>.

The fragmentation patterns of compounds (47a-d) have also been studied, with the loss of N_2 being the primary decomposition route of both doubly and singly charged molecular ions <85OMS(20)416>.

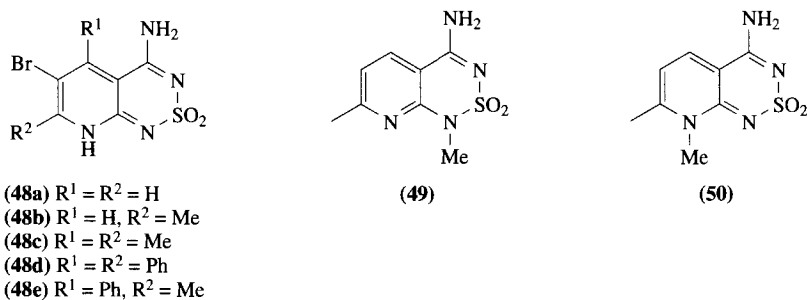
7.17.3.2.3 IR spectroscopy

There is nothing to report in this area.



7.17.3.2.4 UV spectroscopy

Data from the UV spectra of pyridothiadiazines (**48a–e**) suggest that in water the preferred tautomer is the N(8)—H form, as has been observed for related heterocyclic systems <91SC827>. The UV–visible absorption spectra of pyrido[2,3-*c*][1,2,6]thiadiazines (**49**) and (**50**) were determined as part of a study into their use as laser dyes <93MI 717-07>.



7.17.3.2.5 Other spectroscopic methods

The fluorescence spectra of compounds (**49**) and (**50**) were recorded over a range of pH values and in several solvent systems as part of a study into their use as laser dyes <93MI 717-07>.

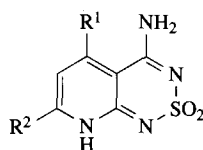
7.17.4 THERMODYNAMICS AND AROMATICITY

There is nothing to report in this area.

7.17.5 REACTIVITY OF FULLY-CONJUGATED RING SYSTEMS

7.17.5.1 1*H*-Pyrido[2,3-*c*]-1,2,6-thiadiazines

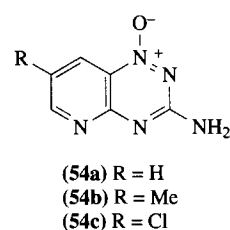
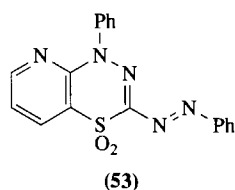
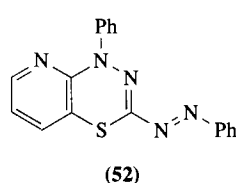
Bromination of pyridothiadiazines (**51a–e**) using NBS in methanol yielded the bromo derivatives (**48a–e**) in good yield (71–85%). Bromination was regiospecific and was not accompanied by any bromination of the substituents <91SC827>.



- (51a) $R^1 = R^2 = H$
 (51b) $R^1 = H, R^2 = Me$
 (51c) $R^1 = R^2 = Me$
 (51d) $R^1 = R^2 = Ph$
 (51e) $R^1 = Ph, R^2 = Me$

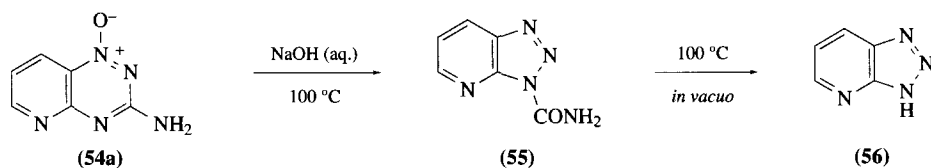
7.17.5.2 1*H*-Pyrido[2,3-*e*]-1,3,4-thiadiazines

Oxidation of the pyrido[2,3-*e*]-1,3,4-thiadiazine (**52**) to the corresponding dioxide (**53**) was achieved using H_2O_2 in AcOH in 61% yield <80JOC3677>.



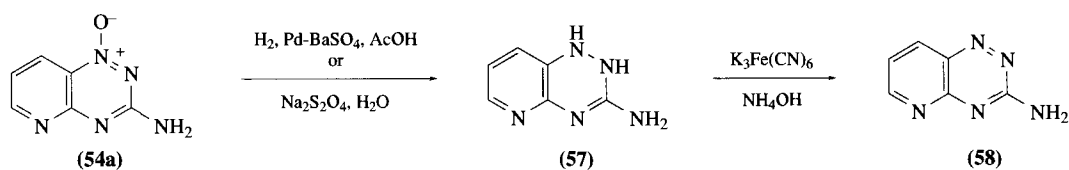
7.17.5.3 Pyrido[2,3-*e*]-1,2,4-triazines

The triazine 1-oxide (**54a**) undergoes a base-catalyzed rearrangement to yield the triazolopyridine carboxamide (**55**). Further heating delivers triazolopyridine (**56**) (Scheme 1) <62JOC2504>.



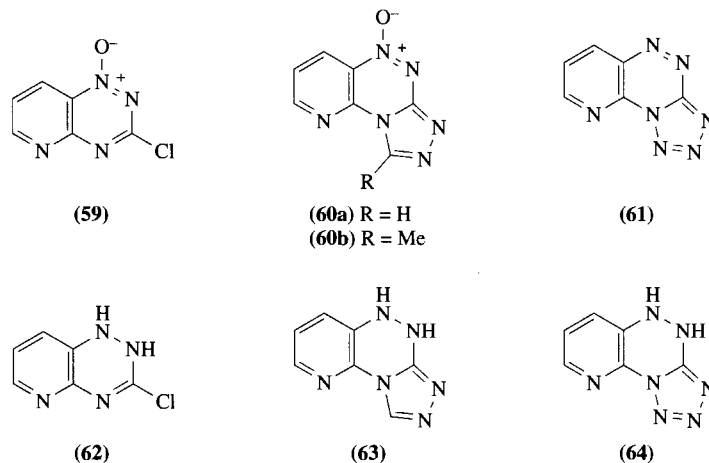
Scheme 1

Conversion of the triazine 1-oxide (**54a**) to 3-aminopyrido[2,3-*e*]-1,2,4-triazine (**58**) can be achieved by reduction to the dihydro triazine (**57**) followed by oxidation using $K_3Fe(CN)_6$. 3-Aminopyrido[2,3-*e*]-1,2,4-triazine (**58**) is obtained in an overall yield of 57% (Scheme 2) <62JOC2504>.



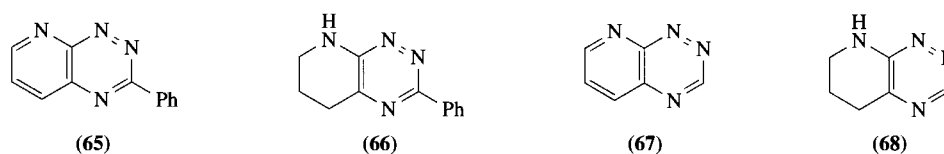
Scheme 2

The triazine 1-oxides **(59)** and **(60a)** and tetrazolo[5,1-*c*]triazine **(61)** react with aqueous $\text{Na}_2\text{S}_2\text{O}_4$ to give the corresponding dihydro derivatives **(62)**, **(63)** and **(64)** in yields of 57%, 68%, and 60%, respectively <73JHC575>.



7.17.5.4 Pyrido[3,2-*e*]-1,2,4-triazines

Catalytic hydrogenation of 3-phenylpyrido[3,2-*e*]-1,2,4-triazine **(65)** over a palladium catalyst gave a 90% yield of the dihydro compound **(28)**. This is an unusual result as the position of the nitrogen atom of the pyridine ring does not seem to affect the formation of 1,4-dihydro derivatives of such pyrido-1,2,4-triazines whereas its position is crucial in the reduction of related bicyclic heterocycles. Electrochemical reduction of the pyrido-1,2,4-triazine **(65)** in both protic and aprotic media yielded the dihydro derivative **(28)** quantitatively. Reduction of compound **(65)** using LAH delivered the triazine **(66)** (35%) whilst the parent pyrido-1,2,4-triazine system **(67)** gave the triazine **(68)** (10%). Here, the position of the pyridine nitrogen appears to be crucial in determining the course of the reaction <81JOC4754>.

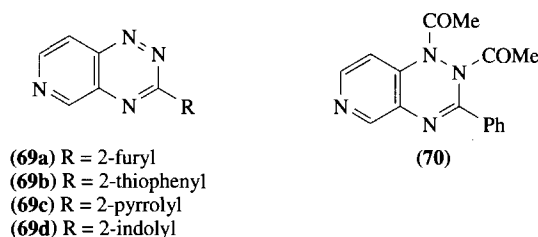


An investigation into the reactivity of a variety of pyrido-1,2,4-triazines towards nucleophiles revealed some interesting facts. Reaction of the parent triazine **(67)** with NH_4OH in the presence of $\text{K}_3\text{Fe}(\text{CN})_6$ gave the 5-hydroxy compound **(36)** in only 15% yield after 5 days. It appears that the pyridine nitrogen atom must be in the β -position to achieve good rates of reactivity <92CJC2828>.

7.17.5.5 Pyrido[3,4-*e*]-1,2,4-triazines

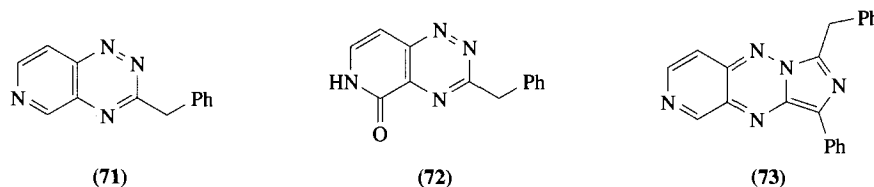
Catalytic hydrogenation of 3-phenylpyrido[3,4-*e*]-1,2,4-triazine **(45b)** over a palladium catalyst gave the 1,4-dihydro compound **(29)** in a 90% yield; this is an unusual result as the position of the pyridine nitrogen atom does not seem to affect the formation of 1,4-dihydro derivatives (see also Section 7.17.5.4). Electrochemical reduction of the pyrido-1,2,4-triazine **(45b)** in both protic and

aprotic media yielded the 1,4-dihydro derivative (**29**) quantitatively; analogous reduction of related 3-substituted systems (**69a-d**) also delivered the corresponding 1,4-dihydro products <81JOC4754>.

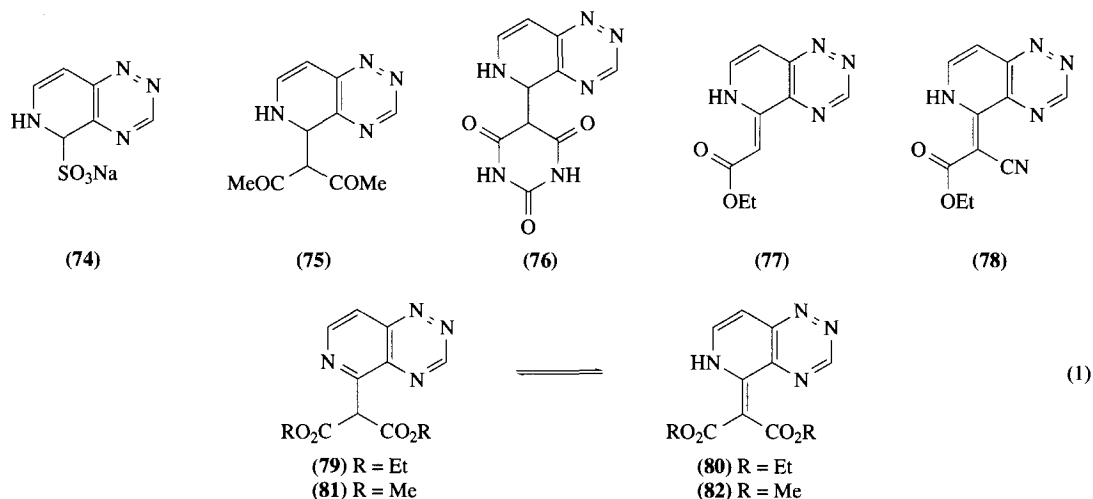


Reduction of compound (**45b**) using LAH was not so straightforward, delivering the triazine (**30**) in 50% yield; the position of the pyridine nitrogen appears to be crucial in determining the course of the reaction <81JOC4754>. Electrochemical reduction of pyrido-1,2,4-triazine (**45b**) in aprotic media in the presence of Ac_2O resulted in a 3:1 mixture of the diacyl compounds (**70**) and (**33**). Compound (**70**), which was isolated in 22% yield from the mixture, is the kinetic product and compound (**33**) is the thermodynamic product <81JOC4754>.

3-(Phenylmethyl)pyrido[3,4-*e*]-1,2,4-triazine (**71**) was degraded at 60°C for five weeks to yield a complex mixture of colored products. Among these were 3-(phenylmethyl)pyrido[3,4-*e*]-1,2,4-triazine (**72**) and the 3-phenyl-1-(phenylmethyl)imidazo[3,4-*b*]-1,2,4-triazine (**73**) <82JHC1533>.

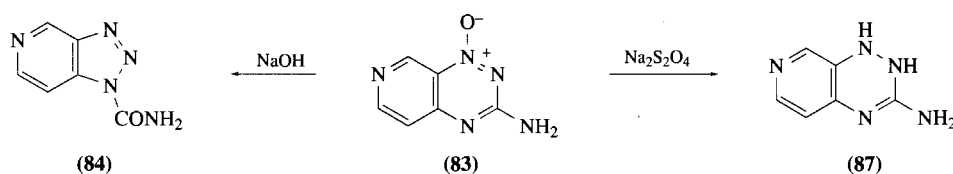


Investigations into the outcome of reactions of various nucleophiles with pyrido[3,4-*e*]-1,2,4-triazine (**39**) demonstrated some interesting facts. Reaction occurs exclusively in the pyridine ring, always *peri* to the triazine moiety, and the pyridine nitrogen must be in a β -position for a good rate of reaction. Thus, triazine (**39**) reacted with NH_4OH in the presence of $\text{K}_3\text{Fe}(\text{CN})_6$ to deliver the 5-hydroxy compound (**37**) in 30% yield after 24 hours. Reaction of the triazine (**39**) with NaHSO_3 gave the sodium salt (**74**) (20%). 2,4-Pentane dione reacted with compound (**39**) to give dihydro compound (**75**) in 35% yield, and triazine (**39**) delivered a 40% yield of the barbituric acid derivative (**76**). Similar reactions occurred with other activated methylene species: triazine (**39**) reacted with ethyl acetoacetate to give compound (**77**) (60%) while ethyl cyanoacetate reacted to deliver compound (**78**) (45%). With malonic acid esters tautomeric adducts resulted: reaction with diethyl malonate gave a 60% overall yield of the tautomeric compound represented by structures (**79**) and (**80**). In CDCl_3 the ratio of the tautomers (**79**) and (**80**) was 40:60, whilst in d_6 -DMSO the ratio was 24:76. Reaction of triazine (**39**) with dimethyl malonate gave a 65% overall yield of the tautomeric compound represented by structures (**81**) and (**82**) (Equation (1)) <92CJC2828>.

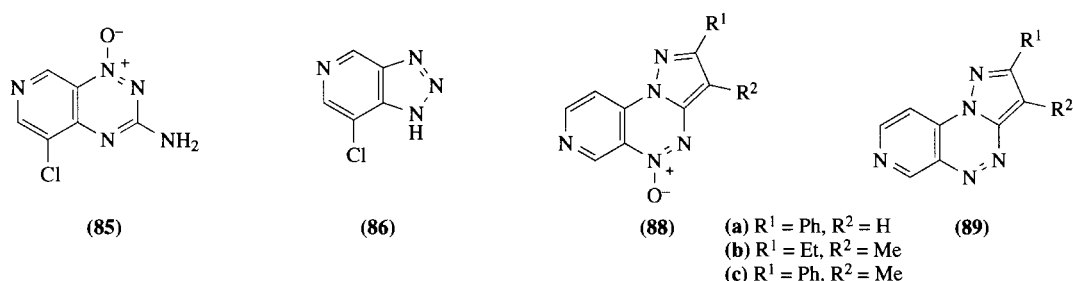


7.17.5.6 Pyrido[4,3-*e*]-1,2,4-triazines

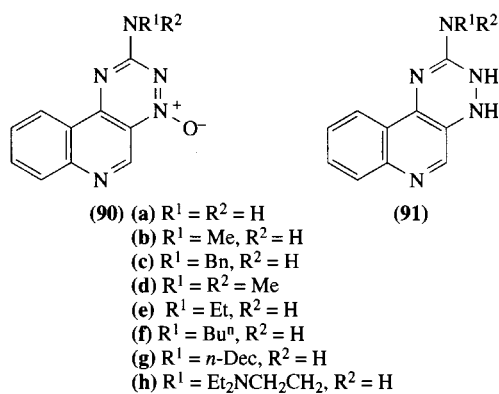
The pyrido-1,2,4-triazine 1-oxide (**83**) underwent a ring contraction on reaction with aqueous NaOH at 100°C to give the isomeric triazolo[4,5-*c*]pyridine (**84**) (40%) <71JHC47>. The chloro derivative (**85**) underwent a similar rearrangement to give compound (**86**) <76MI 717-01>. Alternatively, treatment of compound (**83**) with Na₂S₂O₄ gave air-sensitive 1,2-dihydro 3-amino-pyrido[4,3-*e*]-1,2,4-triazine (**87**) (Scheme 3) <71JHC47>. Treatment of the pyrido-1,2,4-triazine *N*-oxides (**88a-c**) with Na₂S₂O₄ delivered the corresponding pyrido-1,2,4-triazines (**89a-c**) in 68–78% yield <76JPR835>.



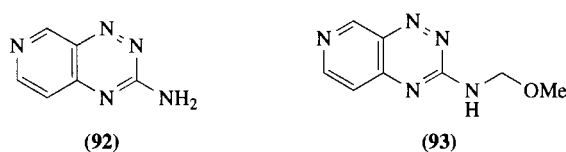
Scheme 3



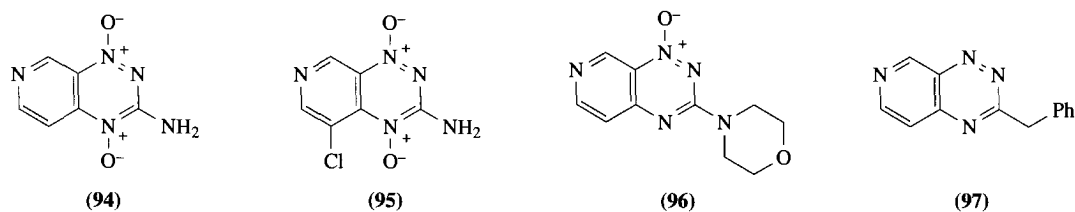
Catalytic hydrogenation of the *N*-oxide (**90a**) gave 1,2-dihydro-3-amino-1,2,4-triazino[6,5-*c*]quinoline (**91a**) (80%) <73GEP(O)2322418>. Hydrogenation of the *N*-oxide (**90a**) gave the corresponding aminotriazine (**47a**) <76MI 717-02>.



Photoreduction of 3-aminopyridine[4,3-*e*]-1,2,4-triazine 1-oxide (**83**) at 254 nm in either aqueous methanol or HCl delivered the pyrido-1,2,4-triazine (**92**): subsequent photolysis in anhydrous methanol gave the methoxymethyl derivative (**93**) <76MI 717-03>.

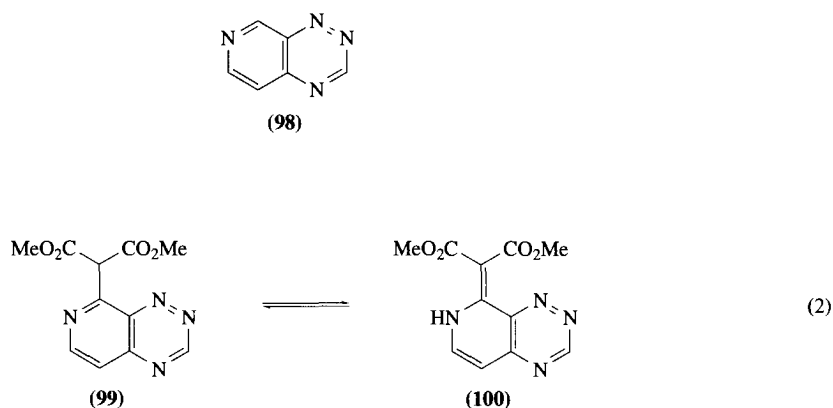


Compounds (**83**) and (**85**) were oxidized to the corresponding 1,4-dioxides (**94**) and (**95**) and treatment of these with amines led to a variety of products. For example, compound (**94**) gave products such as the 3-morpholinyl derivative (**96**) or the 3-benzylpyrido[4,3-*e*]-1,2,4-triazine (**97**) <76MI 717-01>.



Solutions of the *N*-oxides (**90a-h**) in ethanol were hydrogenated (Pd/C) to give aromatized pyrido-1,2,4-triazines (**47a-h**). If, however, ethanolic HCl was added to the mixtures after the catalyst had been removed but before evaporation of the solvent the hydrochloride salts of compounds (**91a-h**) were delivered <81JHC1537>.

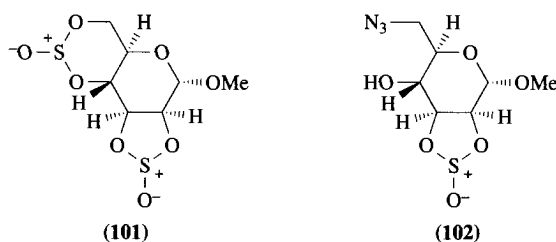
Reaction of the parent triazine (**98**) with NH_4OH in the presence of $\text{K}_3\text{Fe}(\text{CN})_6$ gave the 8-hydroxy compound (**38**) (10%). Triazine (**98**) also reacted with dimethyl malonate to deliver a 30% overall yield of an 8-substituted compound, shown to exist as the tautomeric forms (**99**) and (**100**). In CDCl_3 solution the tautomeric ratio between compounds (**99**) and (**100**) is 30:70 (Equation (2)) <92CJC2828>.



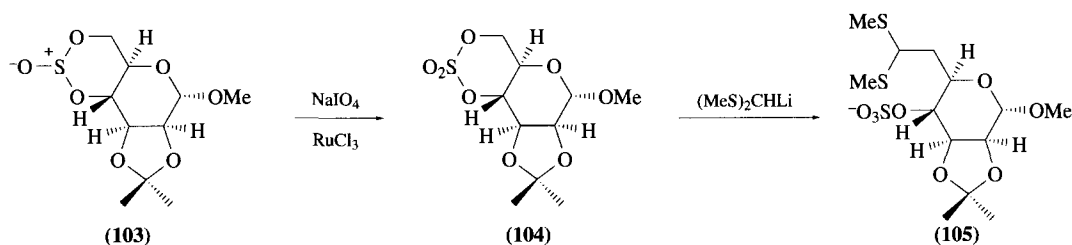
7.17.6 REACTIVITY OF NONCONJUGATED RING SYSTEMS

7.17.6.1 Pyrano[3,2-*d*]-1,3,2-dioxathiins

The disulfoxide (**101**) when treated with NaN_3 in DMF reacted to give the methyl manno-pyranoside (**102**) in 72% yield <85TL6343>.



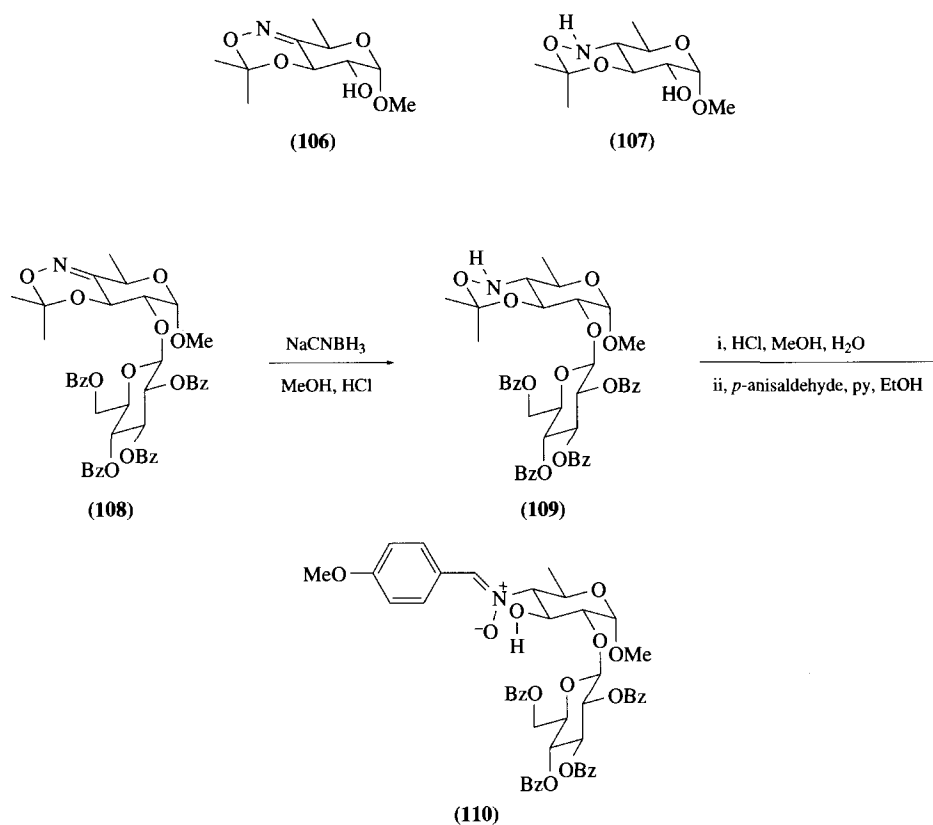
The sulfoxide (**103**) can be readily oxidised to the sulfate (**104**) in good yield. Subsequent reaction of compound (**104**) with a masked carbonyl equivalent nucleophile provided the mannopyranose sulfate (**105**) (Scheme 4) <92CAR(224)193>.



Scheme 4

7.17.6.2 1H,6H-Pyrano[3,4-c]-1,5,2-dioxazines

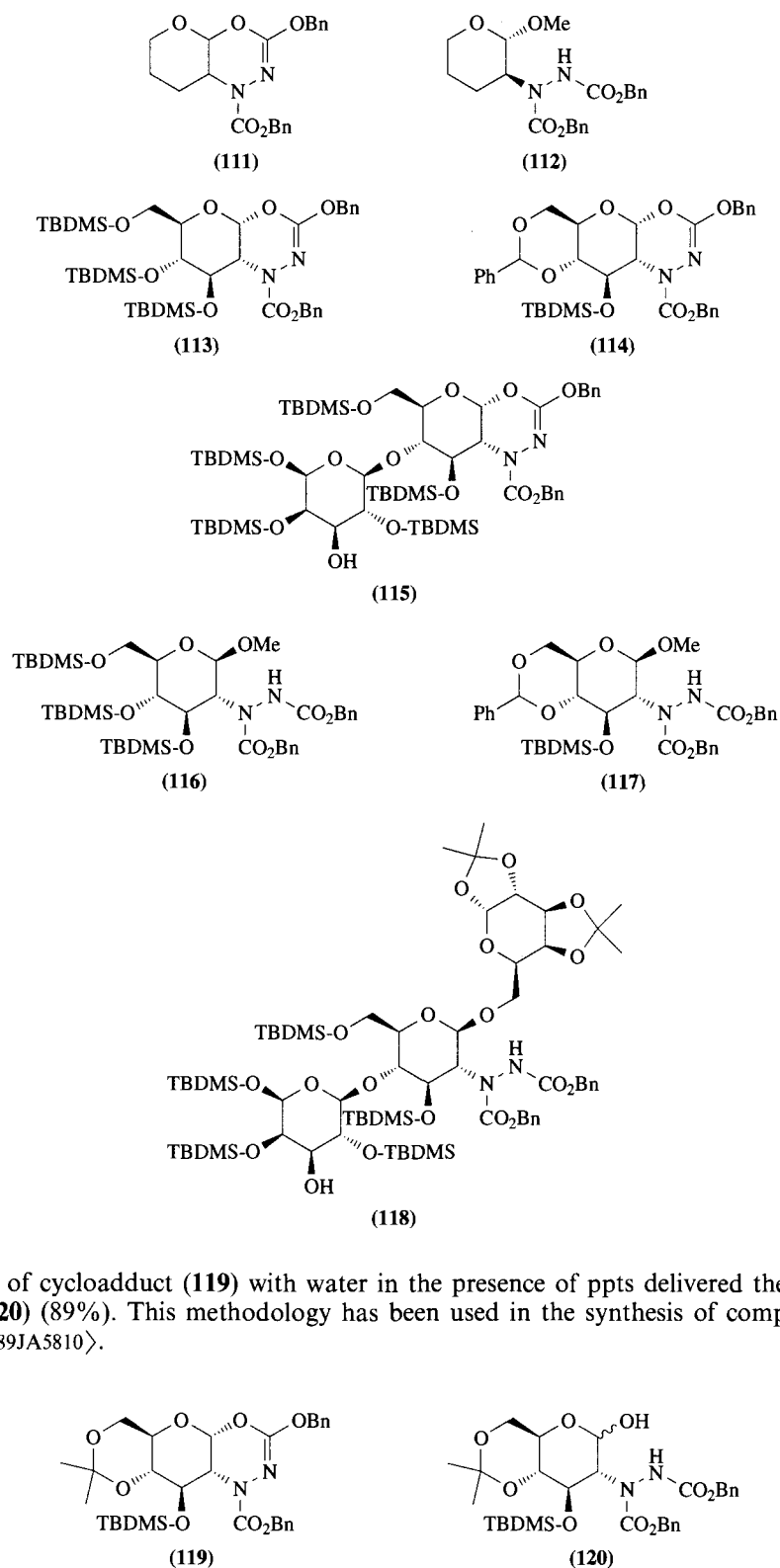
NaCNBH_3 reduction of the pyrano-1,5,2-dioxazine (**106**) gave the corresponding carbohydrate derivative (**107**) in 69% yield (96% based on recovery of starting material). Similarly, reduction of disaccharide (**108**) delivered the corresponding derivative (**109**) in a yield of 60% (98% based on recovery of starting material). Subsequent hydrolysis of the ketal moiety of compound (**109**) followed by reaction with *para*-anisaldehyde gave an 80% yield of disaccharide (**110**) (Scheme 5) <92CC1494>.



Scheme 5

7.17.6.3 1*H*,6*H*-Pyrano[3,2-*e*]-1,3,4-oxadiazines

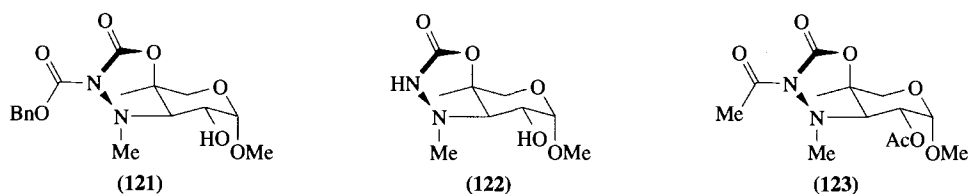
The simple cycloadduct (**111**) was converted into the glycoside (**112**) (80%) after treatment with TsOH in methanol. Similar treatment when applied to cycloadducts (**113**), (**114**), and (**115**) converted them to the corresponding glycosides (**116**), (**117**), and (**118**) in good yield (<87JA285, 89JA2995).



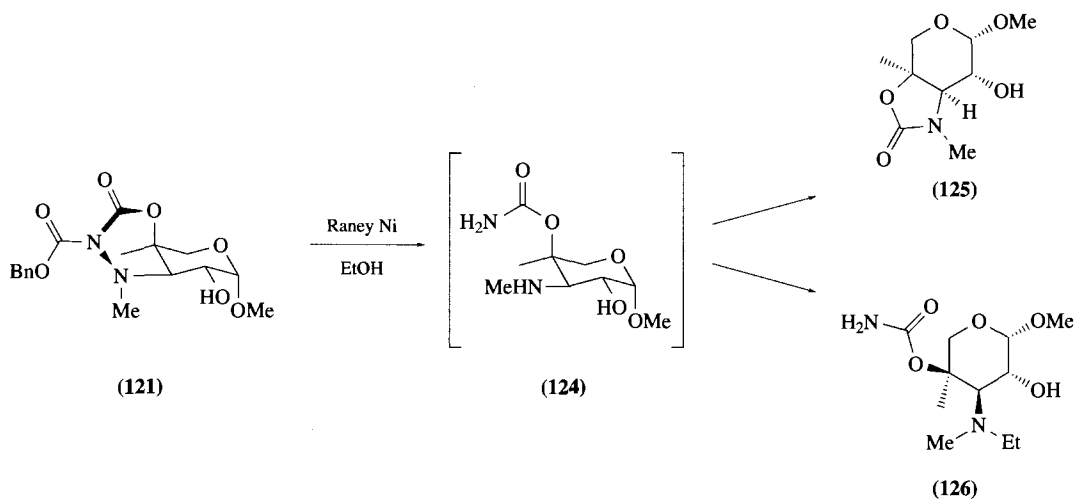
Treatment of cycloadduct (**119**) with water in the presence of ppts delivered the carbohydrate derivative (**120**) (89%). This methodology has been used in the synthesis of complex nucleoside derivatives (<89JA5810).

7.17.6.4 Pyrano[4,3-*e*]-1,3,4-oxadiazines

The oxadiazine (**121**) was subjected to catalytic hydrogenation to give a quantitative yield of compound (**122**) and subsequent treatment with Ac₂O in pyridine delivered the diacetate (**123**) <82JOC523>.



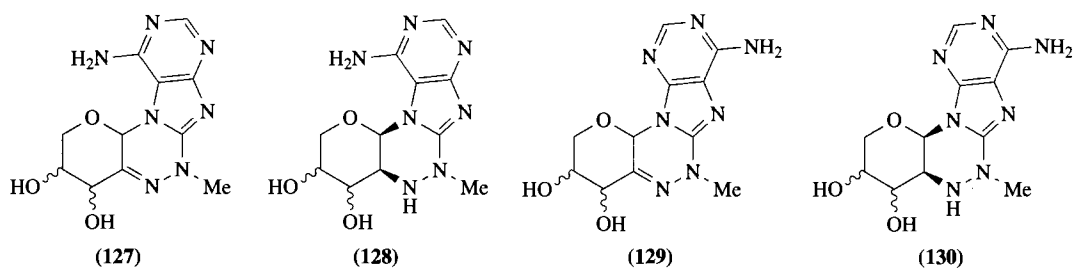
Oxadiazine (**121**) was treated with Raney nickel in ethanol to deliver compounds (**125**) (10%) and (**126**) (24%) via a common intermediate (**124**). The *N*-ethyl group in compound (**126**) is derived from the solvent (Scheme 6) <82JOC523>.



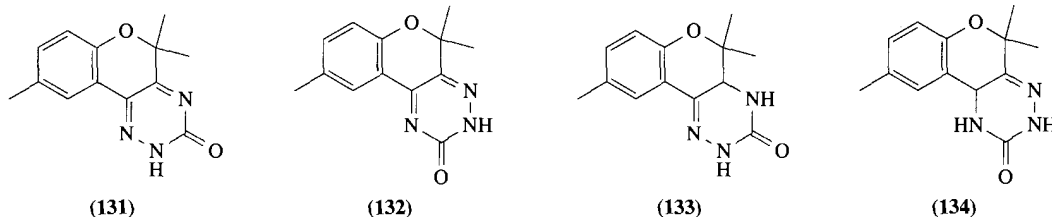
Scheme 6

7.17.6.5 1*H*-Pyrano[2,3-*e*]-1,2,4-triazines

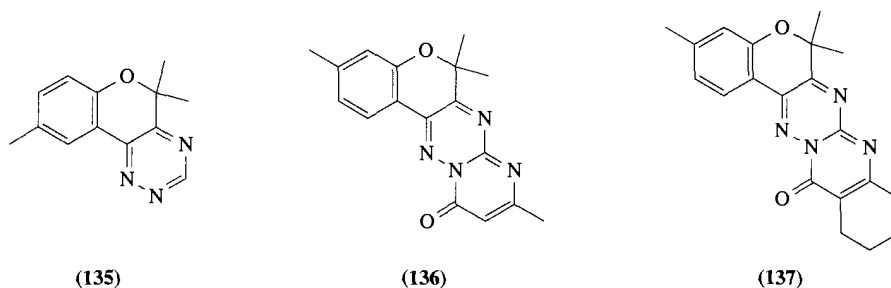
The pyrano-1,2,4-triazine derivative (**127**) was converted into the saturated system (**128**) in a three-step sequence of acetylation, hydrogenation, and subsequent deacetylation. The isomeric triazine (**129**) was similarly transformed into the saturated counterpart (**130**) <82MI 717-01>.

7.17.6.6 2*H*-Pyrano[3,4-*e*]-1,2,4-triazines

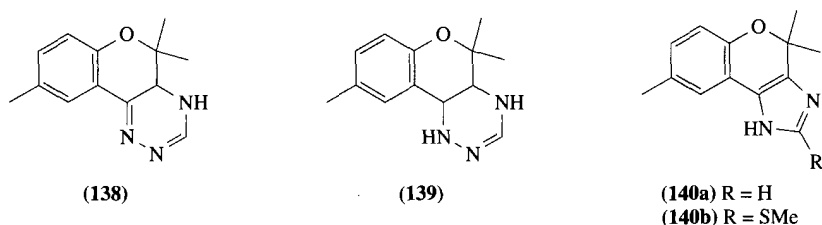
Reduction of the pyrano-1,2,4-triazin-3-one (**131**), as a mixture with the isomer (**132**), gave the dihydro compounds (**133**) and (**134**) in an overall yield of 60% <85JHC33>.



Attempted reduction of the pyrano-1,2,4-triazine (**135**) using zinc in AcOH yielded only a resinous mixture of products. No reaction was observed when compound (**135**) was treated with NaBH₄ or LAH <86JHC491>. However, the addition of a pyrimidine moiety to the ring system enabled chemical reduction and the best results were obtained using NaBH₄. Thus, compound (**136**) gave the tetrahydro derivative (**26**) (70%). The triazinone (**137**) was also reduced to the corresponding tetrahydro compound (**27**) (72%) <90JHC1917>.

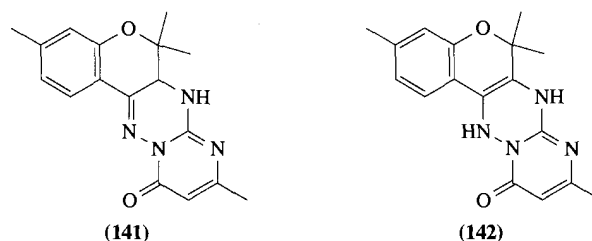


Triazine (**135**) did react using electrochemical methods. At very high pH (pH 13) this triazine (**135**) was reduced to yield 68% of the dihydro compound (**138**). Further reduction of compound (**138**) at lower pH (pH 6.5) delivered the tetrahydrotriazine (**139**) (39%). Alternatively, triazine (**135**) underwent a ring contraction to give the pyranoimidazole (**140a**) (55%) when electrochemical reduction was attempted at neutral pH <86JHC491>.

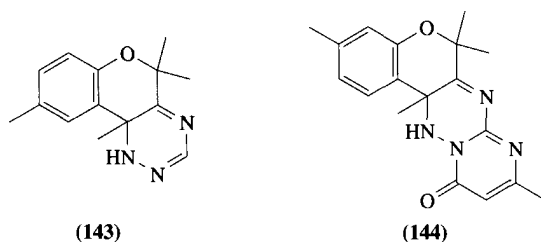


Elaborated pyranotriazine (**136**) was also electrochemically reduced under neutral conditions to yield 78% of the dihydro compound (**141**). This reaction is thought to have occurred via the isomeric dihydro compound (**142**). Compound (**142**) was found to be stable in the slightly acidic reaction medium and under an inert atmosphere, but attempts to isolate it led to quantitative recovery of the starting material (**136**) <90JHC1917>.

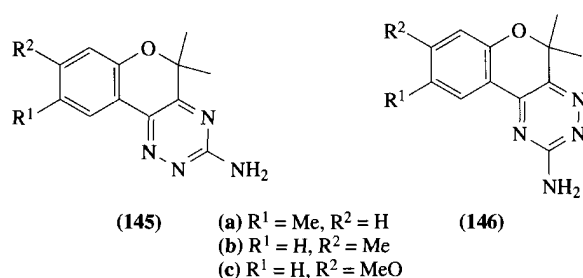
The pyrano-1,2,4-triazine (**135**) reacted with methylmagnesium iodide to deliver compound (**143**)



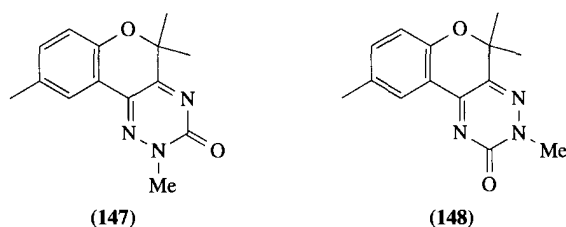
(64%) <86JHC491>. Similarly, compound **(136)** reacted with methylmagnesium iodide to deliver a 64% yield of compound **(144)** <90JHC1917>.



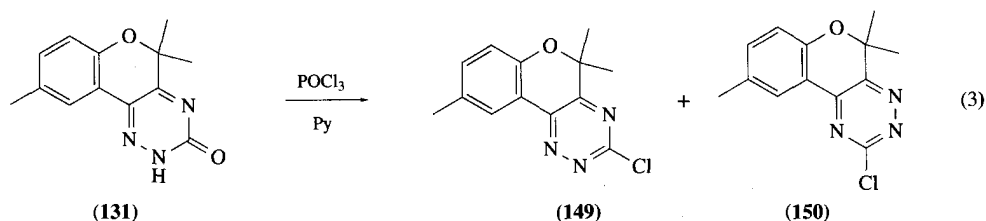
A 2 : 1 mixture of the aminotriazine **(145a)** and the isomer **(146a)** was refluxed in the presence of NaOH to give the corresponding triazin-3-ones **(131)** and **(132)** in the same ratio <86JHC721>.



A mixture of pyrano-1,2,4-triazin-3-one **(131)** with the isomeric triazin-3-one **(132)** was methylated using KOH and Me₂SO₄ to give a mixture of the corresponding methylated derivatives **(147)** and **(148)** (86%) <85JHC33>.



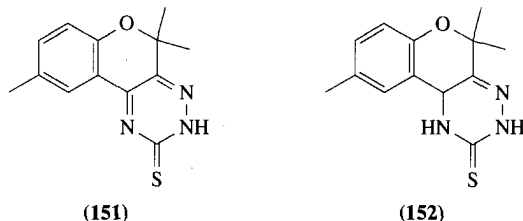
The triazin-3-one **(131)** reacted with POCl₃ in pyridine to give a mixture of the chlorotriazine **(149)** and the isomer **(150)**; the undesired isomer **(150)** made up around 15% of the product mixture (Equation (3)) <86JHC721>.



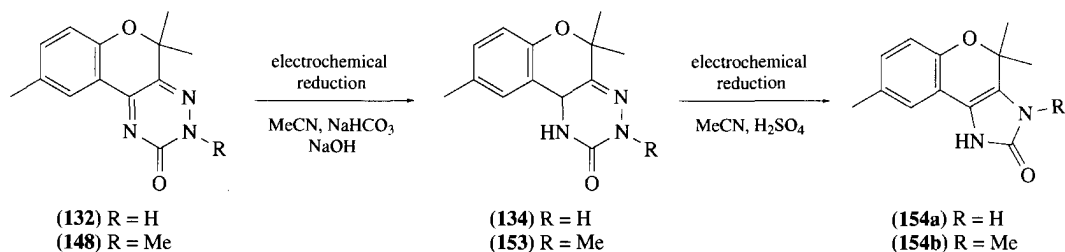
7.17.6.7 1H-Pyrano[4,3-e]-1,2,4-triazines

Reduction of the pyrano-1,2,4-triazin-3-one **(132)** using zinc powder in AcOH gave the dihydro compound **(134)** (85%). Analogous reduction of pyrano-1,2,4-triazin-3-thione **(151)** delivered com-

pound (**152**) (66%). Reduction of a mixture of compound (**132**) and the isomeric pyrano-1,2,4-triazin-3-one (**131**) delivered the dihydro compounds (**134**) and (**133**) in an overall yield of 60% <85JHC33>.

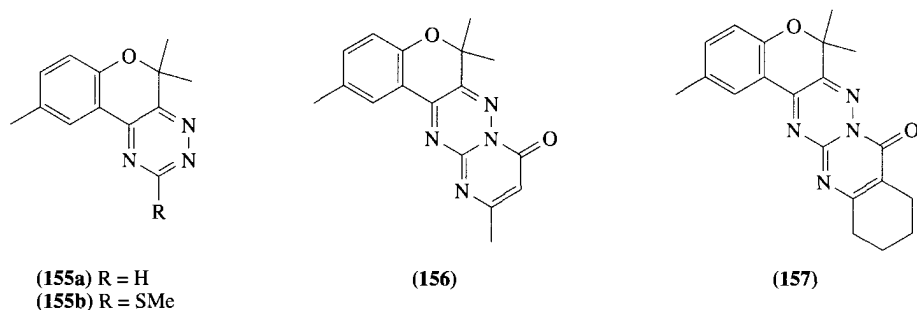


Electrochemical reduction of pyrano-1,2,4-triazin-3-ones (**132**) and (**148**) delivered the corresponding dihydro derivatives (**134**) and (**153**) in yields of 81% and 85%, respectively. Further electrochemical treatment of the compounds (**134**) and (**153**) provoked a ring contraction, leading to the pyranoimidazol-2-ones (**154a,b**) in 83% and 68% yield, respectively. Unexpectedly, attempted reaction of compounds (**134**) and (**153**) with NaBH_4 in ethanol resulted in oxidation to the triazin-3-ones (**132**) and (**148**) (Scheme 7) <86JHC491>.

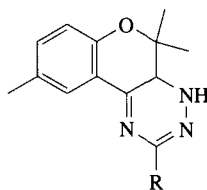


Scheme 7

Attempted reduction of the [1]benzopyrano-1,2,4-triazines (**155a,b**) using zinc in AcOH yielded only a resinous mixture of products. No reaction was observed when these compounds (**155a,b**) were treated with NaBH_4 or LAH <86JHC491>. However, the addition of a pyrimidine moiety modifies the situation and catalytic hydrogenation, LAH and NaBH_4 all give reduced products. Thus, hydrogenation of compound (**156**) in the presence of a palladium catalyst delivered the tetrahydro derivative (**24**) (33%). Reduction of compound (**156**) using LAH gave compound (**24**) in 50% yield. The best results were obtained using NaBH_4 which gave the tetrahydro derivative (**24**) in a yield of 70%. The triazinone (**157**) was also reduced to the corresponding tetrahydro compound (**25**) (80%) <90JHC1917>.

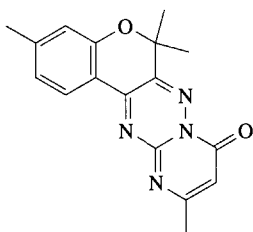


The triazines (**155a,b**) did react using electrochemical methods: at very high pH (pH 13) they were efficiently reduced to the dihydro compounds (**158a,b**) in yields of 79% and 66%, respectively. Pyrano-1,2,4-triazine (**155a**) underwent a ring contraction at neutral pH to deliver the pyranoimidazole (**140a**) (69%). Further reaction of compound (**158b**) at neutral pH (pH 6.5) was also possible, delivering the pyranoimidazole (**140b**) (74%) via a ring contraction <86JHC491>.

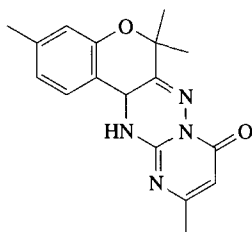


(158a) R = H
(158b) R = SMe

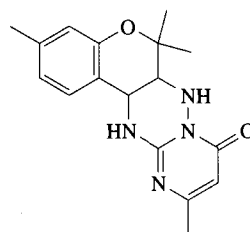
The elaborated pyranotriazine (**159**) was also reduced electrochemically under neutral conditions to yield the dihydro compound (**160**) (85%). The reaction is thought to have occurred via the isomeric dihydro compound (**161**): compound (**161**) was found to be stable in the slightly acidic reaction medium and under an inert atmosphere but any attempts to isolate compound (**161**) led to quantitative recovery of the starting material (**159**) <90JHC1917>.



(159)

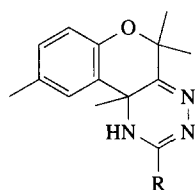


(160)

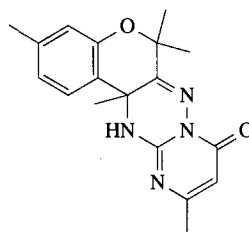


(161)

Pyrano-1,2,4-triazines (**155a,b**) reacted with methylmagnesium iodide giving the dihydro compounds (**162a,b**) in 9% and 65% yield, respectively <86JHC491>. Similarly, compound (**159**) reacted with methylmagnesium iodide to deliver a 59% yield of compound (**163**) <90JHC1917>.



(162a) R = H
(162b) R = SMe



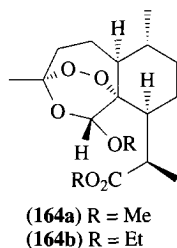
(163)

The pyrano-1,2,4-triazin-3-one (**132**) was methylated using KOH and Me₂SO₄ to give compound (**148**) (84%). In an analogous reaction, a mixture of triazinone (**132**) and the isomeric pyrano-1,2,4-triazin-3-one (**131**) yielded a mixture of methylated derivatives (**147**) and (**148**) in an overall yield of 86% <85JHC33>.

Triazin-3-one (**132**) reacted with POCl₃ in pyridine to give the 3-chlorotriazine (**150**) (74%) <86JHC721>.

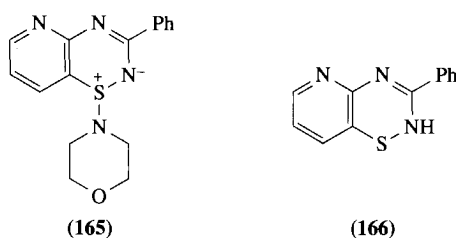
7.17.6.8 3H,6H-Pyrano[2,3-e]-1,2,4-trioxines

Acid degradation of artemisinin (**9**) in either methanol or ethanol gives a mixture of compounds which includes the 1,2,4-trioxanes (**164a,b**). Both compounds (**164a,b**) were as active *in vitro* as artemisinin (**9**) <90H(31)1011>.



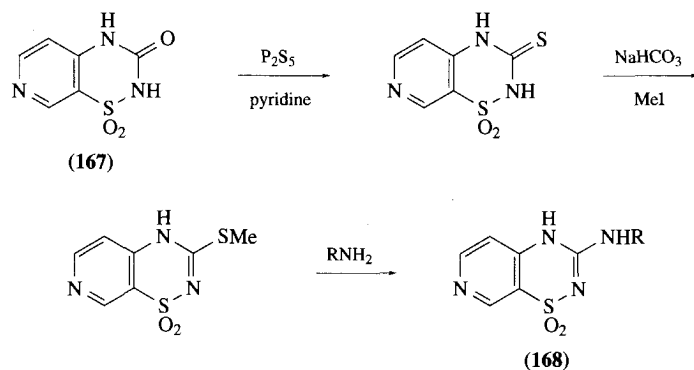
7.17.6.9 2*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazines

The thiadiazine derivative (165) decomposed thermally to afford the 2*H*-compound (166) <83JCS(P1)55>.



7.17.6.10 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

2*H*,3*H*,4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazinone 1,1-dioxide (167) was converted into the series of compounds (168a-j), which are inhibitors of insulin release, via the sequence of reactions shown in Scheme 8 <93JMC3211>.



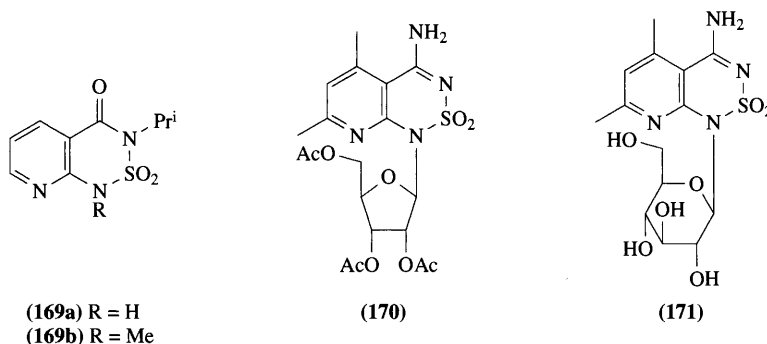
(a) R = H; (b) R = Prⁿ; (c) R = Prⁱ; (d) R = Buⁿ; (e) R = CH(Me)CH₂Me; (f) R = CH₂CH(Me)₂;
(g) R = CH(Me)CH(Me)₂; (h) R = cyclopentyl; (i) R = cyclohexyl; (j) R = *N*-morpholinyl

Scheme 8

7.17.6.11 1*H*-Pyrido[2,3-*c*]-1,2,6-thiadiazines

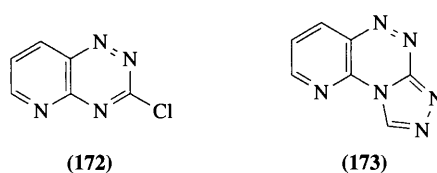
The pyridothiadiazinone dioxide (169a) was successfully methylated using MeI to yield the *N*-methyl derivative (169b) <77USP4014888>. Methylation of pyrido[2,3-*c*]-1,2,6-thiadiazines yields both N-1 and N-8 monomethyl derivatives. For example, methylation of compound (51b) delivers the *N*-methylated systems (49) and (50) <86CS607>.

1*H*-Pyrido[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxides may be glycosylated under standard conditions to yield glycosides of potential biological interest. Thus, the pyrido-1,2,6-thiadiazine dioxide (**51a**) yielded nucleosides (**170**) and (**171**) <90MI 717-01>.

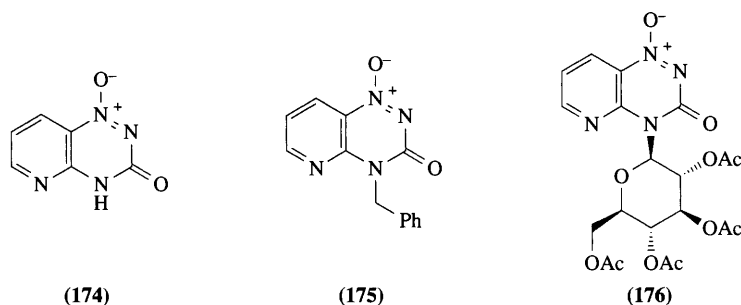


7.17.6.12 Pyrido[2,3-*e*]-1,2,4-triazines

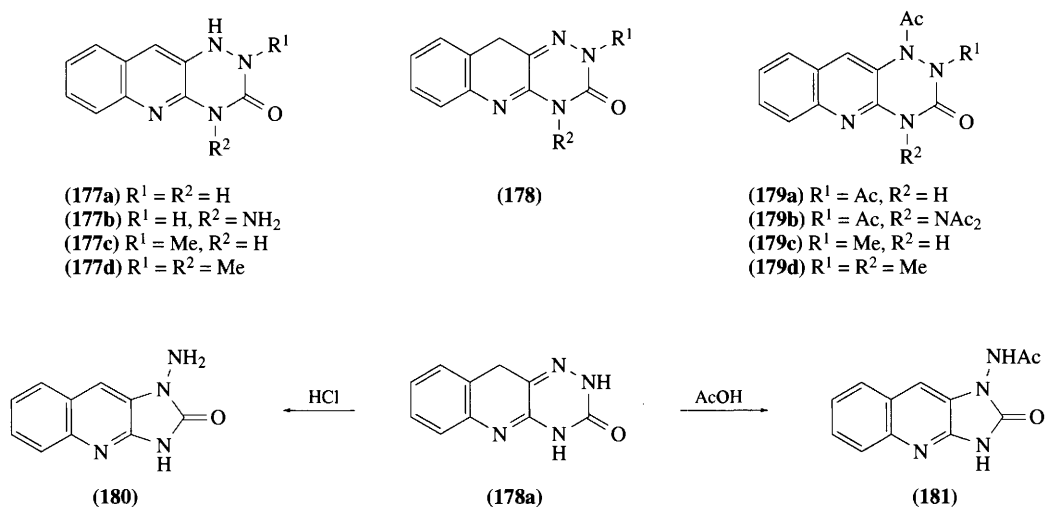
Oxidation of the dihydro compound (**62**) to yield 63% of 3-chloropyrido[2,3-*e*]-1,2,4-triazine (**172**) was achieved using K₃Fe(CN)₆; oxidation of compound (**63**) using FeCl₃ delivered the triazine (**173**) (70%) <73JHC575>.



Methylation of the sodium salt of 3*H*,4*H*-pyrido[2,3-*e*]-1,2,4-triazin-3-one 1-oxide (**174**) using MeI did not occur, even after refluxing the mixture in acetonitrile for 20 hours. *N*-Benzylation was possible, delivering 36% of the benzyl derivative (**175**). The sodium salt of compound (**174**) was also treated with a solution of acetobromoglucose in DMF producing the β -glycoside (**176**) (4%) <82JHC497>.



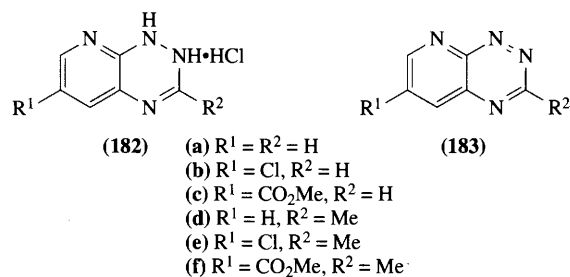
The triazino[5,6-*b*]quinolines (**177a-d**), tautomers of (**178a-d**), may be acetylated to give the derivatives (**179a-d**) in high yield <82JHC313>. By refluxing the triazinoquinoline (**178a**) in acid a series of imidazo[4,5-*b*]quinoline derivatives is accessible. For example, treatment of compound (**178a**) with HCl delivers the imidazoquinoline (**180**) (92%) and treatment with AcOH gives the imidazoquinoline (**181**) (82%) (Scheme 9) <84CCC2628>.



Scheme 9

7.17.6.13 Pyrido[3,2-e]-1,2,4-triazines

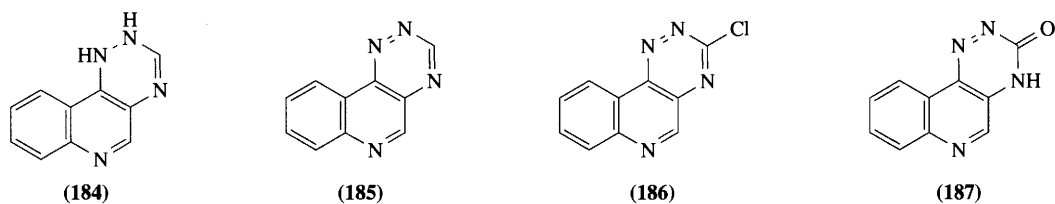
Treatment of the pyrido-1,2,4-triazine hydrochlorides (**182a-f**) with $K_3Fe(CN)_6$ yields the aromatized compounds (**183a-f**) in 71–87% yield <71JHC41>.



7.17.6.14 Pyrido[3,4-e]-1,2,4-triazines

Aromatization of the 1,2-dihydro pyrido-1,2,4-triazines (**46a,b**) with $K_3Fe(CN)_6$ in NH_4OH gives the fully conjugated pyrido-1,2,4-triazines (**39**) and (**45a**) in 81% and 87% yield, respectively <71JHC47>. Dehydrogenation of 1,2-dihydro-1,2,4-triazino[5,6-c]quinoline (**184**) using $K_3Fe(CN)_6$ in NH_4OH yielded 90% of the aromatized triazino[5,6-c]quinoline (**185**) <73GEP(O)2322394, 73GEP(O)2322486>.

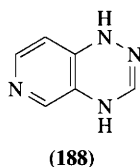
3-Chloro-1,2,4-triazino[5,6-c]quinoline (**186**) was obtained by treatment of the triazin-3-one (**187**) with $POCl_3$ <74JMC244>.



The dihydropyrido-1,2,4-triazine (**29**) when heated under reflux in the presence of Ac_2O gave the diacylated derivative (**33**) in 71% yield. Interestingly, this is not the kinetic product of the reaction. After refluxing for two hours, a mixture of compounds (**70**) and (**33**) is formed in a ratio of 57 : 43. After seven hours the ratio changed to 41 : 59 and after 14 hours the ratio was 26 : 74 <81JOC4754>.

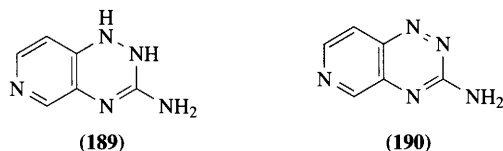
Reductive electrolysis of compound (**29**) in the presence of Ac_2O gave the 1,2-diacetate (**70**) in 22% yield <85CJC3210>.

Treatment of the 1,4-dihydro compound (**188**) with Ac_2O gave the 1,4-diacetate (**31**) in 43% yield. Alternatively, reaction of compound (**188**) with a mixture of AcOH , Et_3N and ethyl chloroformate delivered the 2,6-diacetate (**32**) in a yield of 31% <85CJC3210>.

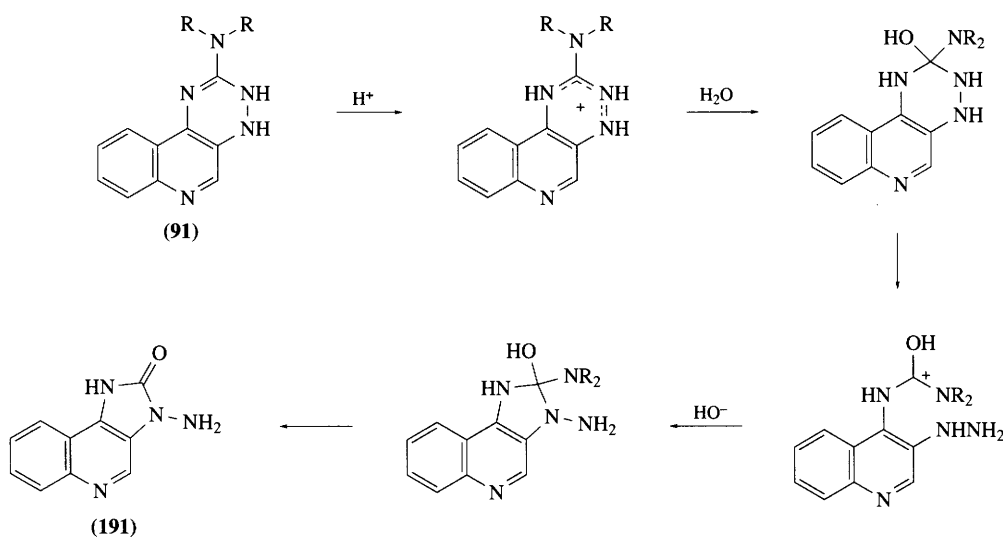


7.17.6.15 Pyrido[4,3-*e*]-1,2,4-triazines

Aromatization of 1,2-dihydro 3-aminopyrido[4,3-*e*]-1,2,4-triazine (**189**) with $\text{K}_3\text{Fe}(\text{CN})_6$ in NH_4OH gave the fully conjugated pyrido-1,2,4-triazine (**190**) (67%) yield <71JHC47>. Dehydrogenation of the 1,2-dihydro compound (**91a**) with $\text{K}_3\text{Fe}(\text{CN})_6$ in NH_4OH yielded the 3-amino-1,2,4-triazino[6,5-*c*]quinoline (**47a**) (94%) <73GEP(O)2322418>.

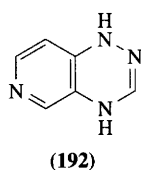


The dihydro compounds (**91a-h**) underwent an interesting transformation when heated in aqueous acid to yield the *N*-aminoimidazoquinoline (**191**). The mechanism of this transformation was determined by labeling studies and is as shown in Scheme 10 <81JHC1537>.



Scheme 10

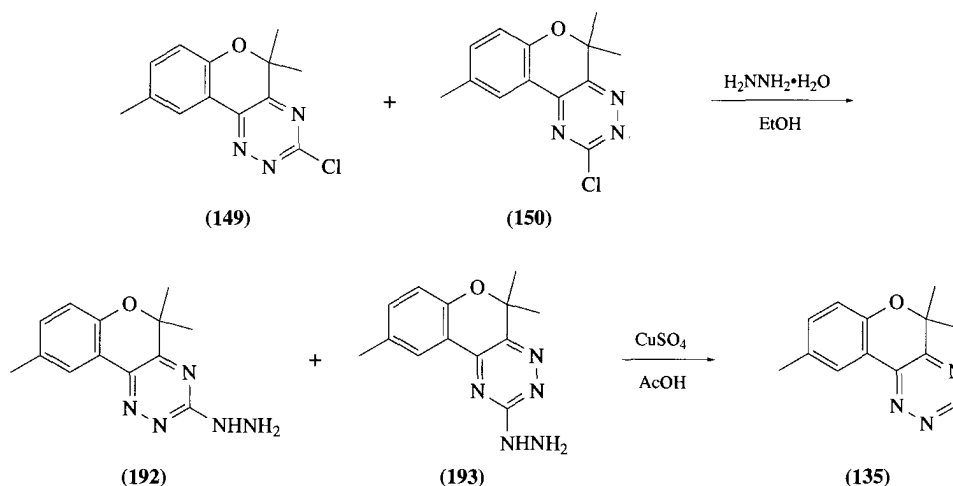
Treatment of the dihydropyrido-1,2,4-triazine (**192**) with Ac_2O gave the 1,4-diacetate (**35**) but in only 3% yield <85CJC3210>.



7.17.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

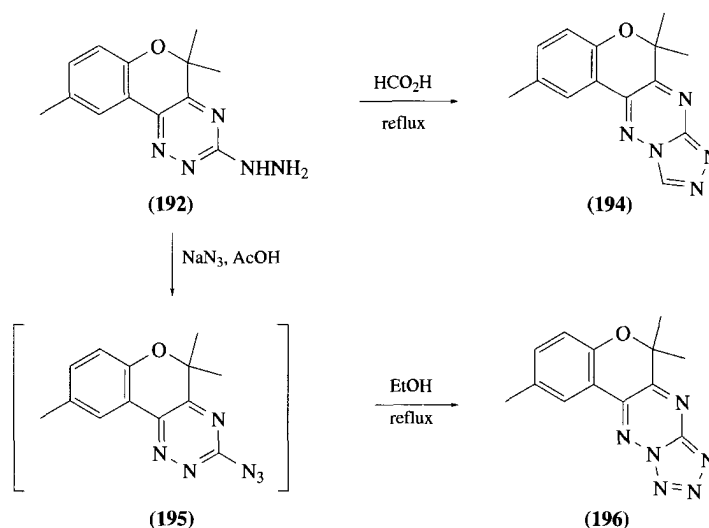
7.17.7.1 2*H*-Pyrano[3,4-*e*]-1,2,4-triazines

Reaction of a mixture of chlorotriazine (**149**) and the isomer (**150**) with hydrazine hydrate delivered 3-hydrazinotriazine (**192**), isolated pure in a yield of 75%, together with the corresponding undesired hydrazinotriazine (**193**). Treatment of compound (**192**) with CuSO_4 in refluxing AcOH yielded 58% of the pyrano-1,2,4-triazine (**135**) (Scheme 11) <86JHC721>.



Scheme 11

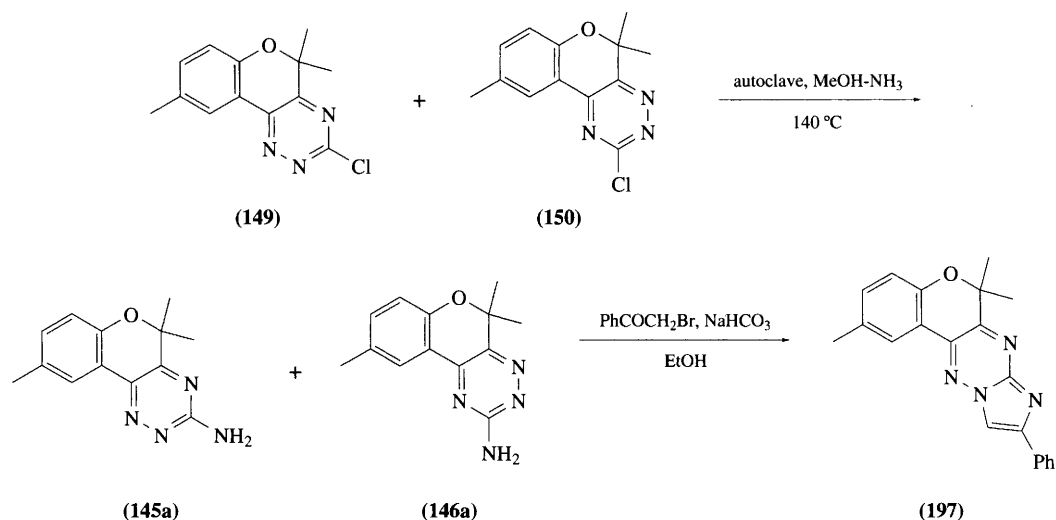
3-Hydrazinotriazine (**192**) also underwent subsequent elaboration: refluxing compound (**192**) in the presence of formic acid gave the triazine derivative (**194**) (54%). Reaction of compound (**192**) with NaN_3 in AcOH, followed by briefly refluxing the product in ethanolic solution, delivered the pyranotriazine (**196**) (88%) via the unstable 3-azidotriazine (**195**) (Scheme 12) <86JHC721>.



Scheme 12

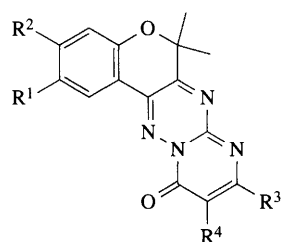
A mixture of 3-chlorotriazine (**149**) and the unwanted chlorotriazine (**150**) could be converted to a mixture of the corresponding 3-aminotriazines (**145a**) and (**146a**) in an overall yield of 67% by treatment with a saturated methanolic solution of NH_3 ; the unwanted isomer (**146a**) was difficult to remove. Subsequent reaction of the 3-aminotriazine (**145a**) (available pure via a cycloaddition

process) with α -bromoacetophenone delivered the triazine derivative (**197**) (77%) (Scheme 13) <86JHC721>.



Scheme 13

The 3-aminopyrano-1,2,4-triazines (**145a–c**) were reacted with several β -ketoesters in the presence of H_3PO_4 , giving the corresponding elaborated triazines (**137**), (**138**), and (**198a–g**) in yields ranging between 31% and 79% <90JHC1917>.



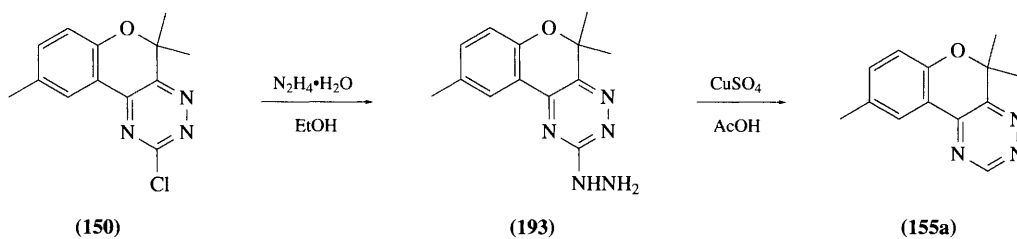
- (**198a**) $\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{R}^4 = \text{H}$
 (**198b**) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_3$
 (**198c**) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_4$
 (**198d**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_3$
 (**198e**) $\text{R}^1 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{MeO}$, $\text{R}^3 = \text{Me}$
 (**198f**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{MeO}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_3$
 (**198g**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{MeO}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_4$
 (**137**) $\text{R}^1 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$
 (**138**) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3, \text{R}^4 = (\text{CH}_2)_4$

7.17.7.2 1H-Pyrano[4,3-e]-1,2,4-triazines

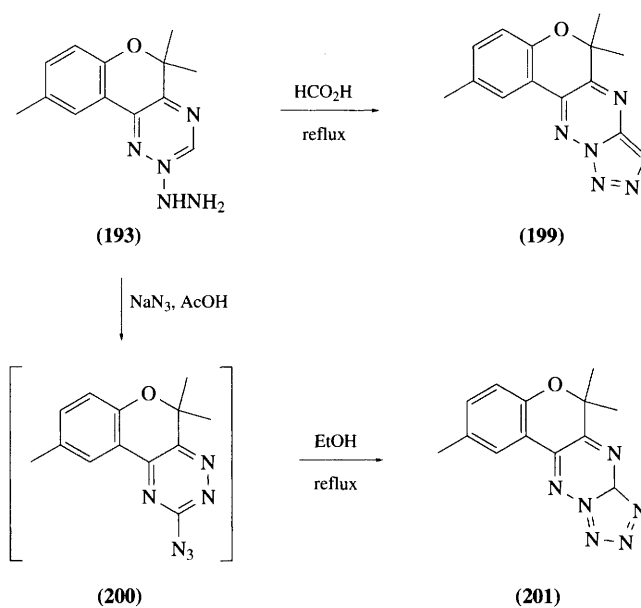
Treatment of pyrano-1,2,4-triazin-3-thione (**151**) with KOH and Me_2SO_4 yielded the triazine (**155b**) (95%) <85JHC33>. 3-Chlorotriazine (**150**) reacted with hydrazine hydrate to give 3-hydrazinotriazine (**193**) (89%) which upon treatment with CuSO_4 in refluxing AcOH yielded the pyrano-1,2,4-triazine (**155a**) (61%) (Scheme 14) <86JHC721>.

Refluxing compound (**193**) in the presence of formic acid delivered the triazine derivative (**199**) (75%). Alternatively, reaction of 3-hydrazinotriazine (**193**) with NaN_3 in AcOH, followed by briefly refluxing the product in ethanolic solution, gave the pyranotriazine (**201**) (79%) via the unstable 3-azidotriazine (**200**) (Scheme 15) <86JHC721>.

3-Chlorotriazine (**150**) could be converted to the corresponding 3-aminotriazine (**146a**) in a yield of 86% by treatment with a saturated methanolic ammonia solution. Subsequent reaction of the

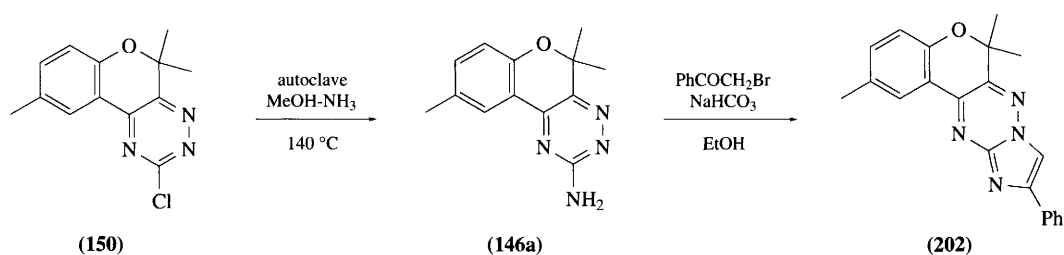


Scheme 14



Scheme 15

3-aminotriazine (**146a**) with α -bromoacetophenone delivered the triazine derivative (**202**) (79%) (Scheme 16) <86JHC721>.

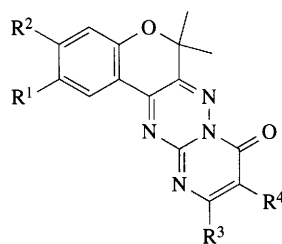


Scheme 16

The 3-aminopyrano-1,2,4-triazines (**146a–c**) reacted with several β -ketoesters in the presence of H_3PO_4 to give the corresponding elaborated triazines (**162**), (**163**), and (**203a–g**) in a broad range of yields <90JHC1917>.

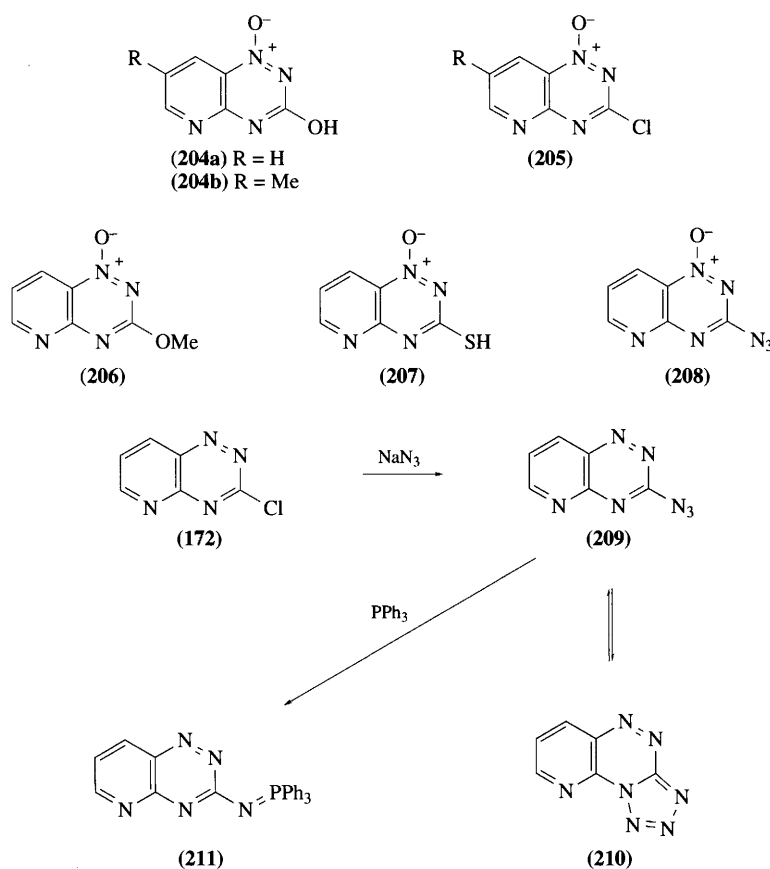
7.17.7.3 Pyrido[2,3-*e*]-1,2,4-triazines

Reaction of the triazine 1-oxides (**54a,b**) with HNO_2 gave the corresponding 3-hydroxy derivatives (**204a,b**) in 88% and 78% yield, respectively. Subsequent treatment of compounds (**204a,b**) with hot



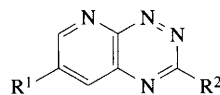
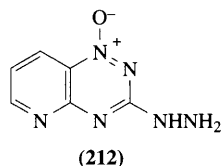
- (203a) $R^1 = R^3 = \text{Me}$, $R^2 = R^4 = \text{H}$
 (203b) $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3, R^4 = (\text{CH}_2)_3$
 (203c) $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3, R^4 = (\text{CH}_2)_4$
 (203d) $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3, R^4 = (\text{CH}_2)_3$
 (203e) $R^1 = R^4 = \text{H}$, $R^2 = \text{MeO}$, $R^3 = \text{Me}$
 (203f) $R^1 = \text{H}$, $R^2 = \text{MeO}$, $R^3, R^4 = (\text{CH}_2)_3$
 (203g) $R^1 = \text{H}$, $R^2 = \text{MeO}$, $R^3, R^4 = (\text{CH}_2)_4$
 (162) $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{Me}$
 (163) $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3, R^4 = (\text{CH}_2)_4$

POCl_3 gave the 3-chloro derivatives (**205a,b**) in good yield. Chloro-substituted compounds (**205a,b**) are very reactive towards nucleophilic species: treatment of 3-chloropyrido[2,3-*e*]-1,2,4-triazine 1-oxide (**205a**) with NaOMe in methanol gave the 3-methoxy derivative (**206**) (69%). Alternatively, treatment of compound (**205a**) with thiourea in ethanol gave the thiol (**207**) (70%) <62JOC2504> and reaction with NaN_3 gave the 3-azido derivative (**208**) (73%) <73JHC575>. Reaction of 3-chloropyrido[2,3-*e*]-1,2,4-triazine (**172**) with NaN_3 , however, yielded the 3-azido derivative (**209**) (26%) together with the triazolo[5,1-*c*]triazine (**210**) (48%). The two compounds (**209**) and (**210**) are interconvertible. 3-Azidopyrido[2,3-*e*]-1,2,4-triazine (**209**) reacted with PPh_3 to deliver the ylide (**211**) (71%) (Scheme 17) <73JHC575>.



Scheme 17

The 3-hydrazino derivative (**212**) underwent reaction with orthoesters to give compounds (**60a,b**) in 70% and 40% yield, respectively <73JHC575>.



- (213a) R¹ = CO₂H, R² = H
 (213b) R¹ = CO₂H, R² = Me
 (183c) R¹ = CO₂Me, R² = H
 (183d) R¹ = CO₂Me, R² = Me

7.17.7.4 Pyrido[3,2-*e*]-1,2,4-triazines

Hydrolysis of the methyl esters (**183c,f**) was achieved under alkaline conditions to give the corresponding carboxylic acids (**213a,b**) in 55% and 60% yield, respectively <71JHC41>.

7.17.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

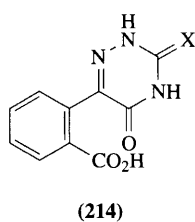
There is nothing to report in this area.

7.17.9 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

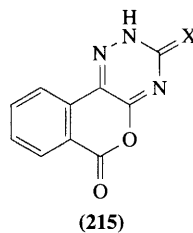
7.17.9.1 Synthesis of the Second Heterocyclic Ring from [6 + 0] Atom Fragments

7.17.9.1.1 1*H*-Pyrano[2,3-*e*]-1,2,4-triazines

2-(6-Azauracil-5-yl)benzoic acid (**214a**) cyclized in the presence of dcc to give the novel ring system (**215a**). The 2-thio derivative (**214b**) reacted similarly to yield compound (**215b**). Further triazine syntheses starting from compounds (**214a,b**) were also reported <92CCCC123>.



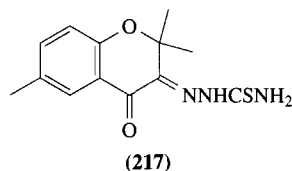
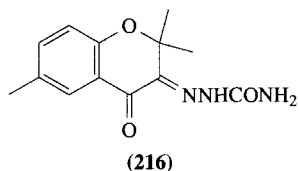
- (a) X = O
 (b) X = S



7.17.9.1.2 2*H*-Pyrano[3,4-*e*]-1,2,4-triazines

By cyclization of the semicarbazone (**216**) under acidic conditions the 2*H*-pyrano[3,4-*e*]-1,2,4-triazin-3-one (**131**) was obtained as a mixture with the 1*H*-pyrano[4,3-*e*]-1,2,4-triazin-3-one (**132**). Reaction in the presence of ethanolic HCl or TFA yielded (**131**) and (**132**) in a ratio of 58:42;

reaction in propanoic acid gave a ratio of 38 : 62. Semicarbazone (**216**) gave compounds (**131**) and (**132**) in a ratio of 43 : 57 when refluxed in the presence of AcOH and semicarbazide hydrochloride <85JHC33>.

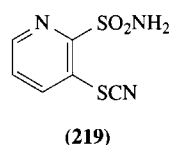
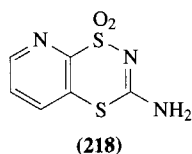


7.17.9.1.3 1H-Pyrano[4,3-e]-1,2,4-triazines

Cyclization of the semicarbazone (**216**) under basic conditions delivered benzopyrano-1,2,4-triazin-3-one (**132**) (90%). A similar reaction of the thiosemicarbazone (**217**) gave the benzopyrano-1,2,4-triazin-3-thione (**151**) (91%). However, by carrying out the cyclization of compound (**216**) in the presence of ethanolic HCl or TFA a mixture of the 1H-pyrano[4,3-e]-1,2,4-triazin-3-one (**131**) and the 2H-pyrano[3,4-e]-1,2,4-triazin-3-one (**132**) resulted (see Section 7.17.9.1.2) <85JHC33>.

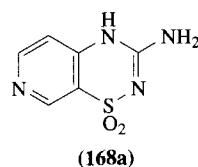
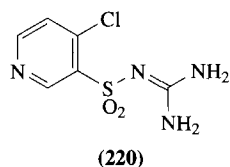
7.17.9.1.4 Pyridof[3,2-e]-1,4,2-dithiazines

Compound (**218**) was prepared from the thiocyanatopyridine (**219**) as a by-product from another synthesis <84MI 717-01>.



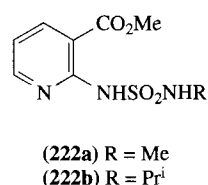
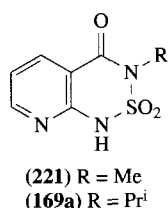
7.17.9.1.5 2H-Pyrido[4,3-e]-1,2,4-thiadiazines

BPDZ 29 (**168a**), a potent inhibitor of insulin release, was prepared by cyclization of the pyridine derivative (**220**) in the presence of K₂CO₃ <93JMC3211>.



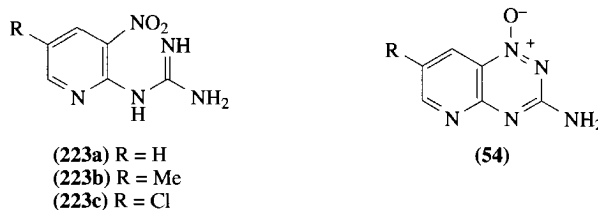
7.17.9.1.6 1H-Pyrido[2,3-c]-1,2,6-thiadiazines

Pyridothiadiazinone dioxides (**221**) and (**169a**) were prepared by NaOMe catalyzed cyclization of the pyridine derivatives (**222a,b**) <77USP4014888>.

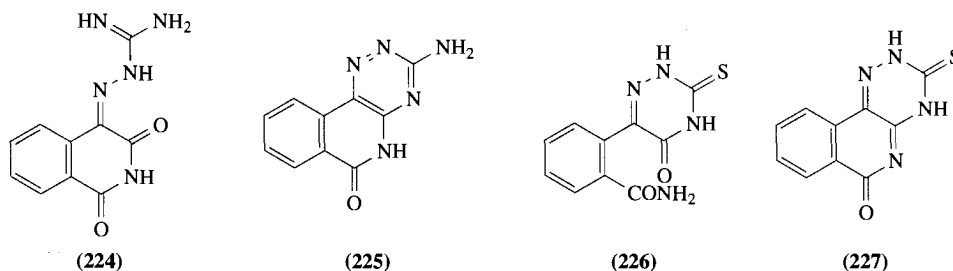


7.17.9.1.7 *Pyrido[2,3-e]-1,2,4-triazines*

Base-catalyzed cyclization of pyridines possessing both nitro and guanidine functions has been used to prepare pyrido[2,3-e]-1,2,4-triazines. Thus, treatment of the pyridines (**223a,c**) with aqueous K_2CO_3 at $100^\circ C$ gave the corresponding triazine-1-oxides (**54a,c**) in 74% and 39% yield, respectively. Pyridine (**223b**) was cyclized using aqueous NaOH at $80-85^\circ C$ to give the triazine 1-oxide (**54b**) (83%) <62JOC2504>.

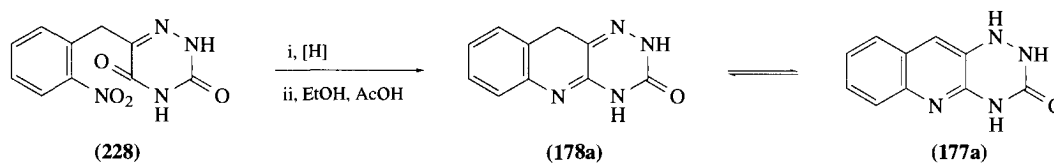


Several 1,2,4-triazinoisoquinolinones have been prepared in 48–79% yield, including some 3-thioketone derivatives, via base-catalyzed cyclization of the corresponding thiosemicarbazones or aminoguanidones. For example, compound (**224**) was cyclized to give the 1,2,4-triazinoisoquinolinone (**225**) <75ZOR2407>.



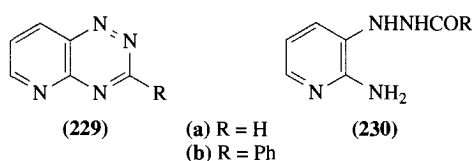
Amide (**226**) was refluxed in AcOH to give the triazinoisoquinolinone (**227**) (76%) <84PHA186>.

Several triazino[5,6-*b*]quinolines have been prepared by the cyclization of a tethered aniline moiety on to a 1,2,4-triazine. Thus, reduction of compound (**228**) followed by cyclization in ethanolic AcOH gave the triazinoquinoline (**178a**) (83%). Compound (**178a**) can be envisaged as existing in two tautomeric forms (**178a**) and (**177a**) in which the quinoline nucleus is intact (Scheme 18) <82JHC313, 84CCC2628>.



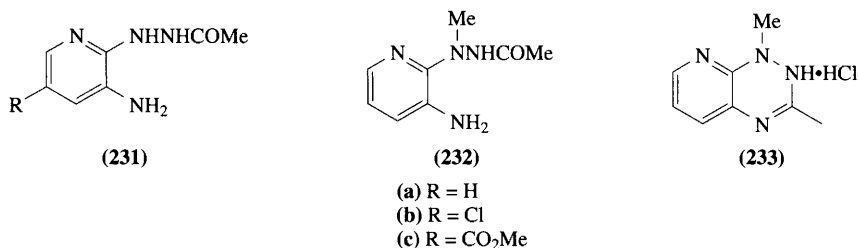
Scheme 18

The parent pyrido[2,3-*e*]-1,2,4-triazine (**229a**) and its 3-phenyl derivative (**229b**) were prepared in 20% and 50% yield, respectively, by treating the corresponding aminopyridines (**230a,b**) with PPA as dehydrating agent <89JHC475>.

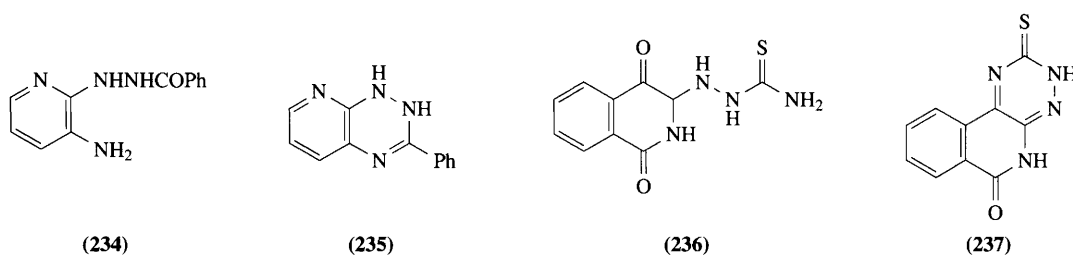


7.17.9.1.8 *Pyrido[3,2-*e*]-1,2,4-triazines*

The aminopyridines (**231a–c**) cyclized rapidly in the presence of alcoholic HCl to give the 1,2-dihydropyrido-1,2,4-triazines (**182d–f**) in 60–83% yield. A similar reaction of the pyridine (**232**) yielded the 1-methylpyrido-1,2,4-triazine (**233**) (86%) <71JHC41>.

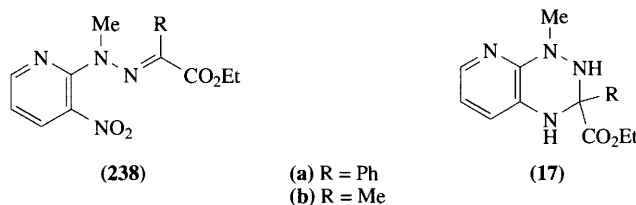


Cyclization of the aminopyridine (**234**) was achieved in the presence of PPA to give the dihydro compound (**235**) (44%). Subsequent oxidation gave 3-(4-phenyl)-pyrido[3,4-*e*]-1,2,4-triazine (**65**) <75MIP10958>. The thiosemicarbazone (**236**) cyclized to give the triazinoisoquinolinone (**237**) (31%) <75ZOR2407>.

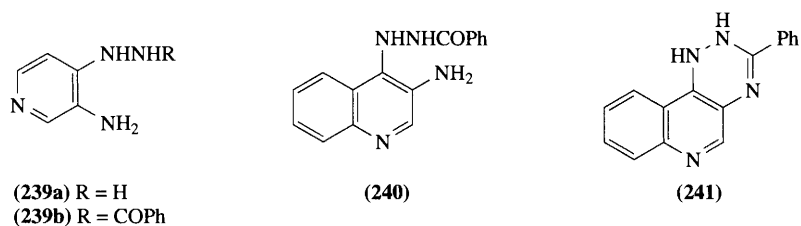


Eight examples of 3-aryl pyrido[3,2-*e*]-1,2,4-triazines were prepared via a reductive cyclization route. Thus, 3-phenylpyrido[3,2-*e*]-1,2,4-triazine (**65**) was prepared from the aminopyridine (**234**) by cyclization followed by oxidation <76CR(C)487>. In another study, seven 3-substituted pyrido-1,2,4-triazines were prepared via an analogous route <76MI 717-04>. This work mirrored the earlier investigations of Lewis and Shepherd <71JHC41>.

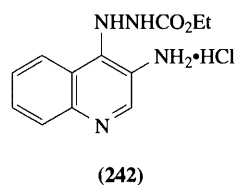
Catalytic hydrogenation of the substituted nitropyridines (**238a,b**) yielded the pyrido-1,2,4-triazines (**17a,b**) in 59% and 87% yield, respectively <87CPB80>.

7.17.9.1.9 *Pyrido[3,4-*e*]-1,2,4-triazines*

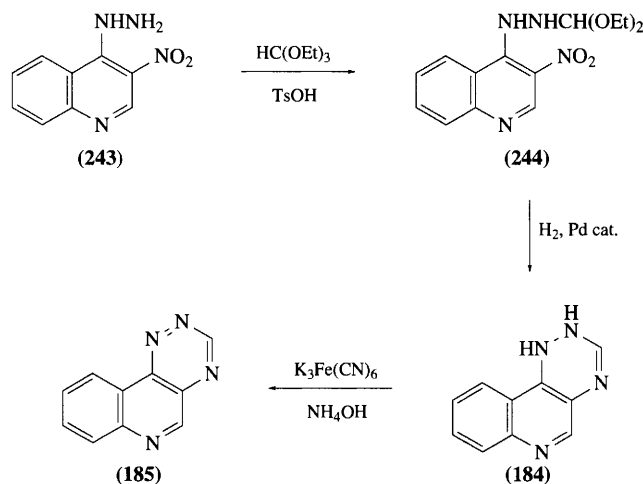
Benzoylhydrazinopyridine (**239b**) was refluxed in methanolic HCl to give the dihydro pyrido-1,2,4-triazine (**46b**) as the hydrochloride (68%) <64JCS4896, 76CR(C)487, 76MI 717-05>. Similarly, treatment of the hydrazinopyridine (**239a**) with methyl orthoformate and ethanolic HCl yielded 80% of 1,2-dihydro pyrido-1,2,4-triazine hydrochloride (**46a**) <71JHC47>. A series of 1,2-dihydro 1,2,4-triazino[5,6-*c*]quinolines were prepared from acyl-substituted hydrazinoquinoline precursors. Thus, the benzoyl derivative (**240**) yielded 3-phenyl-1,2,4-triazino[5,6-*c*]quinoline hydrochloride (**241**) (98%) after refluxing in alcoholic HCl <73GEP(O)2322486>. A number of 3-aryl pyrido[3,4-*e*]-1,2,4-triazines (**69a–e**) were prepared using this strategy <75MIP10959, 81JOC4754>.



The elaborated quinoline hydrochloride (**242**) was reacted with NaOMe in an ethanol/methanol mixture, followed by treatment with AcOH to give the pyridotriazinone (**187**). Subsequent treatment with POCl₃ yielded the chloro derivative (**186**) <72GEP(O)2216241>.

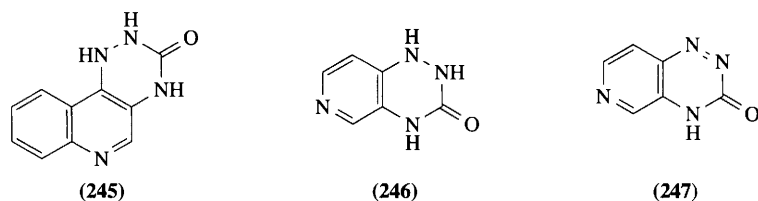


A series of 1,2,4-triazino[5,6-*c*]quinolines have been prepared via a common route. Thus, 4-[β -(ethoxymethylene)hydrazino]-3-nitroquinoline (**244**), prepared from 4-hydrazino-3-nitroquinoline (**243**) by reaction with triethyl orthoformate, was hydrogenated in ethanol over a palladium catalyst to give the dihydro compound (**184**) (96%). Dehydrogenation yielded the desired compound (**185**) (90%) (Scheme 19) <73GEP(O)2322394>.

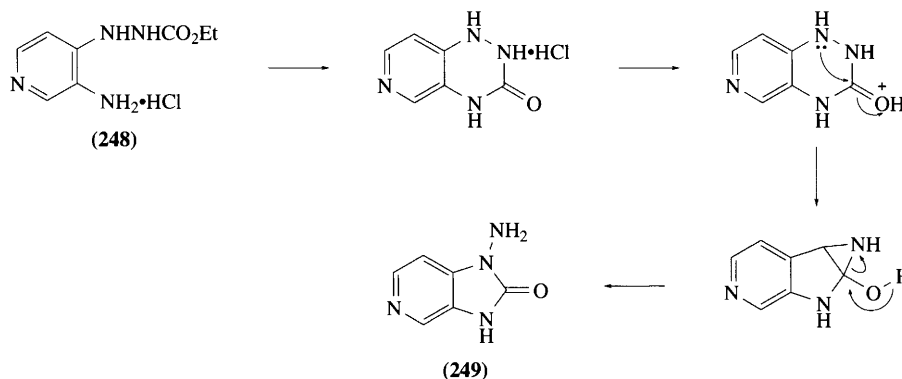


Scheme 19

Cyclization of the quinoline (**242**) to give the tetrahydro compound (**245**) occurred in refluxing AcOH or by treatment of the quinoline (**242**) with NaOMe in ethanol in the presence of air. Oxidation to yield the dihydro derivative (**187**) from compound (**245**) was achieved using LTA <74JMC244>. In a later study, the elaborated quinoline (**242**) was refluxed in methanolic HCl to deliver the tetrahydro triazin-3-one (**245**) (95%). Alternatively, cyclization in refluxing ethanol gave the tetrahydro compound (**245**) (77%) <76JHC601>.

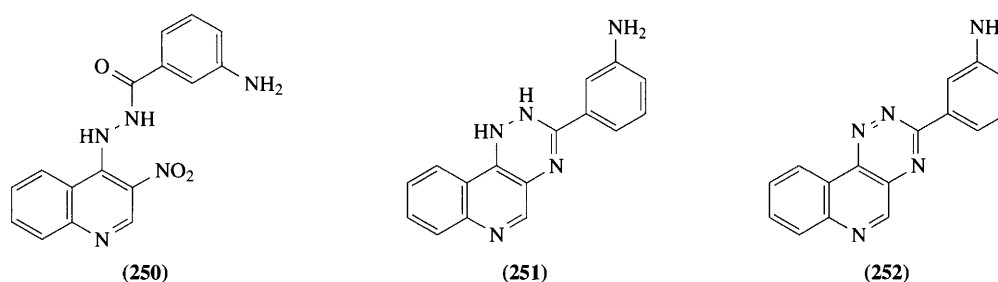


An attempt to isolate the tetrahydro (**246**) or dihydro (**247**) derivatives of the pyrido[3,4-*e*]-1,2,4-triazine ring system from the cyclization of the pyridine (**248**) failed in that the only isolable product was the aminoimidazolone (**249**). This product (**249**), however, is postulated to be derived from the desired compound (**246**) via an intramolecular reaction (Scheme 20) <76JHC601>.



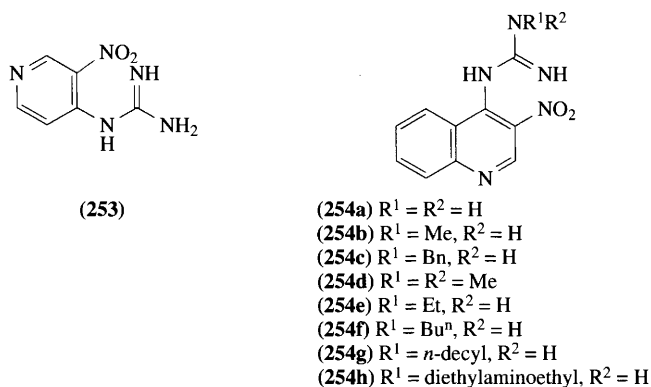
Scheme 20

Several triazinoquinolines were prepared as part of an investigation into their bacteriocidal properties. Reduction of the nitro group of compound (**250**) and concomitant cyclization gave triazine (**251**), which was subsequently dehydrogenated using $K_3Fe(CN)_6$ to yield triazinoquinoline (**252**) <84MI 717-02>.

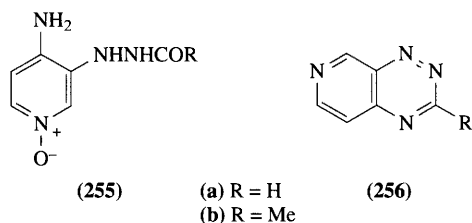


7.17.9.1.10 Pyrido[4,3-*e*]-1,2,4-triazines

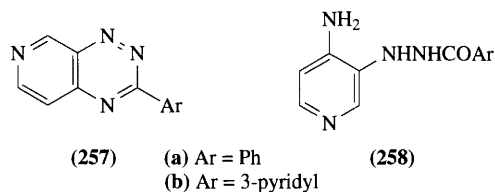
Treatment of the guanidinopyridine (**253**) with an aqueous solution of K_2CO_3 at $100^\circ C$ gave the pyrido-1,2,4-triazine 1-oxide (**83**) (88%) <71JHC47>. 3-Amino-1,2,4-triazine[6,5-*c*]quinoline *N*-oxide (**90**) was similarly prepared in 94% yield by refluxing the elaborated quinoline (**254**) in aqueous K_2CO_3 . Subsequent hydrogenation and dehydrogenation gave 3-amino-1,2,4-triazino[6,5-*c*]quinoline (**91**) <73GEP(O)2322418, 76MI 717-02>. Compounds (**91a-h**) were prepared in yields varying between 62–95% by refluxing an ethanolic solution of the precursor quinolines (**254a-h**) in the presence of NaOH <81JHC1537>.



Cyclization of the hydrazinopyridine *N*-oxides (**255a,b**) in the presence of a dehydrating agent such as MgSO_4 or P_2O_5 delivered the pyrido[1,2,4]triazines (**256a,b**) <73JHC1073>.



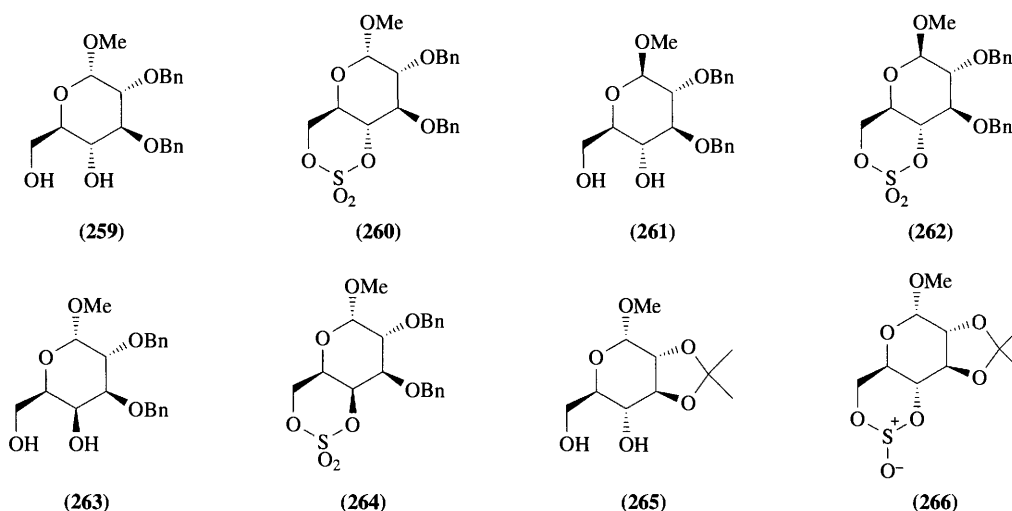
Pyrido-1,2,4-triazines (**257a,b**) were prepared via the cyclization of the corresponding aminopyridines (**258a,b**) followed by oxidation <76CR(C)487>.



7.17.9.2 Synthesis of the Second Heterocyclic Ring from [5 + 1] Atom Fragments

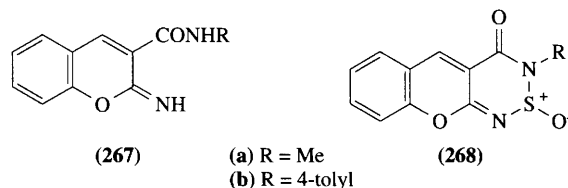
7.17.9.2.1 *Pyrano*[3,2-*d*]-1,3,2-dioxathiins

Reaction of methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside (**259**) with phenyl chlorosulfate and NaH at room temperature yielded 60% of the 4,6-cyclic sulfate (**260**). Analogously, the β -glucoside (**261**) gave the corresponding 4,6-cyclic sulfate (**262**) (67%). Methyl 2,3-di-*O*-benzyl- α -D-galactopyranoside (**263**) delivered the 4,6-cyclic sulfate (**264**) (52%) in an identical reaction <89CAR(189)123>. Reaction of SOCl_2 with the protected mannopyranose (**265**) gave the sulfoxide (**266**) <92CAR(224)193>.



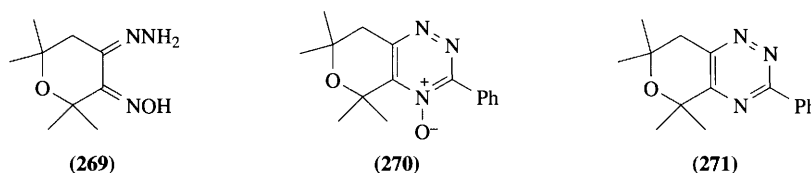
7.17.9.2.2 *Pyrano*[2,3-*c*]-1,2,6-thiadiazines

Reaction of the amides (**267a,b**) with SOCl_2 gave the 4-oxo-3,4-dihydro-1-benzopyrano[2,3-*c*]-1,2,6-thiadiazine 2-oxides (**268a,b**) in 83% and 90% yield, respectively <79CB1012>.



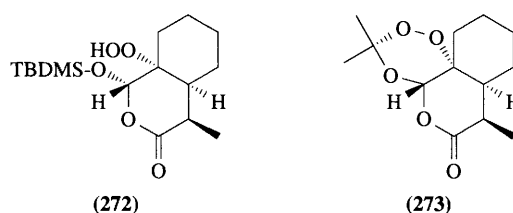
7.17.9.2.3 2H-Pyrano[3,4-e]-1,2,4-triazines

A series of 1,2,4-triazine 4-oxides was prepared according to a literature precedent. Thus, treatment of the hydrazonooxime (269) with triethyl orthobenzoate delivered the pyrano[3,4-*e*]-1,2,4-triazine 4-oxide (270). Subsequent treatment with triethyl phosphite gave the parent 1,2,4-triazine (271) <73TL1429, 81JMC490>.



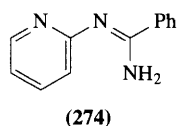
7.17.9.2.4 3H,6H-Pyrano[2,3-e]-1,2,4-trioxines

Treatment of the hydroperoxide (272) with TFA and acetone delivered the trioxane (273) (73%) <94T957>.



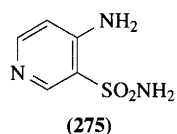
7.17.9.2.5 2H-Pyrido[2,3-e]-1,2,4-thiadiazines

1-Morpholino-3-phenylpyrido[2,3-*e*]-1,2,4-thiadiazine (165) was prepared in a yield of 32% from *N*-(2-pyridyl)benzamidinium (274) and 4,4'-thiobismorpholine <83JCS(P1)49, 83JCS(P1)55>.



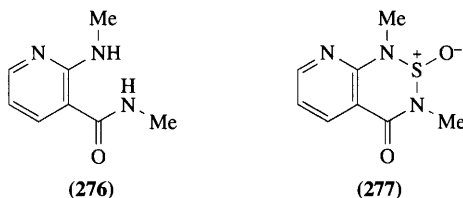
7.17.9.2.6 2H-Pyrido[4,3-e]-1,2,4-thiadiazines

2H,3H,4H-Pyrido[4,3-*e*]-1,2,4-thiadiazinone 1,1-dioxide (167) was prepared by the reaction of 3-amidosulfonyl-4-aminopyridine (275) with urea <93JMC3211>.

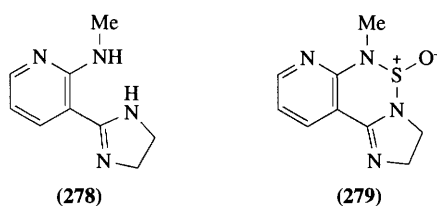


7.17.9.2.7 1H-Pyrido[2,3-c]-1,2,6-thiadiazines

Treatment of the aminonicotinamide (**276**) with SOCl_2 gave the pyrido-1,2,6-thiadiazinone 2-oxide (**277**) (56%) <85JHC193>.

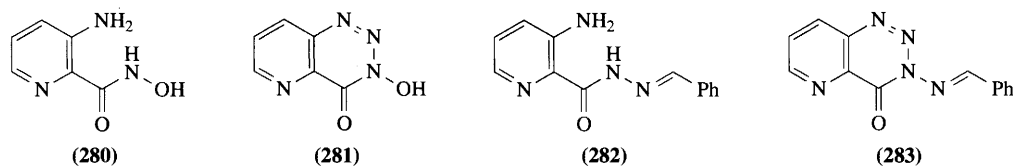


Reaction of the aminoimidazolylpyridine (**278**) with SOCl_2 gave the imidazo[1,2-*b*]pyrido[3,2-*d*]-1,2,6-thiadiazine derivative (**279**) (43%) <85SC1013>.



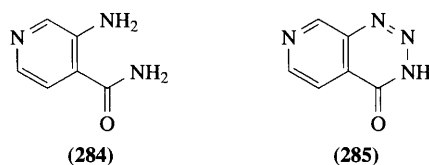
7.17.9.2.8 Pyrido[3,2-d]-1,2,3-triazines

Treatment of the hydroxamic acid (**280**) with HNO_2 yielded the pyrido-1,2,3-triazin-4-one (**281**) <60JCS2157>. Diazotization of the aminopyridine (**282**) using amyl nitrite gave the 3*H*,4*H*-pyrido[3,2-*d*]-1,2,3-triazin-4-one (**283**) <78JOC393>.



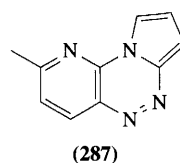
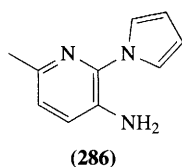
7.17.9.2.9 Pyrido[3,4-d]-1,2,3-triazines

Diazotization of 4-acetamido-3-aminopyridine (**284**) using HNO_2 gave 3*H*,4*H*-pyrido[3,4-*d*]-1,2,3-triazin-4-one (**285**) <78JOC393>.

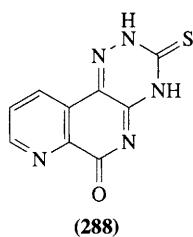


7.17.9.2.10 Pyrido[2,3-e]-1,2,4-triazines

Diazotization of the amino group of the pyrrole-substituted pyridine (**286**) using NaNO_2 in aqueous AcOH , together with a concomitant cyclization, gave the pyridotriazine (**287**) (64%) <85CPB4242>.

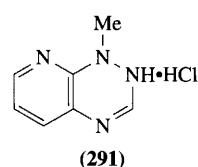
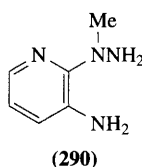
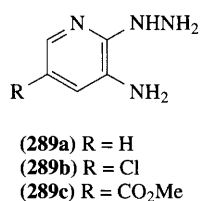


Cyclization of the picolinic acid derivative (**213b**) was achieved using NH_4OH in the presence of dcc to give the triazinopyridone derivative (**288**) (82%) <86PHA284>.



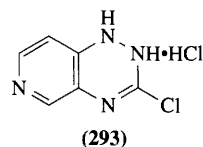
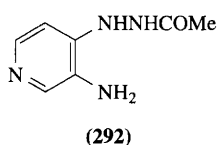
7.17.9.2.11 Pyrido[3,2-e]-1,2,4-triazines

Reaction of the hydrazinopyridines (**289a–c**) with triethylorthoformate and HCl gave 1,2-dihydropyrido-1,2,4-triazine hydrochlorides (**182a–c**) in 80–87% yield. Similar reaction of the 1-(3-amino-2-pyridyl)-1-methylhydrazine (**290**) gave the 1-methyl pyrido-1,2,4-triazine (**291**) (63%) <71JHC41>. The reaction of hydrazine (**290**) with ethyl phenylglyoxylate yielded the pyrido-1,2,4-triazine (**17a**) (68%) <87CPB80>.



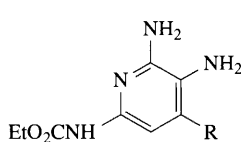
7.17.9.2.12 Pyrido[3,4-e]-1,2,4-triazines

Treatment of the hydrazinopyridine derivative (**292**) with triethyl orthoformate and concentrated HCl yielded 60% of the 1,2-dihydropyrido-1,2,4-triazine hydrochloride (**293**) <71JHC47>.

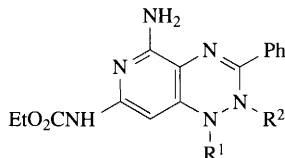


The dihydrotriazines (**295a–c**) were prepared from the hydrazinopyridine derivatives (**294a–d**) by reaction with methyl benzimidate hydrochloride in the presence of Et_3N and water. Dihydrotriazines (**295a–c**) were all converted to the pyrido[3,4-e]-1,2,4-triazine (**296**) on purification. For example, a mixture of pyridines (**294a**) and (**297**) yielded a 5 : 1 mixture of dihydrotriazine (**295a**)

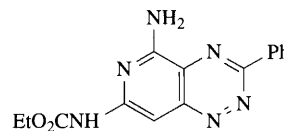
and pyrido[3,4-*e*]-1,2,4-triazine (**296**) after 19 hours. Reaction of the hydrazinopyridine (**294a**) in the absence of water gave the pyrido[3,4-*e*]-1,2,4-triazine (**296**) cleanly without the intermediacy of the dihydro compound (**295a**) <90JMC3044>.



(**294a**) R = NHNH₂
 (**294b**) R = NHNHMe
 (**294c**) R = NMeNH₂
 (**294d**) R = NMeN=CHPh
 (**297**) R = NH₂



(**295a**) R¹ = R² = H
 (**295b**) R¹ = H, R² = Me
 (**295c**) R¹ = Me, R² = H



(**296**)

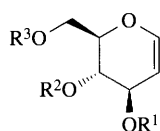
7.17.9.3 Synthesis of the Second Heterocyclic Ring from [4 + 2] Atom Fragments

7.17.9.3.1 1H,6H-Pyrano[3,2-*e*]-1,3,4-oxadiazines

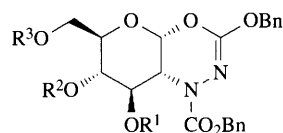
The cycloaddition of dibenzoyl azodicarboxylate with a variety of glycals has been investigated. Dihydropyran (**298**), when irradiated at 350 nm in the presence of dibenzoyl azodicarboxylate, gave a 70% yield of the cycloadduct (**111**). Triacetoxylglycal (**299a**) gave a 3 : 2 mixture of diastereomeric cycloadducts, the major diastereoisomer being (**300a**) in 20% yield, after being heated at 90 °C in the presence of the azodicarboxylate for 2 weeks. The dimethoxy derivative (**299b**) gave a 4 : 1 mixture of diastereoisomers, the major diastereoisomer being (**300b**) in a yield of 60% after irradiation with the azodicarboxylate. The diacetoxyl glycal (**299c**) did not react but glycals (**299d**) and (**301**) were converted diastereoselectively to the corresponding cycloadducts (**113**) and (**302**) in yields of 71% and 86%, respectively, after irradiation with the azodicarboxylate at 350 nm <87JA285, 89JA2995>.



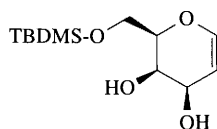
(**298**)



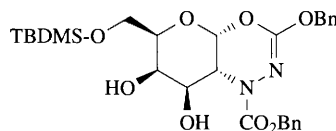
(**299a**) R¹ = R² = R³ = Ac
 (**299b**) R¹ = R² = Me, R³ = Ac
 (**299c**) R¹ = R² = Ac, R³ = TBDMS
 (**299d**) R¹ = R² = R³ = TBDMS



(**300a**) R¹ = R² = R³ = Ac
 (**300b**) R¹ = R² = Me, R³ = Ac
 (**300c**) R¹ = R² = Ac, R³ = TBDMS
 (**113**) R¹ = R² = R³ = TBDMS



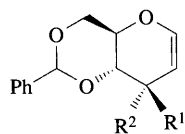
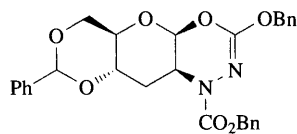
(**301**)



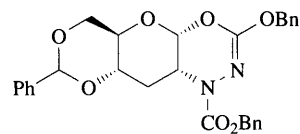
(**302**)

4,6-Protected glycal (**303a**) gave a 70% yield of the cycloadducts (**304**) and (**305**) in a ratio of 4 : 1. Glycal (**303b**) gave a 15 : 1 mixture of diastereomeric cycloadducts, the major diastereoisomer being (**114**) in a yield of 70%, while glycal (**303c**) was converted diastereoselectively to the cycloadduct (**306**) in 70% yield. Finally, disaccharide (**307**) reacted diastereoselectively to deliver a 94% yield of the cycloadduct (**115**) <87JA285, 89JA2995>.

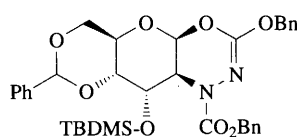
A practical use of this process has been detailed. Glycal (**308**) reacted with dibenzoyl azodicarboxylate to deliver the cycloadduct (**119**) (50%). The elaborated glycal (**309**) also underwent cycloaddition to give cycloadduct (**310**) (84%) <89JA5810>.

(303a) $R^1 = R^2 = H$ (303b) $R^1 = \text{TBDMS-O}, R^2 = H$ (303c) $R^1 = H, R^2 = \text{TBDMS-O}$ 

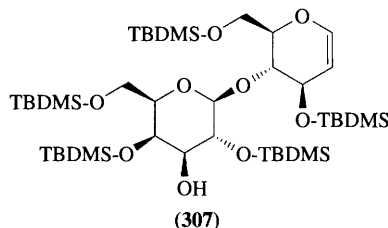
(304)



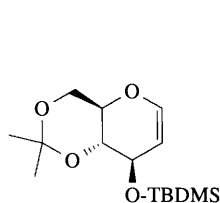
(305)



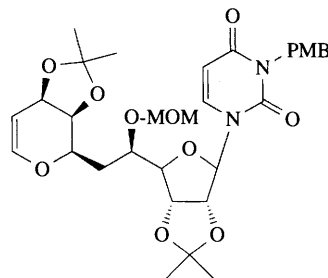
(306)



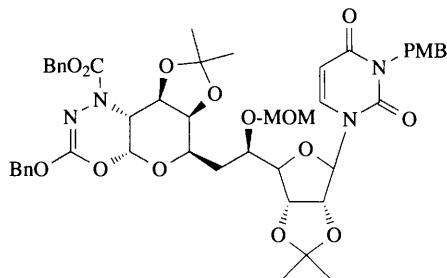
(307)



(308)



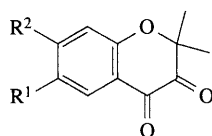
(309)



(310)

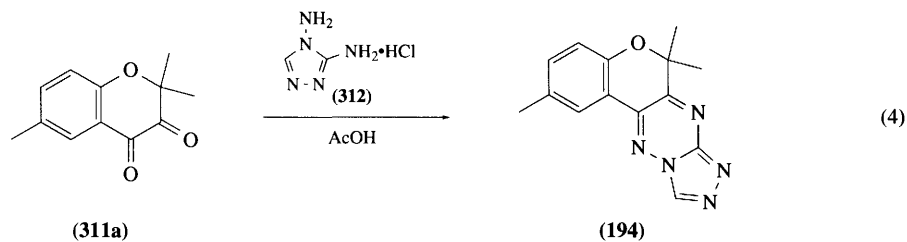
7.17.9.3.2 2H-Pyrano[3,4-e]-1,2,4-triazines

2,2,6-Trimethylchroman-3,4-dione (**311a**) reacted with semicarbazide hydrochloride in refluxing AcOH to give a mixture of pyrano-1,2,4-triazin-3-one (**131**) and the isomeric triazin-3-one (**132**) in a ratio of 45:55 <85JHC33>. 2,2,6-Trimethylchroman-3,4-dione (**311a**) also reacted with formimidoyl hydrazine in methanol in the presence of Et_3N to give the pyrano-1,2,4-triazine (**135**) (54%) <86JHC721>.

(311a) $R^1 = \text{Me}, R^2 = H$ (311b) $R^1 = H, R^2 = \text{Me}$ (311c) $R^1 = H, R^2 = \text{MeO}$

The reaction of 2,2,6-trimethylchroman-3,4-dione (**311a**) with aminoguanidine has also been investigated. In refluxing AcOH, compound (**311a**) reacted with aminoguanidine carbonate to yield 80% of a mixture of the aminotriazine (**145a**) as a 2:1 mixture with the isomeric compound (**146a**). Reaction of chroman-3,4-dione (**311a**) with aminoguanidine hydrochloride in the presence of NaOH gave only the desired aminotriazine (**145a**) (23%). Analogous reactions of 2,2,7-trimethylchroman-3,4-dione (**311b**) and 2,2-dimethyl-7-methoxychroman-3,4-dione (**311c**) gave the corresponding aminotriazines (**145b**) and (**145c**) in 72% and 81% yield, respectively <86JHC721, 90JHC1917>.

3,4-Diamino-(4*H*)-1,2,4-triazole hydrochloride (**312**) reacted in AcOH with 2,2,6-trimethylchroman-3,4-dione (**311a**) to give the pyrano-1,2,4-triazine derivative (**194**) (32%) (Equation (4)) <86JHC721>.



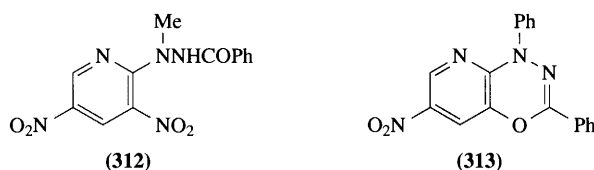
7.17.9.3.3 1H-Pyrano[4,3-e]-1,2,4-triazines

2,2,6-Trimethylchroman-3,4-dione (**311a**) reacted with semicarbazide hydrochloride in refluxing AcOH to give a mixture of pyrano-1,2,4-triazin-3-one (**131**) and the isomeric triazin-3-one (**132**) in a ratio of 45:55. Treatment of compound (**311a**) with thiosemicarbazide hydrochloride under analogous conditions yielded only pyrano-1,2,4-triazin-3-thione (**151**) <85JHC33>.

2,2,6-Trimethylchroman-3,4-dione (**311a**) also reacted with aminoguanidine carbonate to give the aminotriazine (**146a**) (67%). Analogous reactions of 2,2,7-trimethylchroman-3,4-dione (**311b**) and 2,2-dimethyl-7-methoxychroman-3,4-dione (**311c**) gave the corresponding aminotriazines (**146b**) and (**146c**) in 55% and 72% yield, respectively <86JHC721, 90JHC1917>.

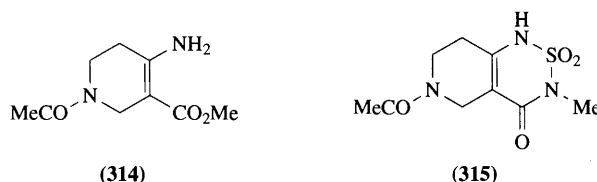
7.17.9.3.4 1H-Pyrido[2,3-e]-1,3,4-oxadiazines

Treatment of the hydrazidopyridine derivative (**312**) with Et₃N in refluxing DMF gave the pyrido-1,3,4-oxadiazine (**313**) (85%) <80JOC3677>.



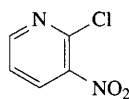
7.17.9.3.5 1H-Pyrido[4,3-c]-1,2,6-thiadiazines

Treatment of the enamino ester (**314**) with *N*-methylsulfamoyl chloride gave a 29% yield of pyrido-1,2,6-thiadiazine (**315**) <78JOC3824>.

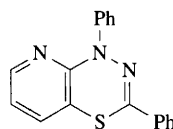


7.17.9.3.6 1H-Pyrido[2,3-e]-1,3,4-thiadiazines

Reaction of 2-chloro-3-nitropyridine (**316**) with *N*-phenylbenzothiohydrazide and Et₃N gave 1,3-diphenyl-1*H*-pyrido[2,3-*e*]-1,3,4-thiadiazine (**317**) (70%). The pyridine (**316**) reacted with dithizone under identical conditions to deliver the pyridothiadiazine (**52**) (75%). Compounds (**317**) and (**52**) are believed to be formed via a Smiles rearrangement <80JOC3677>.

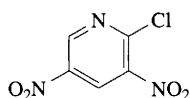


(316)

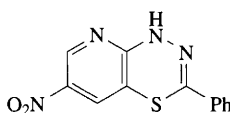


(317)

Condensation of phenylthiohydrazide with 2-chloro-3,5-dinitropyridine (**318**) yielded the pyrido-1,3,4-thiadiazine (**319**) (22%) via a Smiles rearrangement <81JHC799>.



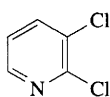
(318)



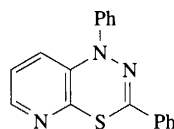
(319)

7.17.9.3.7 1H-Pyrido[3,2-e]-1,3,4-thiadiazines

Reaction of *N*-thiobenzoyl-*N'*-phenylhydrazine with 1,2-dichloro-substituted pyridines provides ready access to the pyrido[3,2-*e*]-1,3,4-thiadiazine ring system. For example, 2,3-dichloropyridine (**320**) yields 1*H*-1,3-diphenylpyrido[3,2-*e*]-1,3,4-thiadiazine (**321**) <77USP4025510>.

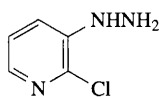


(320)

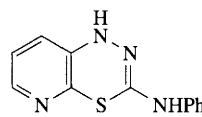


(321)

After several attempts to attain the pyridothiadiazine ring system, 2-chloro-3-hydrazinopyridine (**322**) was reacted with phenyl isothiocyanate in methanol to give the amino-substituted pyrido[3,2-*e*]-1,3,4-thiadiazine (**323**) (30%) <88M333>.



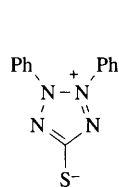
(322)



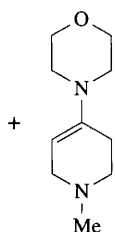
(323)

7.17.9.3.8 1H-Pyrido[4,3-e]-1,3,4-thiadiazines

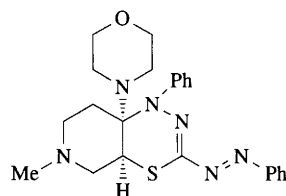
Dehydrodithizone (**14**) reacted with the morpholino enamine (**324**) to give the pyrido-1,3,4-triazine (**13**) (64%) (Equation 5) <76JCS(P1)1673>.



(14)



(324)

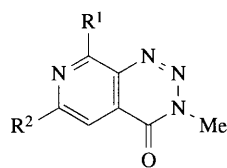


(13)

(5)

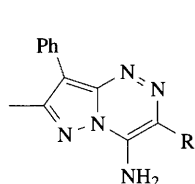
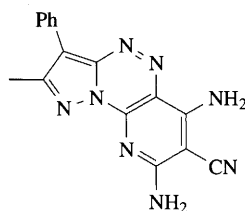
7.17.9.3.9 Pyrido[3,4-d]-1,2,3-triazines

The triazinone derivatives (**325a-c**) were prepared by the reaction of 3-nitropyridine with KCN in methanol, followed by treatment with diazomethane <83YZ1129>.

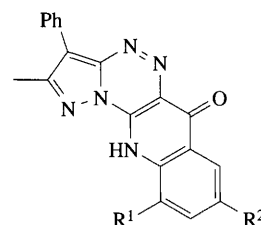
(325a) $R^1 = R^2 = H$ (325b) $R^1 = H, R^2 = MeO$ (325c) $R^1 = MeO, R^2 = H$

7.17.9.3.10 Pyrido[2,3-*e*]-1,2,4-triazines

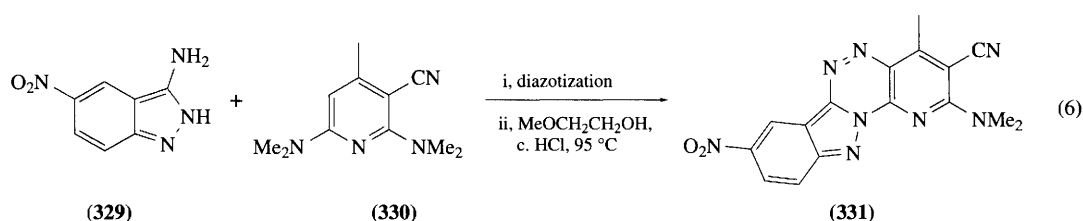
Malononitrile reacted with 7-amino-6-cyano-3-methyl-2-phenylpyrazolo[5,1-*c*]-1,2,4-triazine (326a) in ethanol to give the pyridotriazine (327) (70%). The reaction is thought to proceed via initial attack of malononitrile at the cyano group of the precursor (326a), followed by concomitant cyclization <83G219>. A similar series of compounds were obtained by the reaction of several aniline derivatives with 7-amino-6-ethoxycarbonyl-3-methyl-2-phenylpyrazolo[5,1-*c*]-1,2,4-triazine (326b). Thus, reaction with 1,2-diaminobenzene, 1-amino-4-chlorobenzene, and 1-amino-3-hydroxybenzene yielded pyridotriazinones (328a-c), respectively <84PHA432>.

(326a) $R = CN$ (326b) $R = CO_2Et$ 

(327)

(328a) $R^1 = NH_2, R^2 = H$ (328b) $R^1 = H, R^2 = Cl$ (328c) $R^1 = OH, R^2 = H$

The reaction of diazotized 3-amino-5-nitroindazole (329) with the substituted pyridine (330) under suitable conditions yielded the pyrido[2,3-*e*]-1,2,4-triazine (331). This method has also been used to prepare several pyrido[4,3-*e*]-1,2,4-triazines (Equation 6) <74GEP(O)2417916>.

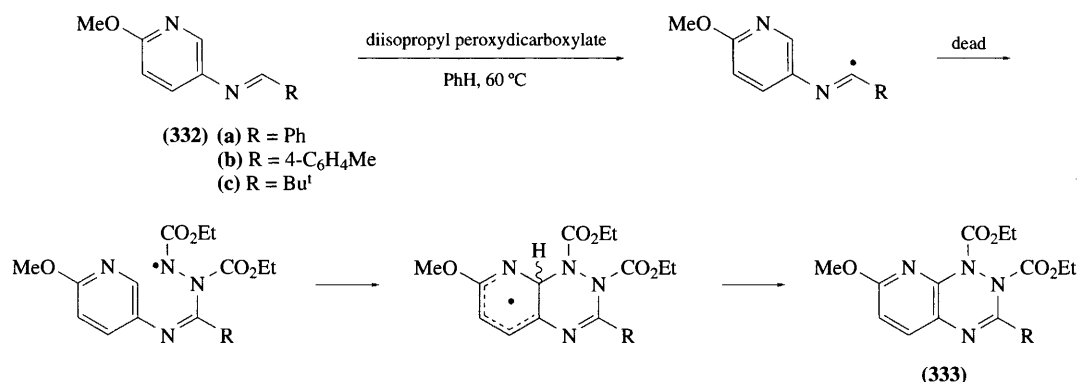


7.17.9.3.11 Pyrido[3,2-*e*]-1,2,4-triazines

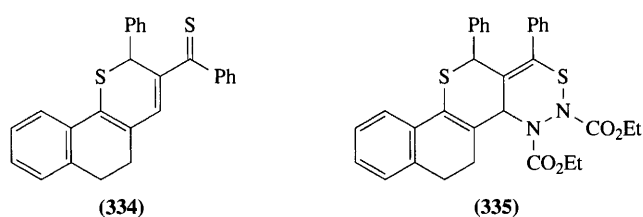
Three pyrido[3,2-*e*]-1,2,4-triazines (333a-c) were prepared from the imines (332a-c) via a free radical annulation reaction onto the nitrogen–nitrogen double bond of dead. For example, compound (333a) is obtained from imine (332a) in 47% yield. The mechanism by which this reaction takes place is shown in Scheme 21 <89CC757>.

7.17.9.3.12 2H,4H-Thiopyrano[4,3-*d*]-1,2,3-thiadiazines

The dienic thioketone (334) reacted with dead to deliver the cycloadduct (335), a substituted thiopyrano[4,3-*d*]-1,2,3-thiadiazine, in 59% yield <90BCJ2540>.

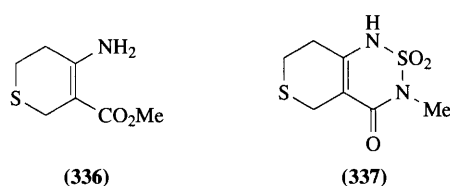


Scheme 21



7.17.9.3.13 Thiopyrano[4,3-c]-1,2,6-thiadiazines

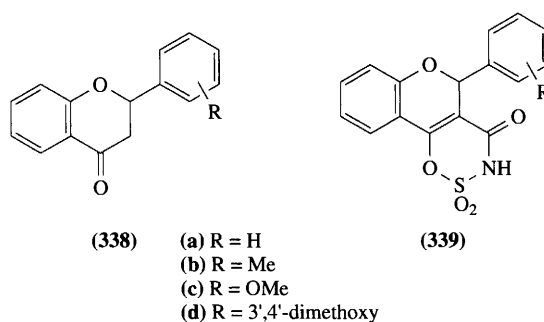
Treatment of the enamino ester (336) with *N*-methylsulfamoyl chloride gave a 77% yield of the thiopyrano-1,2,6-thiadiazine (337) <78JOC3824>.



7.17.9.4 Synthesis of the Second Heterocyclic Ring from [3 + 3] Atom Fragments

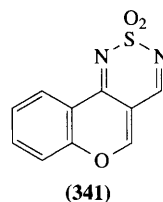
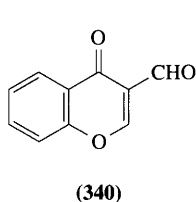
7.17.9.4.1 5H-Pyrano[3,4-e]-1,2,3-oxathiazines

Chlorosulfonyl isocyanate reacted with a variety of flavanones (338a-d) to give the benzo-pyrano[3,4-e]-1,2,3-oxathiazinones (339a-d) in 57–66% yield <87IJC(B)1082>.



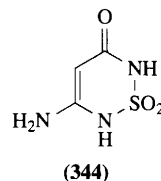
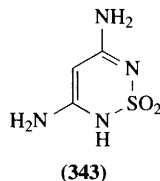
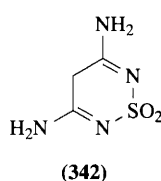
7.17.9.4.2 Pyrano[4,3-c]-1,2,6-thiadiazines

3-Chromonecarboxaldehyde (340) reacted with SO₂(NH₂)₂ in the presence of NaOMe to give the benzopyranothiadiazine dioxide (341) (80%) <77AP(310)417>.



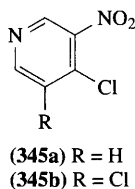
7.17.9.4.3 1H-Pyrido[2,3-c]-1,2,6-thiadiazines

1*H*,4*H*-Diaminothiadiazone dioxide (342) reacts with 1,3-dicarbonyl compounds to deliver pyrido[2,3-*c*]-1,2,6-thiadiazines, for example (51b) <86CS607>. The pyridothiadiazone 2,2-dioxides (21a,b) and (22a,b) were prepared by reaction of 3-substituted 5-amino-1,2,6-thiadiazine 1,1-dioxides (343) or (344) with the corresponding β -keto ester <88AQ89>.



7.17.9.4.4 Pyrido[4,3-e]-1,2,4-triazines

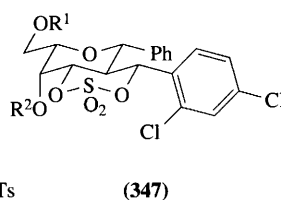
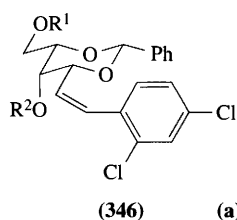
The pyrido-1,2,4-triazines (83) and (85) were prepared in one step from the corresponding nitropyridines (345a,b) by treatment with NaOMe and guanidine, followed by base-catalyzed cyclization <76MI 717-03>.



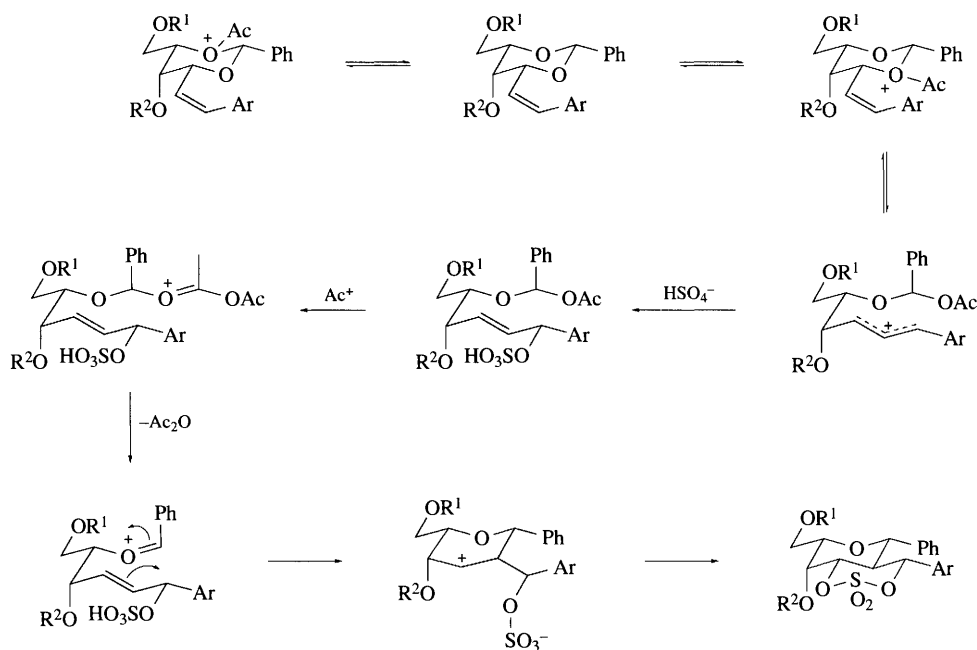
7.17.9.5 Synthesis of the Second Heterocyclic Ring by Miscellaneous Routes

7.17.9.5.1 4H,5H-Pyrano[4,3-d]-1,3,2-dioxathiins

A series of C-glycosylbenzene compounds containing the pyranodioxathiin ring system may be prepared by acetolysis of the corresponding 2,4-*O*-benzylidene hexitol derivatives using acetic anhydride and sulfuric acid via an intramolecular rearrangement, albeit in a very low yield. Thus, acetal (346a) is converted to the pyranodioxathiin (347a) in 3% yield. Similarly, acetal (346b) gives the pyranodioxathiin (347b) (2%). The differentially protected acetal (346c) gives pyranodioxathiin (347c) (14%). The mechanism by which these reactions are thought to proceed is shown in Scheme 22 <92CAR(232)17, 93CAR(239)117>.



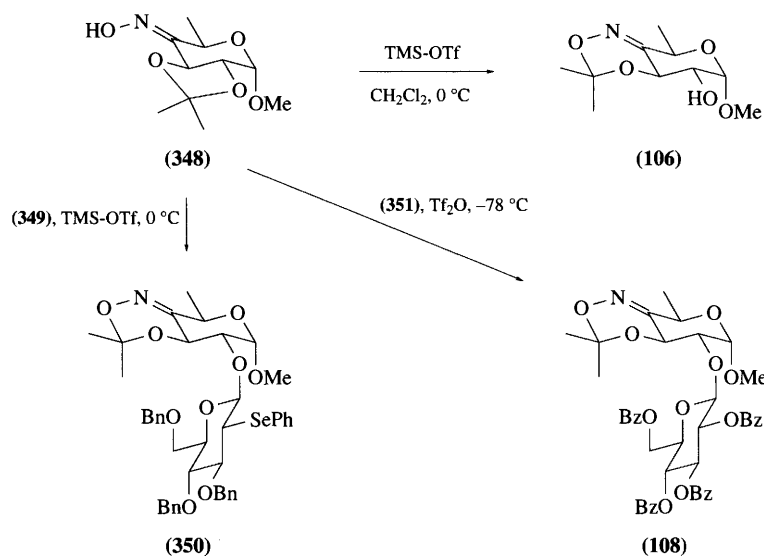
- (a) R¹ = R² = Ts
(b) R¹ = Ac, R² = Me
(c) R¹ = Ac, R² = Ms



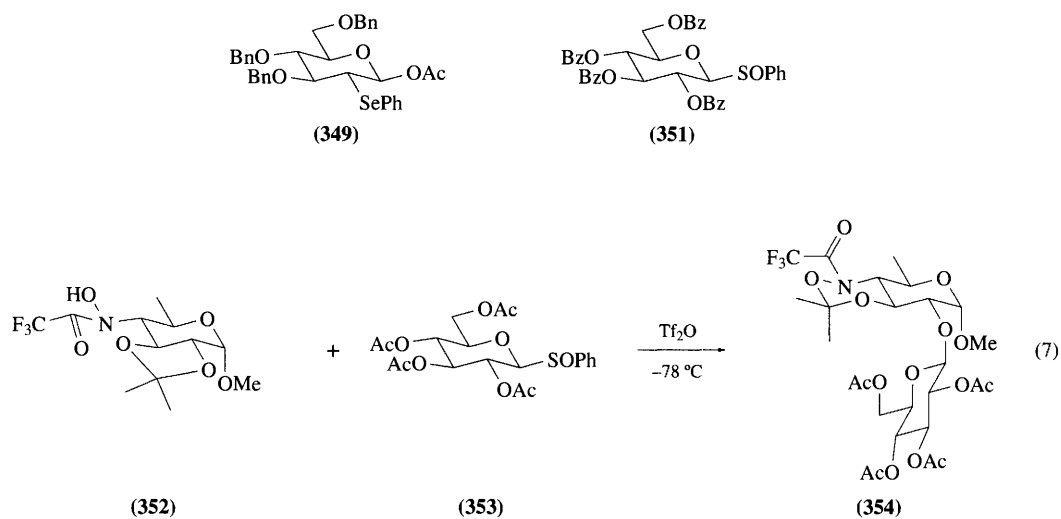
Scheme 22

7.17.9.5.2 1H,6H-Pyrano[3,4-c]-1,5,2-dioxazine

The pyrano-1,5,2-dioxazine ring system has been prepared via a rearrangement of carbohydrate derivatives. Thus, treatment of the oxime (348) with trimethylsilyl triflate at 0 °C delivered the dioxazine (106) (90%). This transformation may also be accompanied by glycoside formation: reaction of oxime (348) with compound (349) in the presence of trimethylsilyl triflate gave the disaccharide (350) (57%). Similarly, reaction of oxime (348) with sulfoxide (351) in the presence of Tf₂O delivered the corresponding disaccharide (108) (95%) (Scheme 23). Alternatively, carbohydrate (352) reacted with the sulfoxide (353) in the presence of Tf₂O to give the disaccharide (354) (61%) (Equation 7) <92CC1494>.

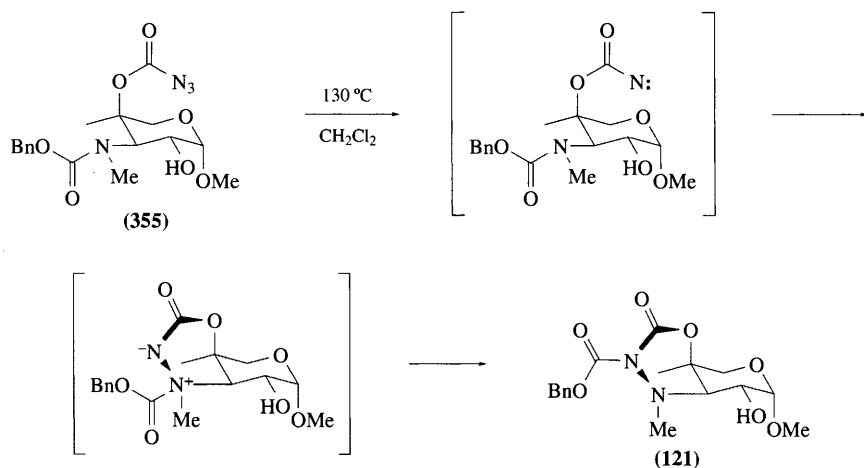


Scheme 23



7.17.9.5.3 Pyrano[4,3-*e*]-1,3,4-oxadiazines

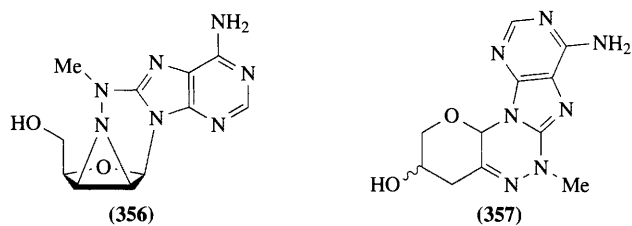
Thermolysis of the azide (355) yielded 22% of the pyrano[4,3-*e*]-1,3,4-oxadiazine (121) via an intramolecular nitrene insertion and migration of the protecting group (Scheme 24) <82JOC523>.



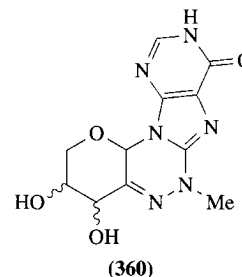
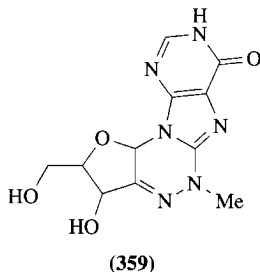
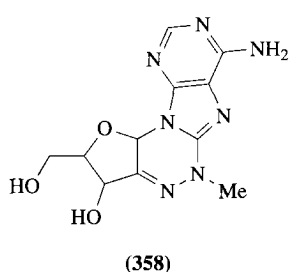
Scheme 24

7.17.9.5.4 1H-Pyrano[2,3-*e*]-1,2,4-triazines

The complex aziridine (356) underwent a rearrangement on acid hydrolysis to deliver 34% of the pyrano-1,2,4-triazine (357) <82JOC4465>.

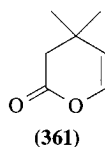


The adenylyl dehydrocyclonucleoside (**358**) was transformed into compounds (**127**) and (**128**), presumably by opening of the furanoside moiety and subsequent closure to form the six-membered ring. The inosine derivative (**359**) was similarly converted into compound (**360**) <82MI 717-01>.

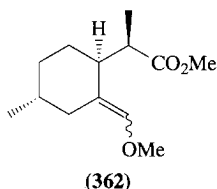


7.17.9.5.5 3H,6H-Pyran[2,3-e]-1,2,4-trioxines

Reaction of the pyrone (**361**) with *para*-benzoquinone and laser irradiation in an oxygen atmosphere gave a mixture of products, including the trioxanes (**40**) and (**41**) in yields of 28% and 9%, respectively <88JOC4986>.



Compound (**362**) gave the trioxane (**19**) (15%) when reacted with singlet oxygen in the presence of acetaldehyde, using rose bengal as sensitizer, followed by treatment with HCl <88CC372>.

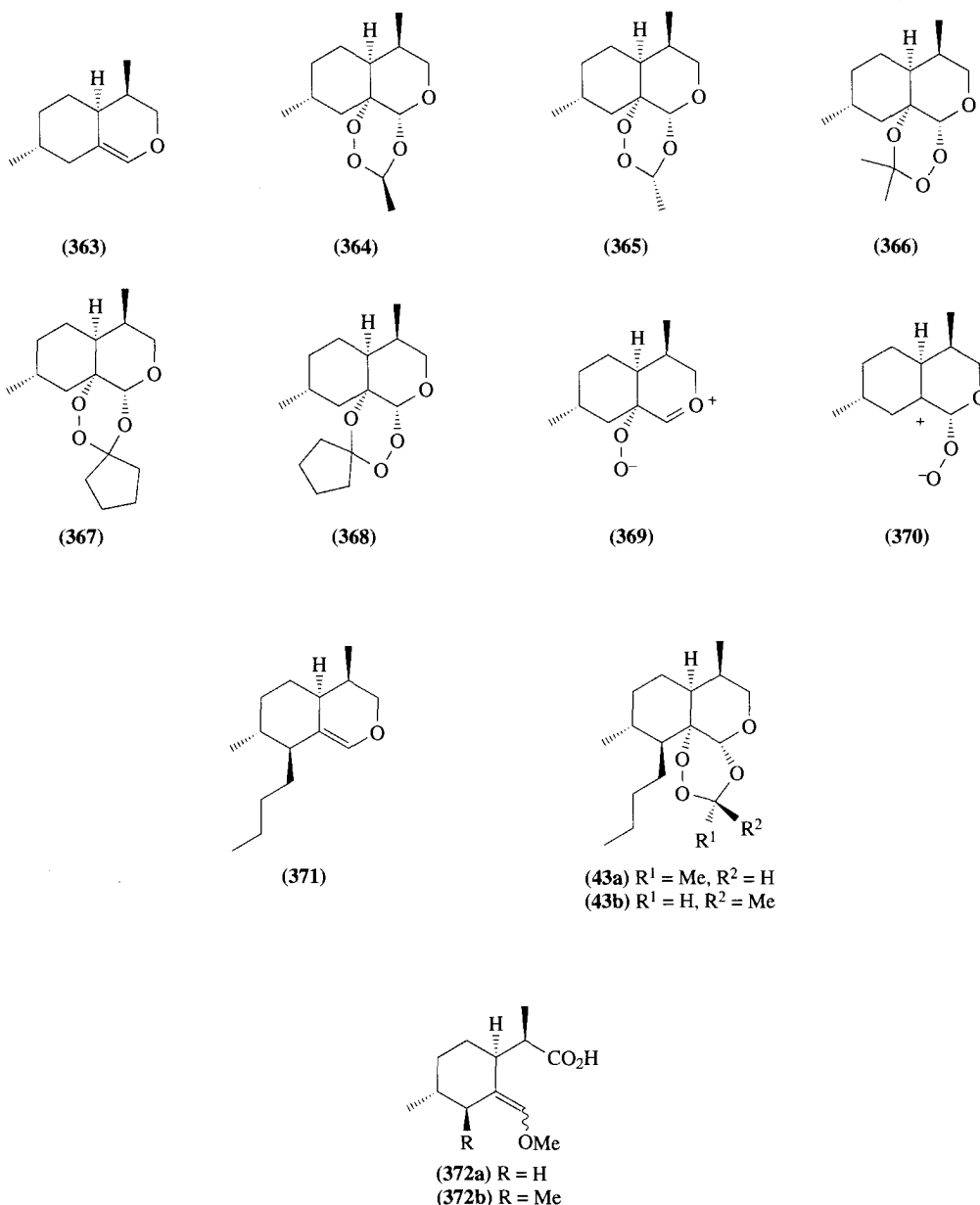


The reaction of compound (**363**) with singlet oxygen in the presence of several aldehydes and ketones has been studied. With acetaldehyde, dihydropyran (**363**) gave the trioxanes (**364**) and (**365**) in the ratio of 12:1 (17% overall yield). Compound (**363**) could be reacted with singlet oxygen in dichloromethane and subsequently treated with trimethylsilyl triflate and acetone to give trioxanes (**18**) and (**366**) in yields of 59% and 5%, respectively. Dihydropyran (**363**) also gave trioxanes (**367**) and (**368**) in 61% and 8% yield, respectively, from reaction with singlet oxygen and subsequent treatment with trimethylsilyl triflate and cyclopentanone. All of the trioxane products are postulated to have arisen via the zwitterionic intermediates (**369**) or (**370**) <88HCA2042>.

In an analogous reaction to that described above, compound (**371**) was reacted with singlet oxygen in the presence of acetaldehyde, giving a mixture of the trioxanes (**43a**) and (**43b**) in a ratio of 1.3:1 and an overall yield of 31% <90H(31)2125>.

Ozonolysis of the model compounds (**372a,b**) followed by treatment with amberlite 15 in the presence of an aldehyde or a ketone yielded several pyrano-1,2,4-trioxanes. Reaction of compounds (**372a,b**) in the presence of acetone delivered the corresponding trioxanes (**44**) and (**20**) in yields of 25% and 32%, respectively. An analogous reaction of compound (**372a**) in the presence of acetaldehyde gave the trioxane (**44**) (23%) <90CC1487>.

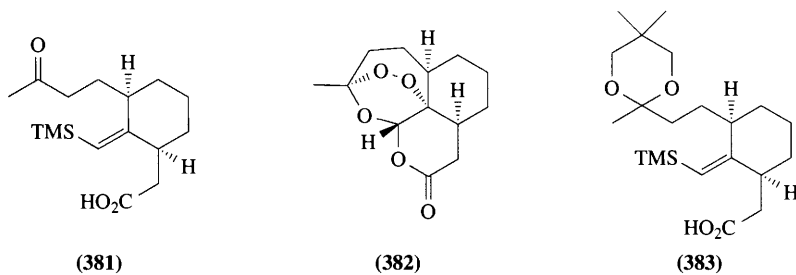
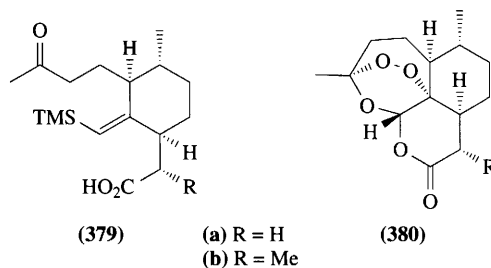
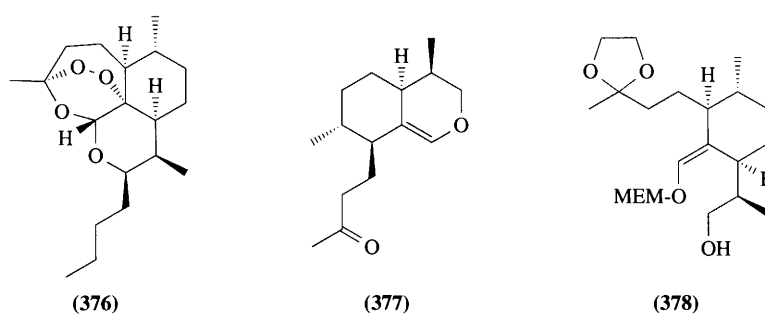
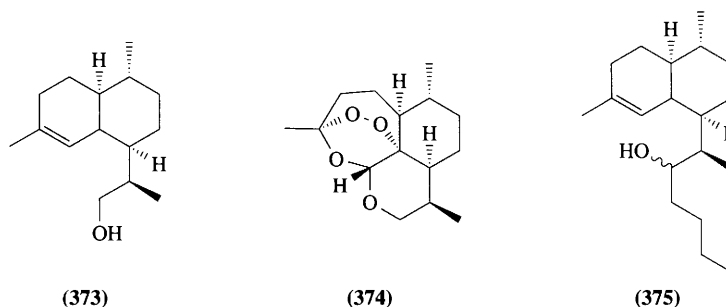
The main thrust of much research into the synthesis of the 3H,6H-pyran[2,3-e]-1,2,4-trioxine ring system (**10**) has been directed towards the total synthesis of artemisinin (**9**), a naturally occurring pyrano-1,2,4-trioxane, and its analogues. Reaction of compound (**373**) with singlet oxygen, followed by treatment with strongly acidic Dowex resin, delivered the artemisinin precursor (**374**) (18%) <89TL5973>. Analogous treatment of compound (**375**) gave the trioxane (**376**) (12%) <90SL743>. The



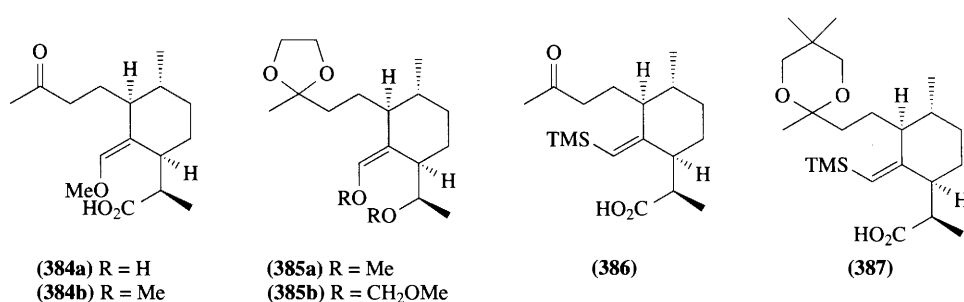
reaction of singlet oxygen with compound (377) and subsequent treatment with trimethylsilyl triflate gave trioxane (374) (62%) <90CC726>. Compound (378) also reacted with singlet oxygen and delivered trioxane (374) (65%) after treatment of the reaction mixture with CSA <92TL1029>.

Ozonolysis may also be used to form artemisinin analogues. Ozonolysis of compounds (379a,b), followed by subsequent treatment with TFA, gave the trioxanes (380a,b) in 39% and 37% yield, respectively <87TL4629>. Amberlite 15 was used as the acidic component of the process to convert compound (381) to the trioxane (382) in a yield of 53% <89JOC1792>. Ozonolysis of compound (383), followed by treatment with silica and aqueous H_2SO_4 , gave a 61% yield of trioxane (382) <92JA974>.

Finally and most notably, many total syntheses of the natural product artemisinin (9) have included the incorporation of oxygen as the crucial synthetic step. Compound (384a) delivered artemisinin in a yield of 30% after reaction with singlet oxygen and subsequent treatment with formic acid <83JA624>. An analogous reaction of its methyl ester (384b), though using HClO_4 , gave artemisinin in 28% yield <86T819>. CSA was used to convert the intermediate formed by reaction of compounds (385a,b) with singlet oxygen into artemisinin in yields between 30% and 35% <92TL1029>. Ozonolysis of compound (386) followed by treatment with TFA delivered

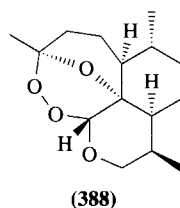


artemisinin in a yield of 37% ^{<87TL4629>}. Compound (387) was similarly reacted with ozone and subsequent treatment with silica followed by aqueous H₂SO₄ gave a 35% yield of artemisinin ^{<92JA974>}. The latter methodology has been used to prepare a wide range of artemisinin analogues ^{<93JMC4264>}.



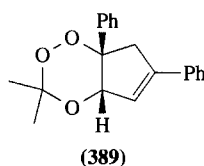
7.17.9.5.6 3H,5H-Pyrano[3,2-e]-1,2,4-trioxines

Pyrone (361) reacted with *para*-benzoquinone when subjected to laser irradiation in an oxygen atmosphere to give a mixture of products which included the trioxane (42) (18%) <88JOC4986>. Reaction of compound (371) with singlet oxygen, followed by treatment of the reaction mixture with trimethylsilyl triflate, gave the trioxane (388) (6%) <90CC726>.



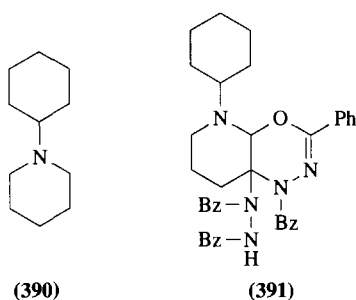
7.17.9.5.7 3H,5H-Pyrano[3,4-e]-1,2,4-trioxines

Ozonolysis of the cyclopenta-1,2,4-trioxine (389) in dichloromethane at -78°C delivered compounds (15) and (16) in yields of 43% and 27%, respectively. Trioxane (16) was formed via oxidation of the bridgehead phenyl moiety of compound (389) <86HCA941>.



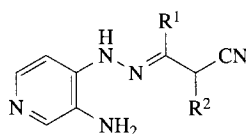
7.17.9.5.8 1H-Pyrido[3,2-e]-1,3,4-oxadiazines

Reaction of the tertiary amine (390) with three equivalents of dibenzoyldiimide yielded the pyrido-1,3,4-oxadiazine (391) (65%) via the intermediacy of an enamine generated from the amine (390) <77JCS(P2)1977>.



7.17.9.5.9 Pyrido[4,3-e]-1,2,4-triazines

Treatment of the pyridylhydrazones (392a-d) with ethanolic NaOH delivered the pyrido-1,2,4-triazine oxides (88a-d) in 52–87% yield <76JPR835>.

(392a) $R^1 = \text{Ph}$, $R^2 = \text{Me}$ (392b) $R^1 = \text{Ph}$, $R^2 = \text{H}$ (392c) $R^1 = \text{Et}$, $R^2 = \text{Me}$ (392d) $R^1 = \text{Me}$, $R^2 = \text{H}$

7.17.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER BICYCLIC RING SYSTEM

7.17.10.1 Pyrido[4,3-*e*]-1,4,2-dioxazines

The cycloadducts (**12a–d**) all rearrange thermally to give the pyrido[4,3-*e*]-1,4,2-dioxazines (**11a–d**) <85JOC2080>.

7.17.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND COMPARISON OF THE ROUTES AVAILABLE

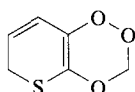
It appears that, apart from such specialized methods of synthesis that have been developed as part of an overall effort to prepare analogues of artemisinin (**9**), the most popular and effective general methods for preparing the ring systems described involve the cyclization of a ring component that contains [6 + 0] ring atoms or the insertion of a one atom unit in a [5 + 1] annulation process. These general methods have found wide use, notably in the preparation of triazine-based compounds.

The use of singlet oxygen and ozone in the preparation of the trioxane-based ring systems is a novel departure from traditional methods of chemical synthesis and have provoked wider studies into the mechanism of such processes. Though studied by a handful of workers, these methods of preparation have found wide applicability in the synthesis of a wide range of compounds useful for the treatment of malaria.

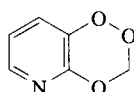
7.17.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Artemisinin (**9**), a naturally occurring compound, used in traditional Chinese medicine, has been the subject of much research and development. It is a potent antimalarial that is effective against *Plasmodium* species which are resistant to other forms of drug therapy. However, artemisinin is not available in large quantities from natural sources and its therapeutic profile could be improved by better solubility. Hence, many artemisinin analogues have been synthesized and tested. The pyrano-1,2,4-trioxine ring system (**10**) appears to be crucial to the antimalarial activity of artemisinin and its analogues <89MI 717-01, 92CSR85, 93MI 717-01, 93MI 717-02, 93MI 717-03, 93MI 717-04, 93MI 717-05, 93MI 717-06, 94MI 717-01, 94MI 717-02, 94MI 717-03, 94MI 717-04>.

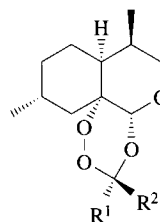
A range of artemisinin analogues have been prepared, including examples incorporating the 3*H*,6*H*-pyrano[2,3-*e*]-1,2,4-trioxine (**10**), 3*H*,6*H*-thiopyrano[2,3-*e*]-1,2,4-trioxine (**393**), and 3*H*-pyrido[2,3-*e*]-1,2,4-trioxine (**394**) ring systems <88MIP8804660>. A patent describing artemisinin analogues with the general structure (**395**) claims that they also possess general antiparasitic activity against protozoa and nematode parasites, enabling their use in the treatment of toxoplasmosis, pneumolystosis, leishmaniasis, and onchocerciasis <89EUP335717>.



(393)

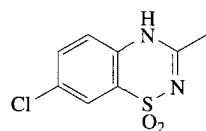


(394)

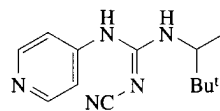


(395)

A series of 3-(alkylamino)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**168a–j**) that are related to diazoxide (**396**) (a compound which induces hyperglycemia *in vivo* through decreased insulin secretion and is a potent pancreatic K_{ATP} channel opener) and pinacidil (**397**) were prepared and tested as inhibitors of insulin release from rat pancreatic islets. Of the compounds tested, BPDZ 44 (**168g**) was chosen for further study as a potential probe for K_{ATP} channels. The compounds tested were the most powerful inhibitors of insulin release reported at that time <93JMC3211>.



(396) diazoxide

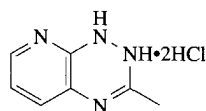


(397) pinacidil

BPDZ 44 (**168g**) has undergone trials to investigate its effects on ^{86}Rb outflow, ^{45}Ca outflow, ^{45}Ca uptake, and insulin release from rat pancreatic islets as compared to diazoxide (**396**). The effects of BPDZ 44 on cationic and secretory events were much more marked than those of diazoxide. BPDZ 44 has again been put forward as a valuable tool for the study of K_{ATP} channels <94E830>. A more detailed study concluded that BPDZ 44 inhibits the release of insulin by activating ATP-sensitive potassium channels. Such an activation leads to a decrease in calcium influx and, hence, a reduction in the intracellular calcium concentration <94MI 717-05>.

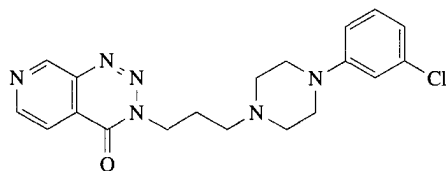
3-Chloro-1,2,4-triazino[5,6-*c*]quinoline (**186**) was found to be as active as nystatin against several species of *Candida* and against *Torulopsis glabrata* <74JMC244>.

1,2-Dihydro-3-methylpyrido[3,2-*e*]-1,2,4-triazine dihydrochloride (**398**) has been shown to be a potent antifungal agent both *in vitro* and *in vivo* in the treatment of a variety of pathogenic fungi <85MI 717-01>. A total of 53 3-substituted pyrido[3,4-*e*]-1,2,4-triazine derivatives and three 3-substituted pyrido[3,2-*e*]-1,2,4-triazine derivatives, synthesized using well-established methods, were thoroughly tested as potential antifungal agents against strains of *Candida*, *Aspergillus*, *Mucor*, and *Trichophyton* species. Several analogues had *in vitro* antifungal activity that was equal to or greater than the widely used compounds miconazole and nystatin, though none of the compounds tested were as potent as amphotericin B <88ANY(544)101, 89JMC2474>.

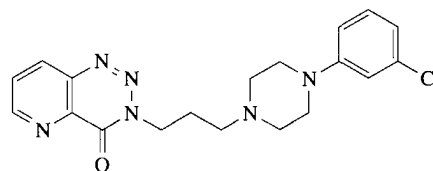


(398)

A number of 8-aryl substituted pyrido[3,4-*d*]-1,2,3-triazin-4(3*H*)-ones have been found to be most efficacious as inhibitors of xanthine oxidase, potential compounds for the treatment of ischemia and gout <88EUP274654>. A number of 3*H*,4*H*-pyrido[3,2-*e*]-1,2,4-triazine and 3*H*,4*H*-pyrido[3,4-*e*]-1,2,4-triazine 3-acetamides have shown antiinflammatory, diuretic, antihypertensive, and psychotropic effects <89FES279>. During a search for potential antidepressant compounds, the pyrido-1,2,3-triazinone (**399**) was found to be more active than its isomer (**400**) <87EJM337>.



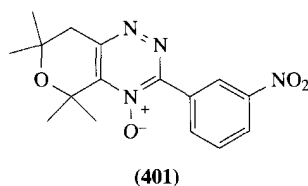
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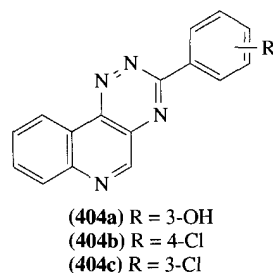
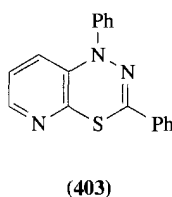
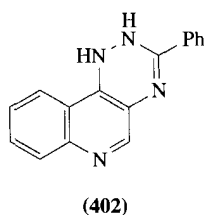
(400)

A series of 1,2,4-triazines were tested for sedative properties as replacements for the benzodiazepines. Among them, compound (**270**) showed a good ED_{50} whereas the nitro derivative (**401**) was hardly active <81JMC490>.

1,2,4-Triazino[5,6-*c*]quinolines, such as compound (**186**), have found use as antimycotic agents <72GEP(O)2216241>. 1,2,4-Triazino[5,6-*c*]quinolines, for example (**185**), their 1,2-dihydro derivatives, for example (**402**), and 3-amino-1,2,4-triazino[6,5-*c*]quinoline (**91a**) and its *N*-oxide (**90a**) have been used as inhibitors of inflammation, and as analgesics and microbicides <73GEP(O)2322394>.



73GEP(O)2322486, 73GEP(O)2322418). Quantitative data concerning their antibacterial and antifungal activities has been reported <74MI 717-01>.

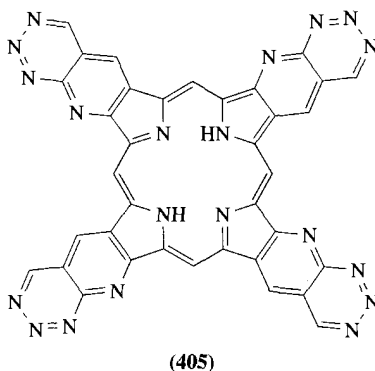


A number of 3-substituted pyrido[3,4-*e*]-1,2,4-triazines and pyrido[3,2-*e*]-1,2,4-triazines, such as compounds (65) and (69e), and their dihydro derivatives have been described as possessing antiinflammatory, antibacterial, and antifungal properties <75MIP 717-01, 75MIP 717-02>. Several triazinoquinolines, for example (252), were found to be useful as bactericides <84MI 717-01>.

A number of 1*H*-pyrido[2,3-*c*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-dioxides and 1*H*-pyrido[4,3-*c*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-dioxides, for example (403), display herbicidal properties <75USP3920641, 77USP4014888>. Four 3-arylpyrido[3,4-*e*]-1,2,4-triazines (404a-c) and (252) have been studied as germination inhibitors <84MI 717-03>.

A series of dyestuffs have been reported which contain the pyrido[2,3-*e*]-1,2,4-triazine and pyrido[4,3-*e*]-1,2,4-triazine nuclei. These compounds have been used to dye a number of fibres fluorescent yellow shades <74GEP(O)2417916>. Another series of polyheterocyclic dyestuffs which contain a pyridotriazine moiety have been patented as fast yellow dyes especially for synthetic fibres <75GEP(O)2355967>. Amongst a number of the compounds prepared as dyestuffs were several 1*H*-pyrido-1,3,4-thiadiazines. The compounds were used to dye polyester fibres fast shades of yellow <77USP4025510>.

Spectroscopic data and calculations suggest that compounds (49) and (50) may be effective laser dyes <93MI 717-07>. Novel tetraazacycloicosines, compounds such as (405) containing pyridotriazine moieties, have found use in optical recording materials for information storage <91JAP(K)13384>. Compounds containing 2*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine and 2*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine nuclei have found use as novel photographic couplers, giving high heat and moisture resistance and light fastness to photographic paper preparations <90EUP398664>.



7.18

Bicyclic 6-6 Systems: Pteridines

WOLFGANG PFLEIDERER
Universität Konstanz, Germany

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7.18.1 INTRODUCTION

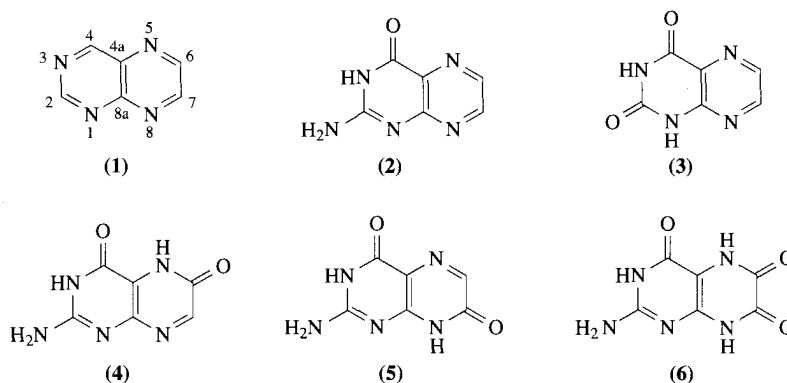
7.18.1.1 Brief Historical Survey

Chemically synthesized pteridines appear in the literature as early as 1857 when Wöhler <1857LA(103)117> and Hlasiwetz <1857LA(103)200> reported the formation of new yellow products from prolonged heating of uric acid in water above 100°C in a sealed tube. But only 100 years later, in 1959, was it shown that some of the fluorescent substances were true lumazine derivatives <59CB2468>.

The first logical synthesis of a pteridine was reported by Kühling in 1894 who oxidized “tolu-alloxazine” to lumazine-6,7-dicarboxylic acid followed by thermal decarboxylation to lumazine (“alloxazine”) <1894CB2116, 1895CB1968>. Gabriel and Colman in 1901 <01CB1234> and Isay in 1906 <06CB250> performed condensation reactions between 4,5-pyrimidinediamines and 1,2-dicarbonyl compounds to “azines” and more versatile syntheses of the pteridine ring-system were achieved by Sachs and Meyerheim in 1908 <08CB3957>.

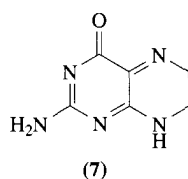
Parallel with these early efforts in synthetic pteridine chemistry, a totally independent development of naturally occurring pteridines started in 1889 with Hopkins’ isolation of yellow purine-like pigments from the wings of the common English brimstone butterfly <1889PCS117, 1889NAT335>. Continuation of this work led to a yellow and a colorless pigment <1891NAT197, 1892NAT581, 1894PRS5, 1895MI 718-01> which were finally reisolated in pure form by Schöpf and Wieland in 1925–26 and named xanthopterin <25CB2178> and leucopterin <26CB2067>, respectively. In 1933 a third pigment, called isoxanthopterin <33LA(507)226>, was isolated and three years later erythropterin <36LA(524)49>, an orange–red pigment from tropical butterflies, was described. Due to their unusual physical properties and severe difficulties with elemental analyses, the constitution of the butterfly pigments remained unknown until 1940 when Purrmann succeeded in the elucidation of the structures of xantho-(4), isoxantho-(5), and leucopterin (6) by logical synthetic means <40LA(544)182, 40LA(564)98, 41LA(548)284>.

This knowledge subsequently initiated much work in isolating new natural pteridines as well as many synthetic approaches to this heterocyclic nucleus; as exemplified by the vitamin folic acid and methotrexate, an antileukemia drug <49JA1753>. The importance of this interdisciplinary field was recognized as early as 1952 by Polonovski, who organized the first symposium. By 1995, 10 periodic international congresses and many more symposia on specific aspects of pteridines followed.

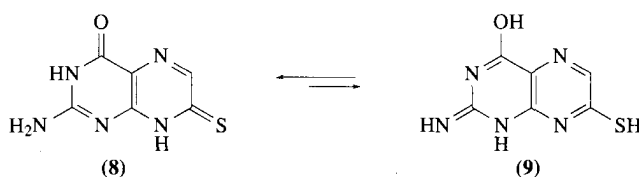


7.18.1.2 Nomenclature and Literature

The term *pteridine* describes the pyrazino[2,3-*d*]pyrimidine nucleus, as proposed by Wieland <41LA(548)83> in 1941, and originates from the Greek word “*pteron*” meaning wing. The numbering of this ring system (1) follows the IUPAC rules; however, the central C=C double bond may be substituted. It has generally been agreed to name 2-amino-4(3*H*)-pteridone (2) *pterin* <63AG993> since most naturally occurring pteridines show the same pattern of substituents at the pyrimidine moiety of the nucleus. Thus, this term is also commonly used as the characteristic part of the trivial name of the natural pteridine derivatives. Similarly, 2,4(1*H*,3*H*)-pteridinedione derivatives (3) are called *lumazines*. Reduced compounds are indicated by the prefixes “dihydro-”, “tetrahydro-”, and so on, with numerals showing the positions of the additional hydrogen atoms. For convenience, the prefix indicating reduction is always placed immediately before the stem name (pterin, biopterin, etc.), even though this conflicts with the general rule that prefixes should be in alphabetical order. Reduced derivatives may also be indicated in abbreviated names by H₂ or H₄ in front of the stem name (7,8-H₂-pterin, H₄-biopterin, etc.). The “quinonoid dihydropterins” have to be considered as 6,7,8-dihydropterins (7) due to the favored tautomeric composition. Chiral centers are designated by the Cahn–Ingold–Prelog rules if the absolute configuration is known, otherwise the symbols (+), (–), or (±) are used to indicate optical activity. Where a stem name exists for a pterin carrying a side chain with one or more asymmetric centers, the stem name designates only the naturally occurring diastereoisomer. Unnatural stereoisomers should be designated by using the stem name with appropriate substituent names and an indication of the configuration at the chiral centers (e.g., *D-erythro*-6-(1,2-dihydroxypropyl)pterin not *D*-biopterin). Often, abbreviations of trivial names are used in a nonsystematic manner leading to much confusion. A three-letter code has been proposed to achieve consistency in nomenclature for the future <90MI 718-10>.



In regard to tautomerisms of functional groups such as amino, hydroxy-, and thiol groups, in nitrogen-containing heterocycles it is generally agreed that the favored tautomers should be represented by the structural formulas. Amino groups exist as such and not in the iminodihydro form whereas the hydroxy and thiol functions (9) located adjacent or *para* to a ring nitrogen atom prefer the thermodynamically more stable amide (lactam) and thioamide (thioxo) configuration (8) (Scheme 1) <B-76MI 718-01>.



Scheme 1

The pteridine literature has been reviewed several times. The excellent monograph by Brown covers for the first time the entire chemistry of this heterocycle <B-88MI 718-01> and more specialized chapters are found in various books <B-84MI 718-03, B-85MI 718-03, B-87MI 718-01, B-92MI 718-01>. The proceedings of three 1980s International Congresses on the Chemistry and Biology of Pteridines <B-86MI 718-02, B-90MI 718-02, B-93MI 718-03> and a series of symposia <B-82MI 718-01, B-83MI 718-02, B-84MI 718-05, B-85MI 718-06, B-87MI 718-03, B-87MI 718-04, B-89MI 718-01, B-92MI 718-02> contain specific information about newer developments in the field.

7.18.2 THEORETICAL METHODS

7.18.2.1 *Ab initio* Methods

Various computational methods were applied to find by *ab initio* calculations new inhibitors of dihydrofolate reductase and to predict their chemical properties and strength of binding with the enzyme. Theoretical SCF/6-31G results for pterin and 5-deazapterin are in good agreement with the experimental facts as are also the modelling of UV/VIS spectra. Free energy perturbation/molecular dynamics (FEP/MD) simulations procure some information about a complex interplay of protein–ligand interactions, including steric, solvation, and favorable hydrophobic effects <B-93MI 718-12>. *Ab initio* SCF calculations with STO-3G and 3-21G basis sets provide valuable information regarding the stability of tautomers, site of protonation, and mechanisms of enzymic and chemical reactions, as exemplified by the quinonoid dihydropterins, the natural substrates for dihydropteridine reductase <85JA6689>. Similarly, full geometry optimizations using the force relaxation method within the *ab initio* SCF/STO-3G framework illustrate with various biologically important pteridines the nonlocalized nature of the effects on the heterocyclic ring structure due to changing substituents, tautomerism, reduction, and protonation patterns and, particularly, propagation of disturbances to the adjacent ring <84JST(109)231>. *Ab initio* and free energy perturbation calculations reveal that a 1*H*:3*H* tautomer ratio of 1:6 exists for pterin in aqueous solution <93CC1199> which is, however, not in agreement with the experimental facts <93MI 718-14>. Extrapolations of the calculated results to folic acid and its binding to dihydrofolate reductase are therefore very speculative.

7.18.2.2 Semiempirical Methods

Tetrahydrobiopterin (135) and some of its biogenetic precursors were the subject of MINDO/3 calculations to obtain comparative information about the alleged lowest energy conformations <B-93MI 718-05>. Similarly, the optimized geometry of the labile key intermediate of tetrahydrobiopterin biosynthesis (6-pyrovyl-5,6,7,8-tetrahydropterin) was calculated indicating that the equatorial staggered conformation of the 6-(1,2-dioxopropyl) sidechain is *trans* oriented regarding H—C(6) and O(1') as well as regarding the carbonyl groups. The calculation of atomic charges and LUMO coefficients of these carbonyl groups suggests that the O=C(2') may be more reactive toward NADPH than O=C(1') <91BBR(176)52>.

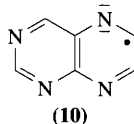
The AM1 SCF-MO method was applied to calculate properties of all possible diazinodiazines and their monocations in order to get information about the site of protonation in these π -deficient heterocycles. Since some of these polyazanaphthalenes, like pteridine, are masked by the covalent hydration phenomenon; the pK_a values belong in fact to their hydrates, solvates, and mixtures of the adducts with the unmodified forms. Pteridine was found to be the strongest base in this series due to the high proton affinity at N-1 <88JOC3900>.

7.18.3 EXPERIMENTAL STRUCTURAL METHODS

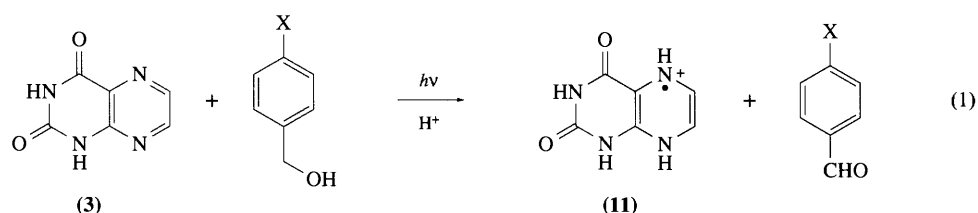
7.18.3.1 Magnetic Spectroscopy (NMR, ESR)

Proton and carbon-13 NMR spectroscopy can be regarded as outstanding tools for structural elucidations. The complicated equilibrium mixtures of 8-alkyl-substituted pterins and lumazines can be unraveled by a combination of ^1H and ^{13}C NMR spectral studies <86JOC2461, 92MI 718-07, 92MI 718-09>.

Reduction of pteridine by potassium allows the formation of the pteridine radical anion (**10**) for which a well-resolved ESR spectrum has been obtained $\langle 89JOM(362)37 \rangle$. However, the low symmetry of the radical should show theoretically a hyperfine-splitting into 1296 lines and eight coupling constants, indicating that such a complex pattern cannot be analyzed by the experimental facts.



Radical cations of dihydropteridines are formed by the photoreduction of lumazine by benzyl alcohol derivatives in the presence of HClO_4 in acetonitrile, via photoinduced electron transfer to the triplet excited state of the protonated species (**11**) (Equation (1)) $\langle 89CL35 \rangle$. The unstable photoreduced product has been characterized by its ESR spectrum.



7.18.3.2 Optical Spectroscopy (UV, IR, Fluorescence, Raman, Photoelectron)

UV spectra play a very important role in the characterization of pteridines and in the determination of tautomeric equilibria as well as $\text{p}K_a$ values. The shape of the spectra, their dependence on the pH and the typical regions of absorbance are characteristic for structurally related pteridine derivatives and are therefore often used for structural assignments and proofs. A comparative study of xanthopterin (**4**) and isoxanthopterin (**5**), respectively, with their corresponding 6- and 7-thioxo derivatives indicates that the thioxo function causes a strong bathochromic shift of almost 70 nm in the neutral species $\langle 92HCA2317 \rangle$. Other striking features are the increased acidity of the thioamide ionization and the hypsochromic shift of the absorption on anion formation.

Analyses of the electronic absorption spectra of some pterin and *N*(5)-deazapterin derivatives using the CNDO/S-CI method show good agreement with the spectra which may be assigned to a group of $\pi-\pi^*$ transitions. There are some differences between calculated values in the gas-phase and solution models but their general level of conformity with experiments is similar. Band shifts caused by methyl substitution, protonation, and replacement of ring nitrogens are predicted and agree well with experimental assignments for tautomeric forms and protonation sites for known compounds $\langle 94CPH55 \rangle$.

Unfortunately, spectrofluorimetric studies of pteridines are rare despite the fact that fluorescence is a very characteristic feature of this class of compounds. Some information regarding pH and solvent dependence is available from 8-alkylpterins $\langle 93MI\ 718-16 \rangle$.

Little is also known about photoelectron spectra of pteridines. The unsubstituted nucleus and its 4-methyl- and 2,4,6,7-tetramethyl derivative have been recorded and analyzed in terms of both a simple Hückel-model and semiempirical calculations $\langle 86CB1275 \rangle$. The assignment of the π - and n -type PE bands of pteridine indicates that the low energy band is associated with an ionization process involving the nitrogen n electrons and followed by π -bands. Furthermore, the $\text{p}K_a$ of free pteridine, which is masked in aqueous solution by partial covalent hydration, is suggested from the PE data to be in the order of -2 .

7.18.3.3 Chiroptical Spectroscopy

Structural correlations on the basis of CD spectra provide good information about the stereochemistry of chiral molecules. The structure of (–)-tetrahydrobiopterin, the cofactor for hydroxylations of aromatic amino acids, was determined by x-ray crystallographic analysis as (6*R*,1′*R*,2′*S*)-6-(1′,2′-dihydroxypropyl)-5,6,7,8-tetrahydropterin (**135**). Its CD spectrum exhibits a negative Cotton

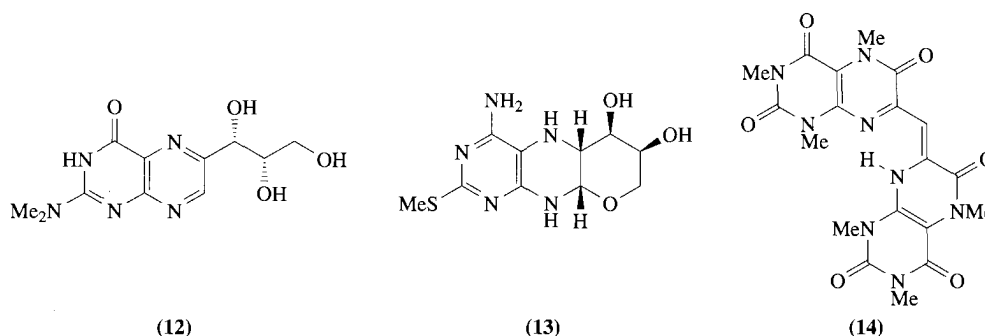
effect in the range of 240–290 nm at pH 3.2. The relationship of a negative Cotton effect with the (*R*)-configuration was used in structural assignments of a series of 6-substituted 5,6,7,8-tetrahydropterins <85MI 718-10>.

7.18.3.4 Mass Spectrometry

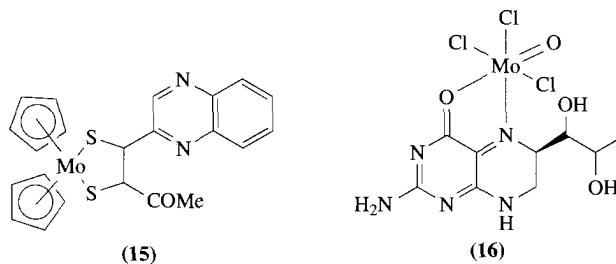
More sophisticated mass spectrometric methods have been found in the electrospray (ES–MS) and plasma desorption (PD–MS) techniques which have successfully been applied directly to nonvolatile pteridines. A small peak can be detected with folic acid at $m/z = 441$ together with the mono-, di-, and trisodium species. The dihydro- and tetrahydro derivatives also give the expected results <83MI 718-05>. Fast atom bombardment (FAB) works also with folic acid in special matrices and is another tool for structural studies <83MI 718-08>. Even in a molar mixture of 5-methyl-5,6,7,8-tetrahydropterin and tris(pentane-2,4-dionato)iron(III), the metal–pterin complex could be detected by ES–MS <92HCA1955>.

7.18.3.5 Diffraction Methods (X-ray, Neutron, Electron)

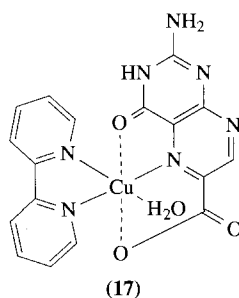
X-ray analysis is often applied to elucidate the structure of complex molecules and can be regarded as the most efficient method in this respect. The unusual structures of euglenapterin (**12**) <86LA1705>, of covalent intramolecular adducts (**13**) <90HCA808> and of a more soluble structural analogue (**14**) of pterorhodin <B-93MI 718-04> have been unambiguously proven in this way.



Structural studies of various pteridine–metal complexes (**16**) <89JA3431, 92JA6294> and (**17**) <92MI 718-08, B-93MI 718-10> and model substances (**15**) <91JA9372> related to the molybdopterin cofactor <93MI 718-01> reveal valuable information of bonding interactions present in the increasing number of pterin-containing molybdenum and tungsten enzymes. In this respect, some kind of model character is associated with the quinonoid dihydropterin–molybdenum complex <91HCA1544>.



Metal-free models showing special structural features can be seen in the crystal structures of *N*²,1',2',3',4'-*O*-pentaacetyl-6-(*D*-arabino-1',2',3',4'-tetrahydroxybutyl)pterin <93AX(C)413>, its 5-benzyloxycarbonyl-5,6,7,8-tetrahydro derivative <93AX(C)1649> and (6*R*)-*N*²,*N*²,*N*(-8),*O*⁴,1',2',3'-heptaacetyl-5-ethyl-5,6,7,8-tetrahydro-*D*-neopterin <86HCA210>. The x-ray analysis of the naturally occurring tetrahydrobiopterin is also available in the form of its dihydrochloride salt <85MI 718-10>. The side chain attached to C-6 takes the equatorial conformation and the hydroxy groups are in the *trans* orientation.



More sophisticated crystal structure determinations of various human dihydrofolate reductase (DHFR) inhibitor complexes <B-93MI 718-11> with second generation antifolate drugs such as 10-ethyl-10-deazaminopterin (**423**), piritrexim (**424**), and trimetrexate (**425**), respectively, have provided valuable information on the mode of inhibitor binding to DHFR and on the role of active site residues in defining the mechanism of action, especially as it relates to drug resistance in chemotherapy. The crystal structure of methotrexate offers insight into the molecular details of hydrogen-bond strength and directionality of drug binding to the enzyme active site <86JA4155>. Furthermore, the x-ray analysis is useful for computer graphic modeling studies of the enzyme active site and for parametrization of molecular mechanics programs, as both processes are important for computer-aided drug design.

7.18.4 THERMODYNAMIC ASPECTS

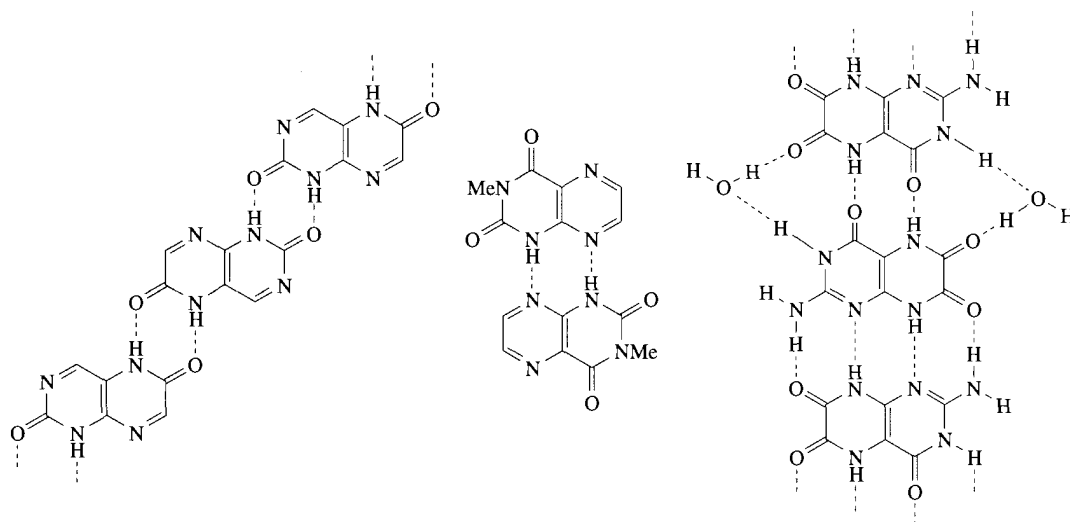
7.18.4.1 Molecular Properties (Melting Point, Boiling Point)

Amino-, hydroxy-, and thiol-substituted pteridines are normally high melting compounds due to their having strong intermolecular hydrogen bonds stabilizing the crystal lattice to a large extent. This thermodynamic stabilization is responsible for the difficulties encountered during elemental analysis of such pteridine derivatives. *O*-, *N*-, and *S*-alkylations, respectively, lower the melting points to the region between 100 and 300°C since the molecules are still of polar character. Distillation of pteridines is only possible in special cases when the polar functionalities are converted into their trimethylsilyl derivatives. Various lumazines have been distilled under high vacuum in the form of their 2,4-bis-trimethylsiloxy derivatives <73CB1401> and even isoxanthopterin <73CB1952> and leucopterin, belonging to the most insoluble and highest melting pteridines of all, can be purified by distillation of their tri- and tetrakis-trimethylsilyl derivatives.

7.18.4.2 Solubilities

The solubility of pteridines in water is directly associated with the number and chemical nature of the substituents. While pteridine itself is quite soluble (1 part in 7 ml of H₂O), attachment of hydrophilic OH, SH, and NH₂ groups decrease the solubility gradually. This is quite contrary to the normal solubilizing effects in the aliphatic and carbocyclic series but the π -electron deficient nitrogen heteroaromatics show an opposite behavior due to aggregation by intermolecular hydrogen bonding (Scheme 2) <63PMH(1)177>.

In the amino-, hydroxy-, and thiol-pteridine series the solubilities decrease by one to several orders of magnitude going from the mono- to the tetrasubstituted derivatives. The most striking decrease is observed in combining amino- and hydroxy substituents in the same molecule. The aggregation theory is indirectly proven by the fact that methylation of the OH, SH, and NH₂ groups and acylation of the amino function improve the aqueous solubility by lowering the number of hydrogen bonds. Dipolar aprotic solvents such as DMF, DMSO, HMPT, etc. are hydrogen bond breakers dissolving the polar components quite well, especially on heating, but also form over-saturated solutions, which makes normal recrystallization of pteridines often problematic. It is unfortunate that little attention is given to the exact measurement of the solubilities needed in general laboratory work.



Scheme 2

7.18.4.3 Chromatographic Properties

The enormous progress in chromatographic techniques in combination with other physical methods has contributed to the solution of difficult chemical problems. Sensitive compounds can be detected and characterized by HPLC as indicated during the oxidation of the (6*R*)- and (6*S*)-diastereoisomers of 5,6,7,8-tetrahydrobiopterin to the (6*R*)- and (6*S*)-quinonoid 6,7,8-dihydrobiopterins which rearrange with a half-life of about five minutes to form the stable 7,8-dihydrobiopterin. <83JC361, 84MI 718-06>. Separation of regioisomers such as 6,8- and 7,8-dimethylpterin can be achieved under special conditions using strong cation exchange columns <92MI 718-11>. The identification and determination of the stereoconfiguration of pterins and lumazines with chiral side chains was successfully performed by ligand exchange chromatography using a reverse-phase column with a chiral mobile phase <92MI 718-05, B-93MI 718-06, 93MI 718-08, 94MI 718-02>. Cation-exchange, reverse-phase, and ion-pair reverse-phase chromatography were evaluated for the separation of various pterins <84JLC2561>. HPLC methods have also been developed for the determination of pteridines in biological samples <83MI 718-09> and in blood cells and plasma <83MI 718-04>.

7.18.4.4 Aromaticity and Chemical Stability

Fully unsaturated six-membered heterocycles possess some degree of aromaticity whereby the substitution of a CH group by an sp^2 -hybridized N-atom causes a more or less severe disturbance of the cyclic resonance depending upon the number and location of the heteroatoms. Electronegative nitrogens partially localize π -electrons of the formal Hückel system and decrease in this way the aromatic character of the nucleus. The pteridine ring system is derived from naphthalene by formal introduction of four N-atoms in 1,3,5 and 8 positions, converting this heterocycle into a strongly π -deficient system of low heteroaromaticity. The molecule shows alternation in bond lengths as a consequence of bond location and increased bond polarization. These properties are clearly reflected in the easy formation of covalent adducts, primarily at the 3,4-double bond. Unfortunately, quantification of the relative aromaticity of such complex molecules as the pteridine ring system is less easily resolved due to changes in atomic parameters of the nitrogen atom in polyazaheterocycles. Aromaticity indices based upon structural and magnetic properties can be used for comparative judgements but are still of qualitative, speculative character. In order to make a comparison of the aromaticities of different heterocycles, it is useful to calculate the resonance energies per π -electron (REPE) by dividing the resonance energy by the number of π -electrons in the molecules. Values for the pteridine nucleus are so far, however, not available.

The Dewar concept leading in the monocyclic series to reliable statements regarding aromaticity has not yet been applied to condensed bicyclic systems disturbed by heteroatoms.

There are intentions to invoke NMR in assessing aromaticity by comparisons of chemical shift data associating a downfield shift with the presence of an aromatic ring current. The validity of

using chemical shifts as a quantitative measure of ring currents has to be questioned due to the complex physical nature of the magnetic susceptibilities of centers adjacent to heteroatoms. As with other approaches to assessment of aromaticity, a major difficulty is the selection of appropriate nonaromatic models.

Chemical stability is not associated with aromaticity and should therefore be discussed independently and under kinetic aspects involving considerations of the transition state and the energy differences to the ground state. Pteridine itself is chemically very labile and is easily attacked by nucleophiles. Ring cleavage then follows. Introduction of electron-donating groups stabilizes the ring system towards acid and base-catalyzed ring scissions and allow electrophilic, nucleophilic, and radical substitution reactions without harming the nucleus.

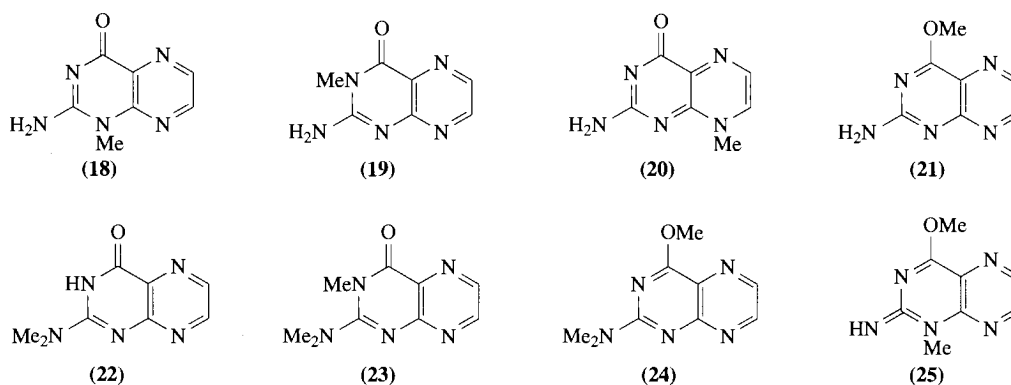
7.18.4.5 Conformations

Conformational studies in the pteridine series involve mainly the tetrahydro derivatives which adopt a half-chair orientation in the tetrahydropyrazine moiety, giving rise to some flexibility and special structural arrangements.

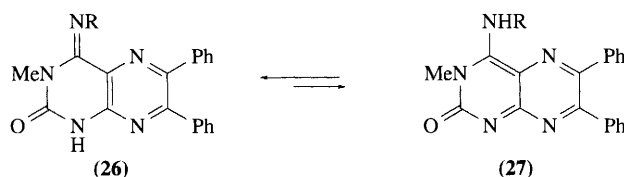
The conformations of 6-, 7-methyl, and *cis*- and *trans*-6,7-dimethyl-5,6,7,8-tetrahydropteridines, respectively, which are tetrahydrobiopterin analogues with enzymatic cofactor activity, were determined in solution by ^1H NMR studies <85B458>. It was noticed that all these compounds, with the exception of the *cis*-6,7-dimethyl isomer, exhibit an unusually small *trans* C(6)-H, C(7)-H spin-spin coupling of 8.5–9.1 Hz. There is a discrepancy between the calculated and experimentally observed values of this coupling, which is attributed to hyperconjugation of the axially oriented C-7—H bond with the π -orbital of the vinylogous amide function of the pyrimidine moiety. It is also concluded from NOE measurements and chemical shift comparisons that the methyl groups markedly prefer equatorial-like orientations and that the tetrahydropterin ring is almost planar except for a pronounced pucker at C-6. The same is true for (6*R*)-5,6,7,8-tetrahydrobiopterin hydrochloride <84AJC355>. It is noteworthy in this connection that acylation at N-5 forces the molecules, as shown for 5-formyl-6-methyl-5,6,7,8-tetrahydropterin <81HCA367> and (6*R*)-pentaacetyl-5,6,7,8-tetrahydrobiopterin <82HCA1094>, into a relatively planar conformation with the C(6)-substituent in a pseudoaxial orientation. Low-temperature UV and CD studies of methotrexate (**422**) in apolar solvents indicate that a bent conformation leads to a stacking interaction between the pterin and benzene nuclei with further stabilization by intramolecular hydrogen bonds <88AG422>.

7.18.4.6 Tautomerism (Prototropy, Ring-chain Tautomerism)

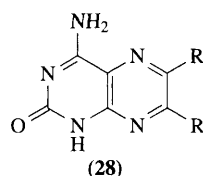
It is generally accepted <B-76MI 718-01> that, for thermodynamic reasons, the tautomeric equilibria of α -hydroxy nitrogen heterocycles favor, with some minor exceptions, the oxo or lactam configuration over the iminol form, while the α -amino analogues are best represented by the amino and not the corresponding imino dihydro tautomer. The most prominent structure of pterin in water is therefore the 2-amino-4(3*H*)pteridone tautomer (**2**) <60CB2015>. This assignment can best be proven by comparison of its UV spectrum with those of blocked tautomers such as 1-methyl- (**18**), 3-methyl- (**19**), 8-methyl- (**20**), *O*⁴-methyl- (**21**) and *N*²-dimethyl- (**22**), *N*²,*N*²,3-trimethyl- (**23**), *N*²,*N*²,*O*⁴-trimethyl- (**24**), and 1,*O*⁴-dimethyl-pterin (**25**), respectively.



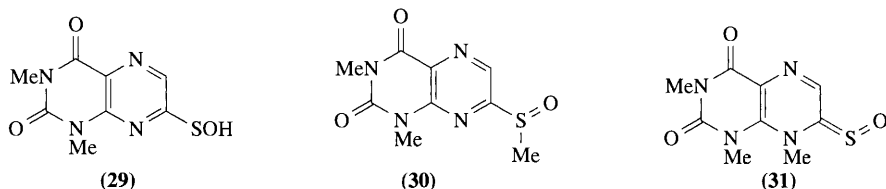
Another general feature of lactams is seen by the fact that the H-atom is always located at the adjacent ring nitrogen atom and not at any vinylogous positions at any other part of the molecule. The thermodynamic stability of an amide function as such reveals a strong localized resonance stabilization and does not take part in cyclic heteroaromatic delocalization. 1-Methylpterins show mainly hypsochromatically shifted UV spectra in comparison to 3-methyl- and unsubstituted pterins, indicating structural differences <93MI 718-14>. The dilactam structure of lumazines has formerly been demonstrated and seems to be of a general nature since the lumazine-6- and 7-carboxylic acids show the same features <93MI 718-18>. A somewhat surprising result was noticed with 4-imino-3-methyl-6,7-diphenyllumazines (**26**) which do not tautomerize to the 4-amino isomer (**27**) despite the fact that a basic amidine and an acidic amide function are present in these molecules (Scheme 3). Furthermore, the 4-amino tautomer would exhibit a vinylogous amide structure but, on the other hand, would also force the π -electron system into an *ortho*-quinonoid arrangement <86MI 718-06>. Isopterins (**28**) behave normally and adopt the 4-amino-2-oxodihydro configuration <63CB2950>.



Scheme 3



Another interesting case is the tautomeric structure of 1,3,6-trimethylumazine-7-sulfenic acid for which OH, SH, and NH-tautomers can be drawn. Structure (**29**) is most likely since the *S*- (**30**) and *N*-methyl (**31**) blocked analogues are spectrophotometrically different <86HCA1095>.

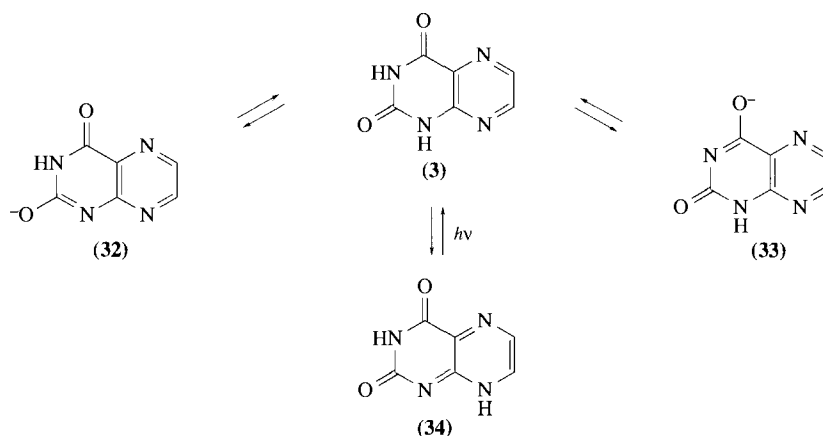


Fluorescence properties of lumazine (**3**) and its 1- and 3-methyl derivatives were studied in aqueous solution and in dependence of the pH to obtain information about the possible tautomeric forms of the various ionic species. Emissions were found for the neutral form at 380 nm, the monoanion at 467 nm, the dianion at 483 nm, and the cation at 505 nm. From similar emissions of 3-methylumazine (but different ones of the 1-methyl isomer), it was concluded that the emitting species is the *N*(8)-H phototautomer (**34**) resulting from an N-1 to N-8 proton transfer in the excited state (Scheme 4) <87MI 718-08>.

At pH 10, the differences in quantum yields of 1- and 3-methylumazine indicate that lumazine is a mixture of the *N*(1)-(**32**) and *N*(3)-deprotonated species (**33**) as already proven from the comparisons of the UV spectra (Scheme 4). The cation, on the other hand, is protonated at N-8, according to the large Stokes' shift. Functional groups of the lactam type show in the lumazine series the expected increases in acidity and basicity, respectively, in the excited state relative to the ground state.

7.18.4.7 Base and Acid Strength (pK_a Values)

Knowledge of the base and acid strengths of nitrogen heterocycles is an important prerequisite for synthetic work and structural assignments on spectral data, and should therefore be determined



Scheme 4

systematically. Pteridines have been investigated in this respect quite intensively in the past. pK_a Values of a broad variety of derivatives are available and provide valuable information.

The exchange of an oxo against a thioxo function induces in principle an increased acidity due to an improved resonance stabilization in the thiolate. Lumazine (3) possesses an acidic pK_a of 7.95 but 2-thio- (6.48), 4-thio- (7.50), and 2,4-dithiolumazine (5.68) are substantially more acidic <74CB3377>. Interestingly, a thioamide group has little influence on the acidity of adjacent amide functions since 1-methyl-2-thiolumazine (8.25) is very close to 1-methylumazine (8.45). An even more striking effect is revealed with 6,7,8-trimethyl-4-thio- (6.97) <89HCA738> and 6,7,8-trimethyl-2,4-dithiolumazine (5.65) <89HCA744> which are three to four orders of magnitude more acidic than their 4-oxo analogues. The 6,7,8-trimethyl-2-thiolumazine (8.23) <66CB3503> is only weakly acidic. Analogously, 1,3-dimethyl-7-thiolumazine (1.67) and its 2-thioxo- (1.38), 4-thioxo- (1.53), and the 2,4-dithioxo derivatives (1.41) <79CB1499> are very strong acids and are isolated as neutral species only below pH 0.

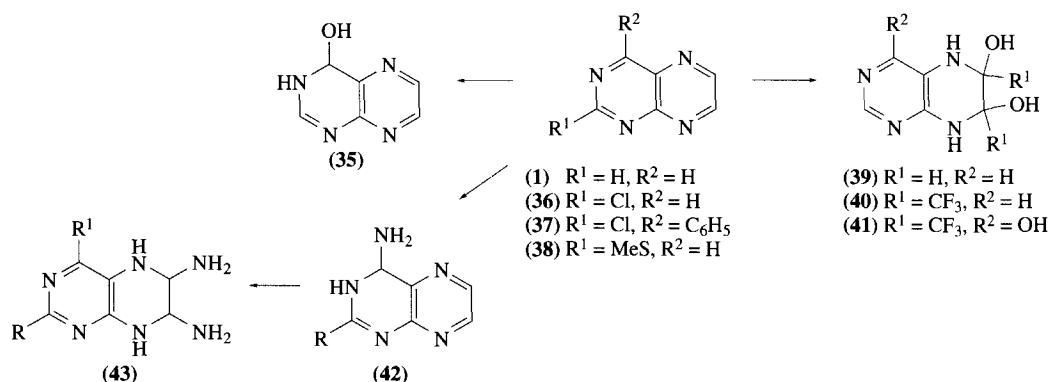
3-Methyl- (26) and 1,3-dimethyl-4-iminolumazines are relatively weak bases with pK_a values of 5.5 indicating that the obvious amidine-type structure has to be regarded as an acylated derivative due to the adjacently attached carbamoyl group <86MI 718-06>.

Comparisons of the isotopic exchange rates of the hydrogen atoms of the 7-methyl group in 7-methyl- and 7,8-dimethylumazines, respectively, in acidic medium indicate that the latter compounds are more activated due to their higher basicity and more favored cation formation. 8-Substituted lumazines, owing to a cross-conjugated π -electron system, are protonated at N-1 and the corresponding heteroaromatic analogues at N-8 leading to the same type of cation <85CJC3290>. The importance of knowing the basic and acidic ionization constants of organic molecules can be seen from studies concerning the interconversions of 6,6,7,7-tetramethyl-5,6,7,8-tetrahydropterin and its 5-methyl- and 7,8-dihydro derivatives involving a series of intermediates of pH-dependent stability <84JA7916>. The basic pK_a of the quinonoid 6,6-dimethyl-6,7-dihydro-8H-pterin was found to be 5.15 with the protonation site at N-3 and a bathochromic shift of the UV spectrum <83B1790>, similar to the behavior of 7,8-dihydropterins.

7.18.4.8 Covalent Adducts

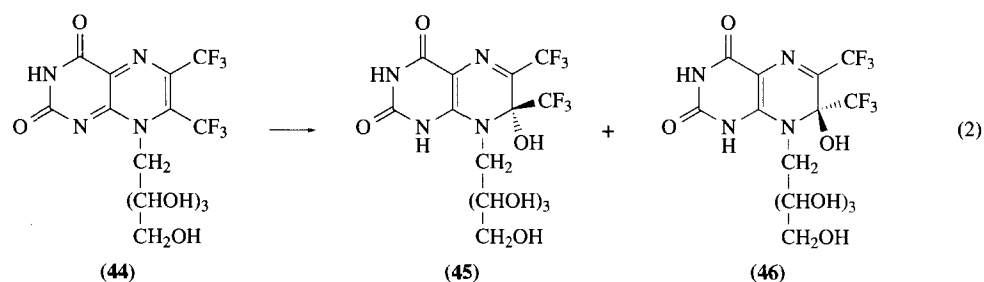
Reversible covalent hydration of $C=N$ bonds has been observed in a number of heterocyclic compounds, of which unsubstituted pteridine is a prototype <76AHC(20)117>. Solvent isotope effects on equilibria of mono- (35) and dihydration (39) of neutral pteridine (1) have been followed by NMR and found to be near unity (Scheme 5) <83JOC2280>.

Pteridine also adds ammonia at low temperature to form 4-amino-3,4-dihydropteridine (42) which is transformed in a slower reaction into 6,7-diamino-5,6,7,8-tetrahydropteridine (43) (Scheme 5). 2-Chloropteridine (36) shows the same behavior, whereas 2-chloro-4-phenylpteridine (37) and 2-methylthiopteridine (38) lead directly to the corresponding 6,7-diamino-5,6,7,8-tetrahydro derivatives (43) (Scheme 5). The 4-amino-3,4-dihydropteridines can easily be oxidized to the 4-aminopteridines <75RTC45>. Covalent hydrations with various 6,7-bis-trifluoromethyl-pteridine derivatives were studied showing that 6,7-bis-trifluoromethylpteridine (40) itself and the cor-

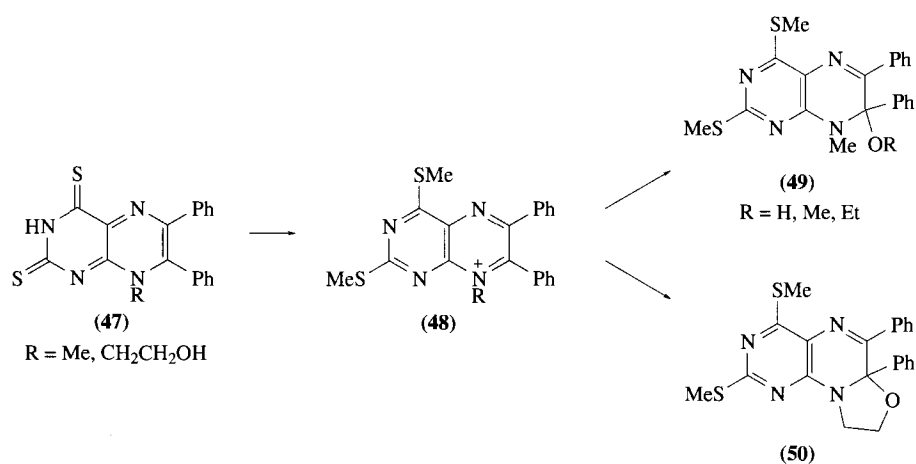


Scheme 5

responding 4(3*H*)-pteridone (41) are hydrated in the 6- and 7-position but the lumazine analogues are not [86JCS(P1)1043]. On the other hand, 8-substituted 6,7-bis-trifluoromethylumazines, owing to a cross-conjugated π -electron system, add water in a 1,7-fashion to reduce the π -electron deficiency [86JCS(P1)1051]. In the case of 6,7-bis(trifluoromethyl)-8-D-ribityllumazine (44), both diastereomeric hydrates (45) and (46) could be separated by preparative HPLC (Equation (2)); one of them interacts stereospecifically with light riboflavin synthase of *Bacillus subtilis* [91JOC4603].



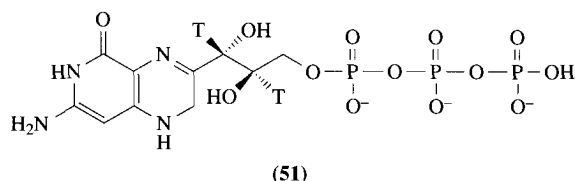
6-Trifluoromethyl-8-D-ribityllumazine, on the other hand, forms an intramolecular cyclic adduct in basic medium and adds sulfur nucleophiles in neutral solution to the 7-position [93JOC4033]. Similarly, methylation of 8-methyl- and 8- β -hydroxyethyl-6,7-diphenyl-2,4-dithiolumazine (47) to the 2,4-bismethylthio derivatives forms cationic species (48) which are so electron-deficient that water or alcohols add to form (49) or an *N*-hydroxyethyl substituent adds intramolecularly to form stable 7,8-dihydropteridines (50) (Scheme 6) [89HCA744]. The structures of 7-methoxy- and 7-ethoxy-7,8-dihydro-8-methyl-2,4-dimethylthio-6,7-diphenylpteridine, respectively, have been proven by x-ray analysis.



Scheme 6

7.18.4.9 Isotope Labeling

Studies of reaction mechanisms and enzymic reactions rely to a great extent on labeled adducts. The anticipated synthesis of the labeled precursors often are achieved only by multistep procedures performed chemically or enzymatically. Isotope-labeled dihydroneopterin 3'-triphosphate (**51**), with ^3H at positions C-1' and C-2', respectively, has been prepared from isotope-labeled glucose as starting material.



Glucose was first converted enzymatically into ribose 5'-phosphate from which GMP was subsequently obtained by the action of phosphoribosylpyrophosphate synthetase and guanosine phosphoribosyl transferase. A two-step phosphorylation to GTP followed by treatment with recombinant GTP-cyclohydrolase I from *E. coli* gave (**51**) <90MI 718-12>. This method also allows ^{14}C -labeling in the 6- and 7-position as well as the carbon sidechain.

7.18.5 REACTIVITY OF FULLY CONJUGATED RINGS

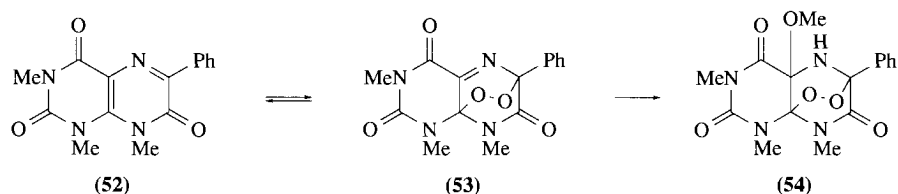
7.18.5.1 Introduction

The pteridine ring system is a typical prototype of a π -electron deficient nitrogen heterocycle favoring nucleophilic displacement reactions due to promoted stabilization of the intermediary σ -complex in the rate-determining addition step. On the other hand, direct electrophilic substitutions such as nitration, nitrosation, sulfonation, halogenation, alkylation, and acylation at the ring carbon atoms are very rare or not at all reported in the pteridine series. Reactivity of the heteroaromatic nucleus depends to a large extent on the nature, the number, and the site of the substituents which all must always be located adjacent to a ring N-atom.

7.18.5.2 Thermal and Photochemical Reactions

The fundamental types of thermally and photochemically induced inter- and intramolecular transformations proceed, in general, with loss of heteroaromaticity. This leads mostly to metastable intermediates prone to further interconversions.

1,3,8-Trimethyl-6-phenyl-7(8*H*)-pteridone (**52**) adds singlet oxygen in a cycloaddition reaction to give the corresponding stable 6,8a-endoperoxide (**53**), which on warming regenerates singlet oxygen (Scheme 7). Irradiation under the same conditions in MeOH in the presence of rose bengal led to the MeOH adduct (**54**) which is also formed from endoperoxide (**53**) on standing in MeOH/ CHCl_3 solution (Scheme 7) <86TL5637>.

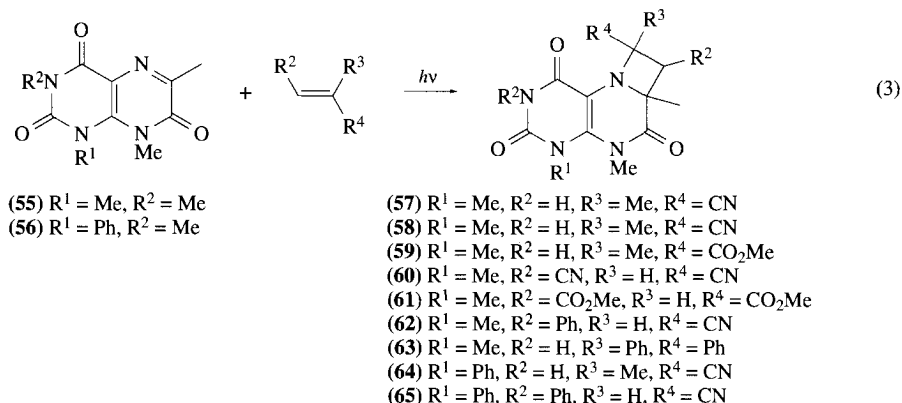


Scheme 7

The endoperoxides revert on warming to the starting pteridine-2,4,7-trione (**52**) with liberation of singlet oxygen which can be trapped using typical singlet oxygen acceptors such as 2,3,4,5-tetraphenylfuran, 4-methyl-2,5-diphenyloxazole, 1,3-diphenyl-benzo[*c*]furan, etc (Scheme 7) <91T2979>.

Irradiation of pteridine-2,4,7-triones (**55**) and (**56**) proceeds in the presence of electron-deficient

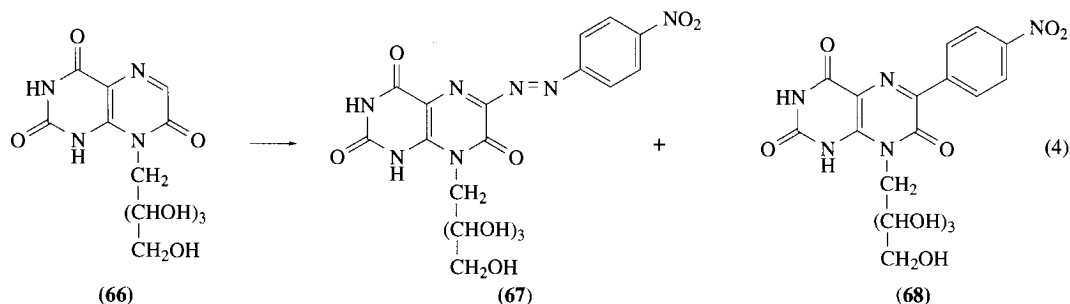
and neutral alkenes, respectively, through a [2 + 2]-cycloaddition reaction in a regioselective but not stereospecific manner along the C=N double bond to give azetidino[1,2-*f*]pteridines (**57**)–(**65**) (Equation (3)) <88CB441>. Prolonged irradiation time led to moderate to excellent yields. The lack of stereospecificity suggests that the formation of the 1:1 cycloadducts may arise from initial interactions between the triplet pteridine-2,4,7-trione with the alkene to give a tight-geometry intermediate such as an exciplex which subsequently forms a 1,4-diradical species followed by cyclization.



Pteridines can also function as catalysts in photooxidations whereby the protonated species of lumazine and aminopterin, respectively, catalyze the substrate-selective photooxidation of benzyl alcohol derivatives by oxygen in the presence of perchloric acid in acetonitrile <89CC816>.

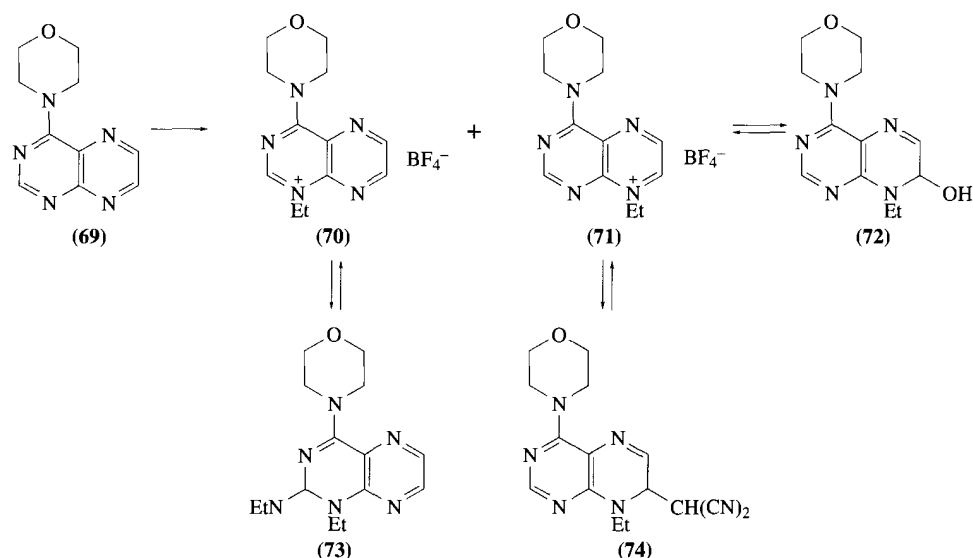
7.18.5.3 Electrophilic Attack at Carbon

There are very few direct electrophilic substitution reactions at the C-atoms of the pteridine nucleus due to its electron-deficient character. However, this deficit can be counteracted by electron-releasing groups and that may be the reason why 8-ribityl-7(8*H*)-lumazinone (**66**) could be attacked by *p*-nitrophenyldiazonium ion to give the 6-*p*-nitrophenylazo derivative (**67**) and, probably via the *p*-nitrophenyl radical, 6-*p*-nitrophenyl-8-ribityl-7(8*H*)-lumazinone (**68**) (Equation (4)) <84HCA570>.



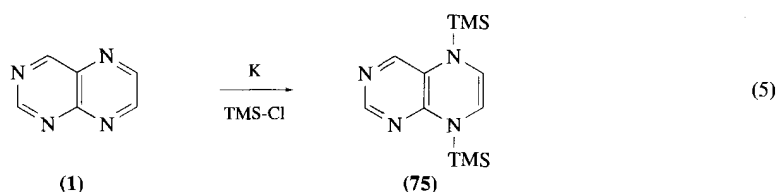
7.18.5.4 Electrophilic Attack at Nitrogen

Quaternization reactions of pteridines at the ring N-atoms will be facilitated by the presence of electron-donating groups at the carbon centers. 4-Morpholinopteridine (**69**) reacts with triethyloxonium tetrafluoroborate to give the isomeric 1- (**70**) and 8-ethylpteridinium salts (**71**) (Scheme 8). The reactivities of these species are different since (**71**) forms a covalent hydrate (**72**) in water but (**70**) does not. Adducts with diethylamine and malononitrile, respectively, are formed in the same manner but have so far, and in analogy to the reactions of the nucleophiles alcohols, amines, and CH-active compounds with (**70**), only been detected by ^1H NMR spectroscopy in solution (**74**) and at reduced temperatures (**73**), respectively (Scheme 8) <85CHE1048>.

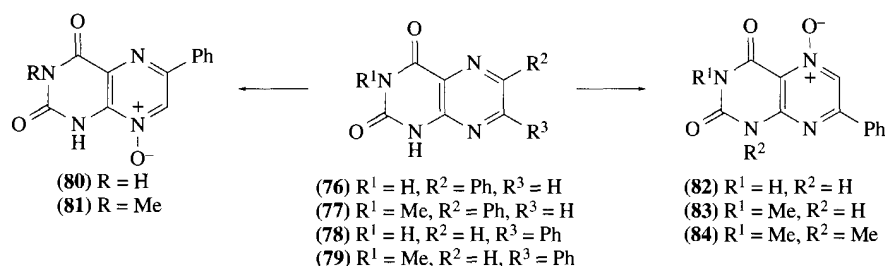


Scheme 8

Reductive silylation of pteridine (1) with potassium and trimethylsilyl chloride in THF leads in low yield to 5,8-bis-trimethylsilyl-5,8-dihydropteridine (75), which was characterized by NMR and is a highly reactive substance due to its conjugated 8π -electron system (Equation (5)) <89JOM(362)37>.



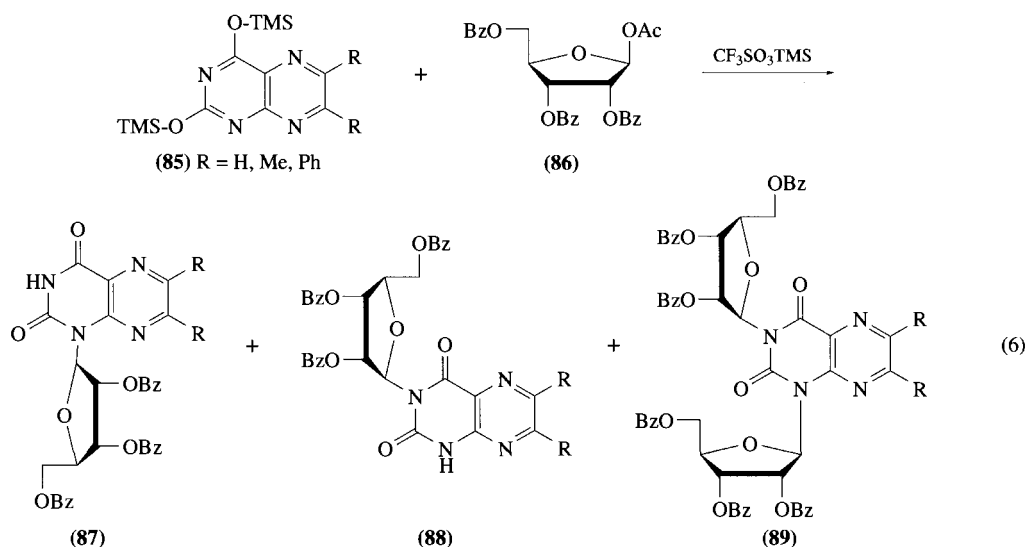
N-Oxidation is another possibility for the modification of a nitrogen heterocycle. In the lumazine series *N*-oxidation at the pyrazine moiety is strongly dependent on adjacent substituents. 6-Phenyl-lumazine (76) and its 3-methyl derivative (77) form the *N*(8)-oxides (80) and (81) while the isomeric 7-phenyllumazines (78) and (79) afford the *N*(5)-oxides (82) and (83) (Scheme 9). Prolonged treatment in TFA with H_2O_2 gave (only with (78) and (79)) the corresponding 5,8 dioxide (Scheme 9) <83LA852>. Steric effects were also seen during methylation by DIM/ OH^- yielding from compound (80) only methylation at N-3 (81). However, the isomer (82) formed the 1,3-dimethyl derivative (84) (Scheme 9).



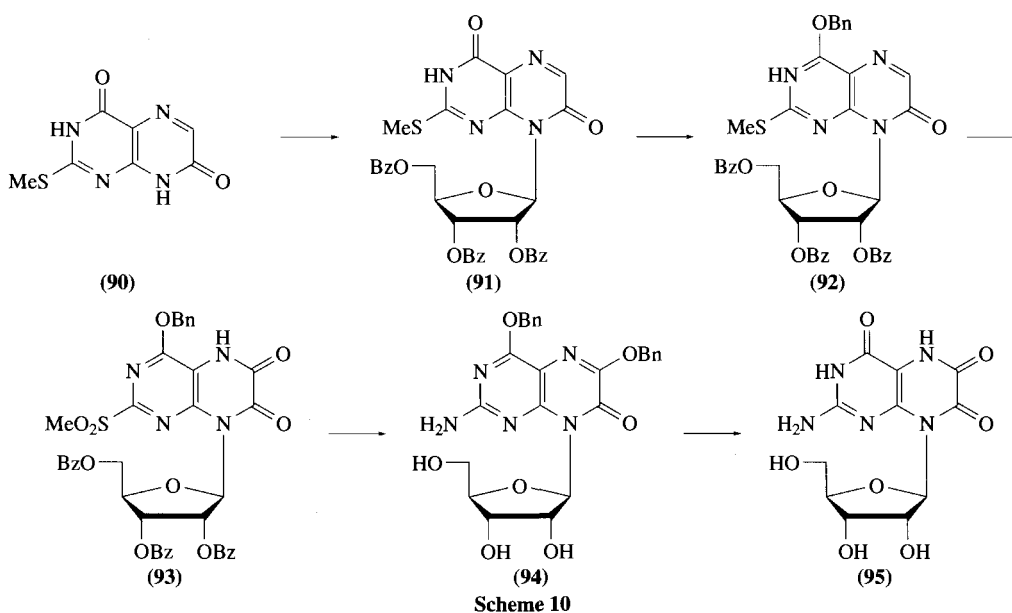
Scheme 9

The synthesis of pteridine nucleosides from pteridones can be considered as an electrophilic attack on a ring N-atom forming an *O,N*-acetal. A large number of N-1, N-3, and N-8 substituted ribo-, 2'-deoxyribo-, arabo-, xylo-, and gluconucleosides have been synthesized and described <B-94MI 718-01>. The best and most universal approach has been recognized in the "silyl-method" based on the Hilbert-Johnson-Birkofer reaction. Lumazine (3) reacts with hexamethyldisilazane to 2,4-bis-trimethylsilyloxypteridine (85), which condenses with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (86) under SnCl_4 , BF_3 or trimethylsilyl triflate catalysis to a mixture of *N*(-1)-mono (87),

N(-3)-mono- (**88**), and *N*(-1),*N*(-3)-diribofuranosides (**89**), depending on the reaction conditions (Equation (6)).



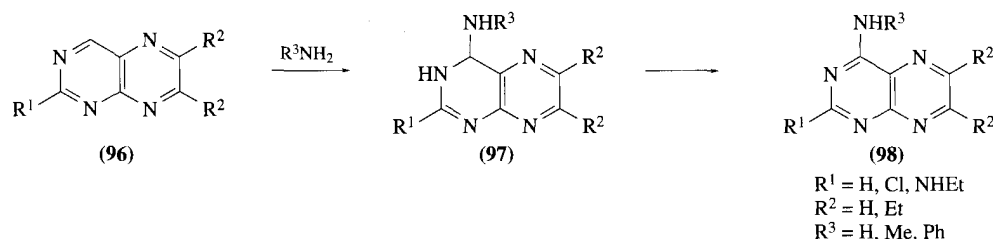
Pteridine-2'-deoxyribonucleosides are more difficult to synthesize since the missing neighboring participation effect of the 2'-*O*-acyl function allows no stereospecific glycosidic bond formation but leads in most cases to an α,β -anomeric mixture which is often difficult to separate into the pure components. The structural assignments of the anomers is also problematic and is best achieved by applying ^1H -NOE difference spectroscopy <92HCA1267> or, even more reliably, x-ray analysis <92HCA1267>. Structurally more complex pteridine nucleosides like leucopterine *N*(-8)- β -D-ribofuranoside (**26**) usually afford a series of reactions since the nucleobases do not react at all. 2-Methylthio-4,7(3*H*,8*H*)pteridinedione (**90**) is preferentially ribosylated in position 8 (**91**). When the 4-oxo function was subsequently protected by *O*-benzylation (**92**), oxidation led to the 2-methylsulfonyl group with simultaneous oxidation at C-6 to give compound (**93**) (Scheme 10). Another *O*-benzylation followed by ammonia treatment afforded 2-amino-4,6-dibenzyloxy-8-(β -D-ribofuranosyl)-7(8*H*)-pteridone (**94**). Debenzylation to (**95**) was achieved by catalytic hydrogenation over Pd/C (Scheme 10) <89ZAAC(577)39>.



Since the beginning of the 1990s studies have been concentrated on the synthesis of more functionalized lumazine nucleosides <90MI 718-06, 93MI 718-17> with further modifications at the sugar moiety <94MI 718-03>.

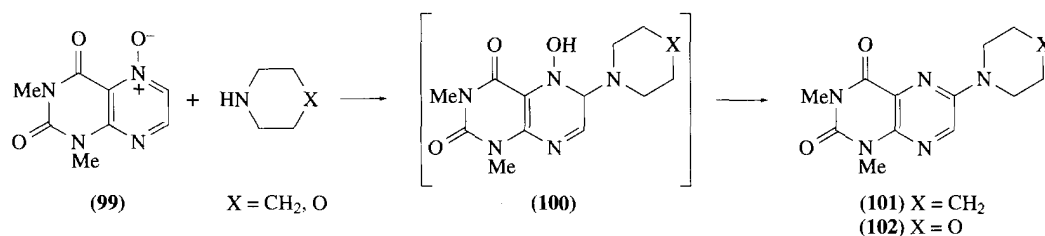
7.18.5.5 Nucleophilic Attack at Carbon

Nucleophilic attack at the ring C-atoms of the pteridine nucleus with substitution of hydrogen is in general difficult due to the unfavored leaving group properties of the hydride ion. These difficulties can be overcome if nucleophilic addition (97) is combined with a subsequent oxidation step, as shown with pteridine itself and some of its 2- and 6,7-substituted derivatives (96) in liquid ammonia and in the presence of KMnO_4 (leading to 4-aminopteridines (98)) (Scheme 11) <82JHC1527, 86JHC477>.



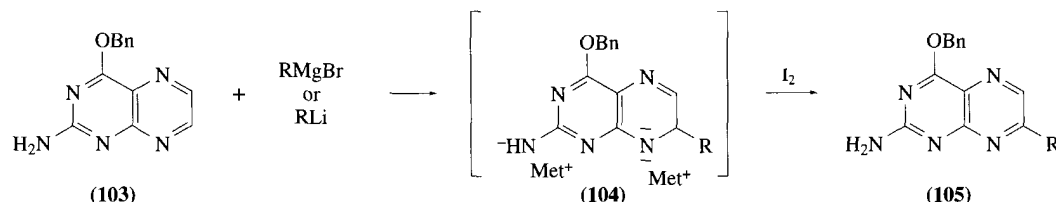
Scheme 11

Similarly 1,3-dimethylumazine undergoes oxidative amination with *t*-butylamine, piperidine, and morpholine at 10–15°C in the presence of soluble $[\text{Ag}(\text{C}_5\text{H}_5\text{N})_2]\text{MnO}_4$ to form the corresponding 7-alkylamino-1,3-dimethylumazines. Formation of the 7-amino derivative was achieved using KNH_2 in liquid NH_3 and KMnO_4 <90KGS1575>. Interestingly, 1,3-dimethylumazine 5-oxide (99) reacts readily at room temperature with piperidine and morpholine, respectively, to give in 90% yield 6-piperidino-(101) and 6-morpholino-1,3-dimethylumazine (102), probably via the intermediary adduct (100) (Scheme 12) <91KGS675>.



Scheme 12

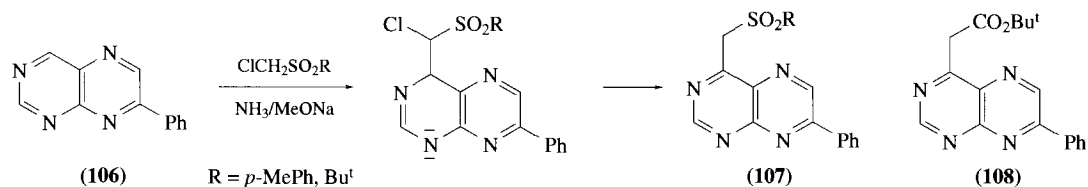
Analogous C—C bond formation can be achieved using Grignard reagents or alkyllithium compounds followed by iodine oxidation. 2-Amino-4-butoxypteridine (103) was transferred in a regioselective manner by two equivalents of the carbanion via the intermediate (104) into the corresponding 7-substituted pteridines (105) in low yields (Scheme 13).



Scheme 13

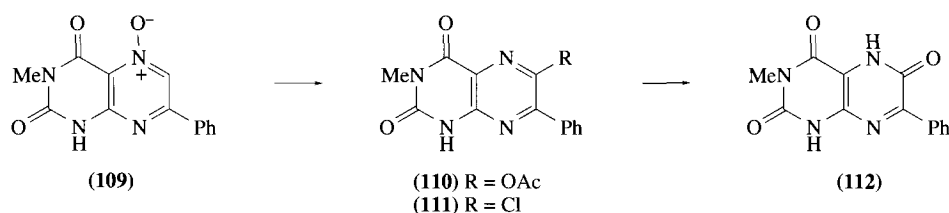
An interesting approach to the displacement of hydrogen in aromatics and heterocycles is the vicarious nucleophilic substitution (VNS) reaction. This generally involves carbanions containing the leaving group at the carbanionic center. The reaction proceeds via addition of the carbanionic species to the heterocycle to give anionic σ -adducts which are stabilized by base induced β -elimination to the substitution product. Pteridine itself is too labile for the VNS reaction, as a strongly

basic medium is necessary. However, 7-phenylpteridine (**106**) reacted with chloromethyl-*p*-tolyl-, chloromethyl-*t*-butyl sulfone, and also *t*-butylchloroacetate in liquid ammonia/CH₃ONa or Bu^tOK/DMF with substitution at the 4-position to give the products (**107**) and (**108**), respectively (Scheme 14) <88JPR789>.



Scheme 14

N-Oxides are also valuable intermediates for nucleophilic attack at the adjacent ring C-atom. 3-Methyl-7-phenyllumazine 5-oxide (**109**) reacts with Ac₂O in a Katada-rearrangement to give 6-acetoxy-3-methyl-7-phenyllumazine (**110**) which, on hydrolysis, or directly on treatment of (**109**) with 1 N KOH, forms 3-methyl-7-phenyl-6(5*H*)pteridone (**112**) (Scheme 15). Similarly, the *N*-oxide (**109**) rearranged with AcCl in TFA to 6-chloro-3-methyl-7-phenyllumazine (**111**) (Scheme 15). 3-Methyl-7-phenyllumazine 5,8-dioxide showed the same reactions while the 8-oxide function was not affected at all <83LA852>.

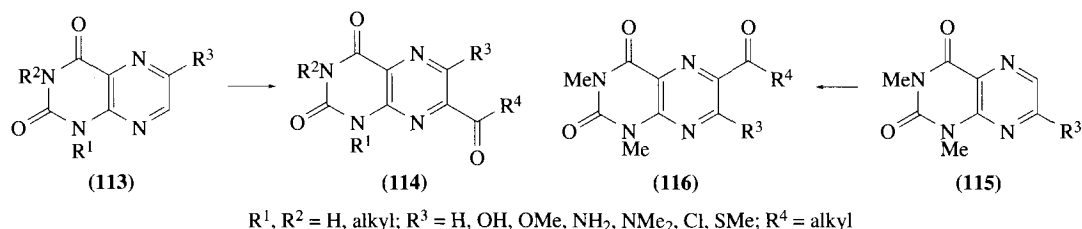


Scheme 15

7.18.5.6 Radical Attack at Carbon

An alternative method for the substitution of a hydrogen atom in π -electron deficient heterocycles is using the nucleophilic character of radicals in homolytic aromatic displacement reactions <74AHC(16)123>. Acylation with acyl radicals derived from aldehydes is an especially important approach since Friedel–Crafts-type reactions are not applicable to pteridines.

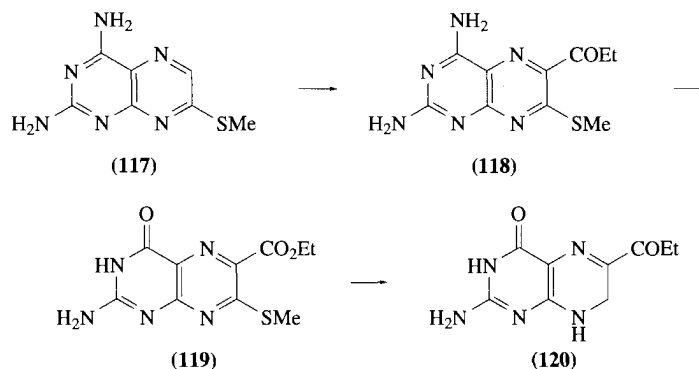
1- and 3-Mono- as well as 1,3-dialkylumazines (**113**) react preferentially at the most deficient 7-position affording the 7-acyl derivatives (**114**) in good yields (Scheme 16). The presence of a 7-alkyl-substituent (**115**) directs the incoming acyl group to the 6-position (**116**) (Scheme 16). Functional groups at C-6 or C-7, including a chloro, hydroxy, alkoxy, alkylthio, or amino substituent, facilitate radical acylation at the unsubstituted site of the pteridine nucleus <84LA1798>.



Scheme 16

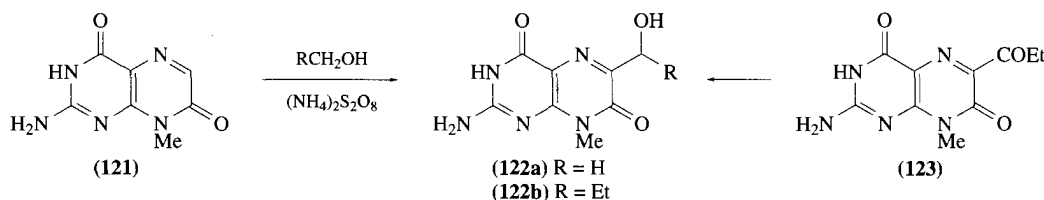
2,4-Diamino-, 4-amino-2-methylthio-, and 2-amino-4-alkoxy-pteridines react similarly <86MI 718-05, 88HCA531>. Deoxysepiapterin (**120**), one of the two yellow *Drosophila* eye-pigments, could be

synthesized by this approach starting from 2,4-diamino-7-methylthiopteridine (**117**) (Scheme 17). Acylation with the propionyl radical gave (**118**) which was hydrolyzed to 7-methylthio-6-propionylpterin (**119**) for further treatment by aluminum amalgam to remove the methylthio group and to reduce to the 7,8-dihydro-6-propionylpterin (**120**) (Scheme 17).



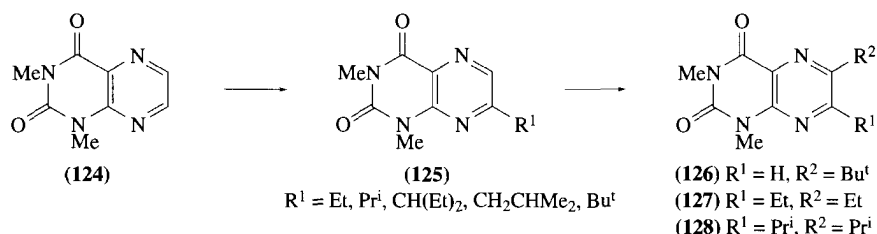
Scheme 17

The revised structure of leucettidine (**443**) was proven by an analogous series of reactions starting from 1-methyl-7-methylthiolumazine <88T3373>. Another possibility for C—C bond formation is revealed in the homolytic 1-hydroxyalkylation using primary and secondary alcohols with ammonium peroxydisulfate in phosphate buffer at pH 5–6. 8-Methyl-isoxanthopterin (**121**) reacted to give several 6-(1-hydroxyalkyl) derivatives of which 6-hydroxymethyl- (*asperopterin B*) (**122a**) and 6-(1-hydroxypropyl)-8-methylisoxanthopterin (*photinuspterin*) (**122b**) are naturally occurring pteridines (Scheme 18) <86TL4179, 93MI 718-15>. Compound (**122b**) can also be obtained by NaBH₄ reduction of 8-methyl-6-propionylisoxanthopterin (**123**) (Scheme 18).



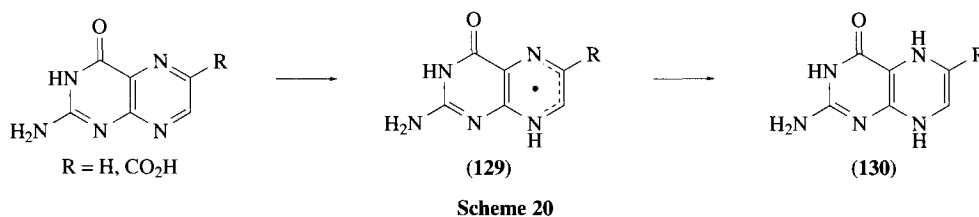
Scheme 18

Radical alkylations of 1,3-dimethylumazine (**124**) also favor the 7-alkyl derivatives (**125**) due to the preferred resonance stabilization of the primary σ -complex in this radical nucleophilic substitution reaction (Scheme 19). Minor amounts of the 6-isomer are observed with *t*-butyl radicals (**126**) and disubstitution is observed with ethyl (**127**) and isopropyl (**128**) radicals (Scheme 19) <86JHC1893>.



Scheme 19

Pulse radiolysis experiments showed that the reaction of pterin and pterin-6-carboxylate, respectively, with CO₂^{•-} at pH 7 produced first a monohydropterin radical (**129**) and in the second reduction step the 5,8-dihydro derivatives (**130**) (Scheme 20). Over the pH range 6–10, titration of the pterins with CO₂^{•-} led to a two-electron equivalent reduction with no incorporation of CO₂ <91JCS(P2)1687>.

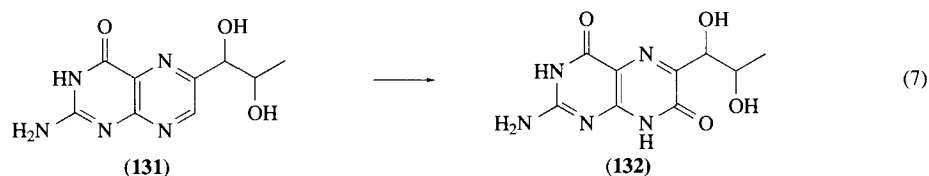


7.18.5.7 Cycloadditions

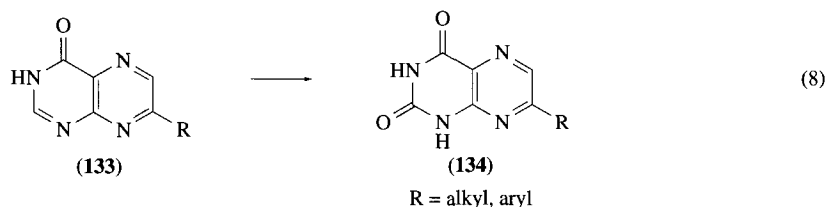
Thermal intermolecular reactions with cyclic transition states have so far not been investigated in the pteridine series despite the facts that transformations of this type are characteristic of compounds with low aromaticity.

7.18.5.8 Enzymatic Reactions

Enzymatic reactions are usually very specific and can therefore be applied as an effective alternative to the chemical synthesis of sensitive molecules even on a preparative scale. The enzymatic conversion of the four stereoisomers of biopterin to the corresponding 7-oxo-biopterin isomers was performed with a new pterin 7-oxidase extracted from carp skin <90MI 718-11>. The chiral centers of the side chains were preserved during this interconversion, and it could be proven from HPLC and CD spectral studies that natural *ichthyopterin* (**132**), first isolated by Hüttel and Sprengling <43LA(554)69> in 1943 from skin and scales of *Cyprinidae* and later found in several species of fish <56MI 718-01, 59LA(625)133, 59ZN(B)358, 60MI 718-01, 76MI 718-02> and also in the integument of the scorpion fly *Panorpa japonica* <83E742>, has the same *L-erythro* configuration as biopterin (**131**) (Equation (7)).

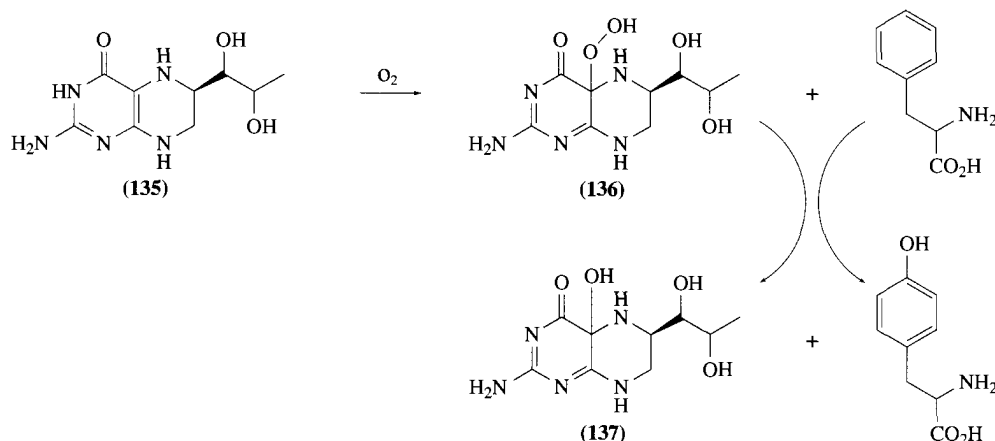


Immobilized and soluble free xanthine oxidase accepts 7-alkyl-, 7-phenyl-, and 7-*p*-substituted-phenyl-4(3*H*)-pteridones (**133**) as substrates which are oxidized to the corresponding 7-substituted lumazine derivatives (**134**) in high yields (Equation (8)) <79RTC224>. The isomeric 6-aryl-4(3*H*)-pteridones are poor substrates for xanthine oxidase and inhibit the oxidation of xanthine to uric acid. With *Arthrobacter* M-4 xanthine oxidase 6-aryl-4(3*H*)-pteridones have also been oxidized exclusively at C-2 <87JHC441>. The 3-alkyl-6-phenyl-4(3*H*)-pteridones are less tightly bound to the enzyme and the presence of an 8-oxide function lowers the binding of the substrate even further <87JHC1109>.



The mammalian aromatic amino acid hydroxylases—phenylalanine, tyrosine, and tryptophan hydroxylase—are a unique class of monooxygenases in their use of tetrahydropterins as obligatory cofactors <88ACR101>. The hydroxylases generate an intermediate from oxygen capable of performing the energetically difficult task of hydroxylating an unactivated aromatic ring. The tetrahydrobiopterin (**135**) participates in the process of O₂ activation directly in forming a 4a-hydroperoxide (**136**) which functions as an oxygen electrophile and reacts, for example, with phenylalanine (Scheme 21). This gives rise to the intermediacy of an arene oxide stabilizing itself by

the NIH shift mechanism <66BBR(25)253> to the corresponding hydroxy compound—tyrosine. The resulting pteridine derivative (**137**) is the covalent hydrate of the quinonoid dihydro species (Scheme 21).

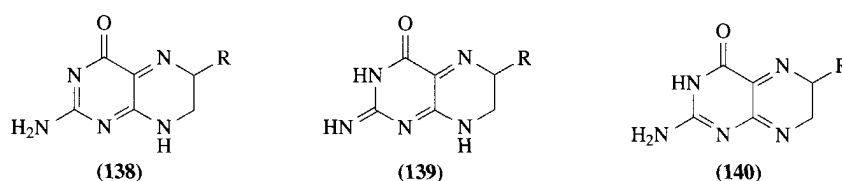


Scheme 21

7.18.6 REACTIVITY OF NONCONJUGATED RINGS

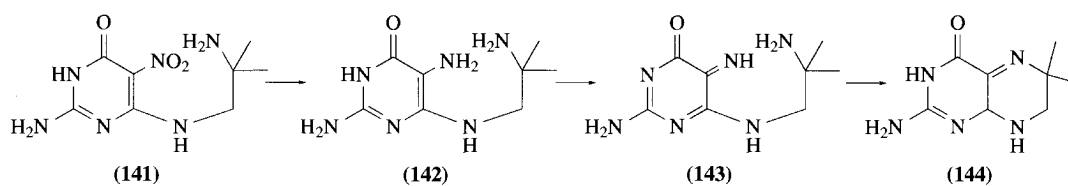
7.18.6.1 Dihydro Derivatives

The chemical properties of the dihydropteridines are quite different depending upon the site of reduction <B-87MI 718-04>. Among the various dihydropteridine derivatives the quinonoid dihydropterins play an important role due to their formation during the course of enzyme turnover of tetrahydropterins in biological hydroxylation reactions of aromatic amino acids <B-74MI 718-01>. The quinonoid dihydropterins may also be generated by a wide variety of chemical oxidants including bromine, 2,6-dichloroindophenol <61JBC(236)804>, and ferricyanide <70CJB278> as well as H_2O_2 and peroxidase <69MI 718-01>. There are several postulated tautomeric structures for the quinonoid dihydropterins (**138**)–(**140**) of which the *para* isomer with an exocyclic amino group (**138**) appears the most likely from NMR and UV data <82JA6871>.



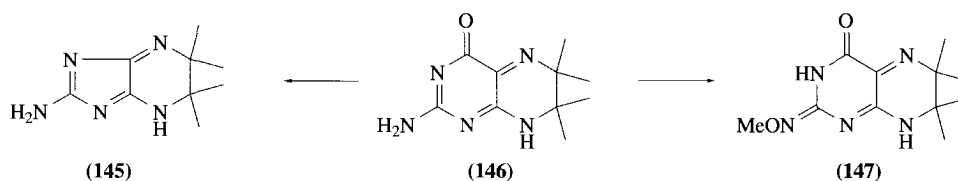
Further proof is derived from ^{15}N NMR studies establishing from the chemical shifts of the ^{15}N resonances that the endocyclic quinonoid 6,7-dimethyl-7,8-dihydro-6*H*-pterin tautomer (**138**; R = Me) is the predominant form in aqueous solution at near neutral pH <85JA3706>. From electrochemical studies with various *N*-methyl-blocked tetrahydropterin derivatives the $2e^-/2H^+$ oxidation process to the quinonoid-type intermediates is confirmed. Unfortunately, the spectra of these compounds obtained by thin-layer spectroelectrochemistry are too similar for an exact assignment and experimental proof of the endocyclic quinonoid tautomer (**138**) <83MI 718-07>. The first stable quinonoid dihydropterin was obtained by the synthesis of 6,6-dimethyl-6,7-dihydro-8*H*-pterin (**144**) from an open-chain pyrimidine precursor (**141**) by an oxidative cyclization (Scheme 22) <83BI790>. An analogous approach was chosen for the stereospecific synthesis of 6(*R*)- and 6(*S*)-propyl-5,6,7,8-tetrahydropterins starting from the corresponding chiral ethanediamines. Oxidative cyclization to the quinonoid dihydropterins was performed, and, subsequently, reduction <92JOC4470>.

The 1,5-quinonoid 6,6,7,7-tetramethyl-6,7-dihydro-8*H*-pterin (**146**) reveals interesting reactivity towards nucleophiles due to the blocked 6-position. Solvolysis with OH^- leads via ring contraction to 2-amino-5,5,6,6-tetramethyl-5,6-dihydroimidazo(4,5-*b*)pyrazine (**145**) and *O*-methylhydroxyl-



Scheme 22

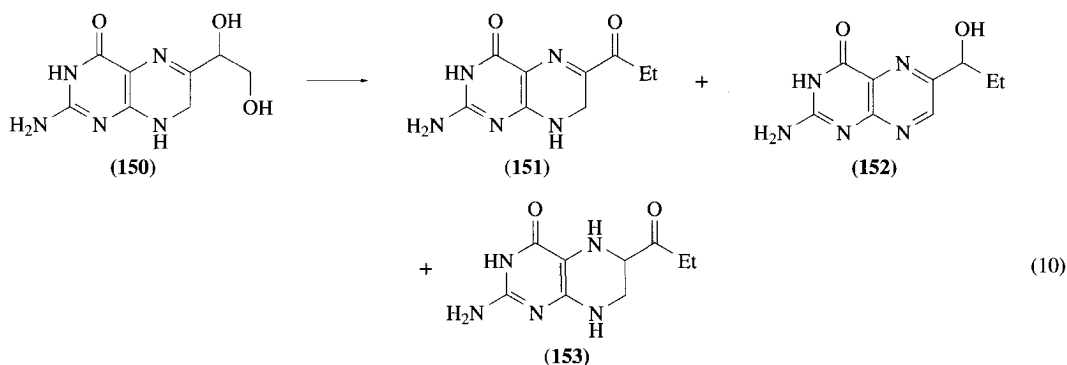
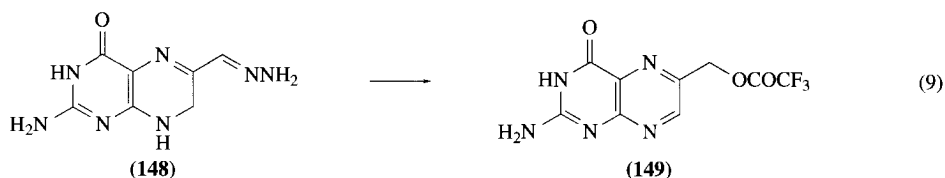
amine reacts with displacement of the 2-amino group to give compound (147) (Scheme 23). Treatment with chlorine led to an unidentified *N*-chloro derivative <86MI 718-01>.



Scheme 23

Despite the instability of the quinonoid 6-monosubstituted-6,7-dihydro-8*H*-pterins it was possible to prepare the 6-methyl- and 6,7-dimethyl-derivatives <85TL4003>, as well as the quinonoid (6*R*)-dihydrobiopterin <86TL585>, as solid materials, by H_2O_2 oxidation in the presence of KI.

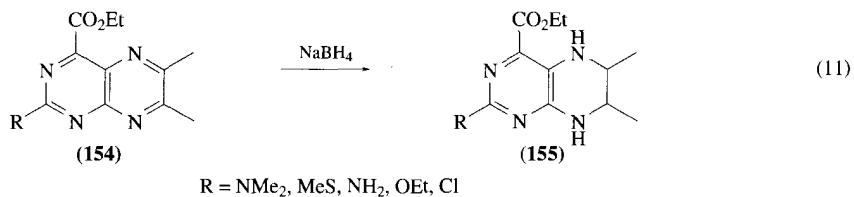
7,8-Dihydropterins can undergo intra- and intermolecular redox reactions involving the heterocyclic ring as well as the sidechains. Treatment of 6-formyl-7,8-dihydro-pterin-hydrazone (148) with trifluoroacetic acid led to 6-trifluoroacetoxyethylpterin (149) (Equation (9)) <65HCA452>. The slow conversion of 7,8-dihydro-6-hydroxymethylpterin in TFA into (149) and 7,8-dihydro-6-methylpterin is the result of an intermolecular redox reaction <84C429>. In a more complex case 7,8-dihydrobiopterin (150) is converted in dilute acetic acid into a mixture consisting of deoxysepiapterin (151), 6-(1-hydroxypropyl)-pterin (152), 5,6,7,8-tetrahydro-6-propionylpterin (153), and biopterin (131) (Equation (10)) <78HCA2731>.



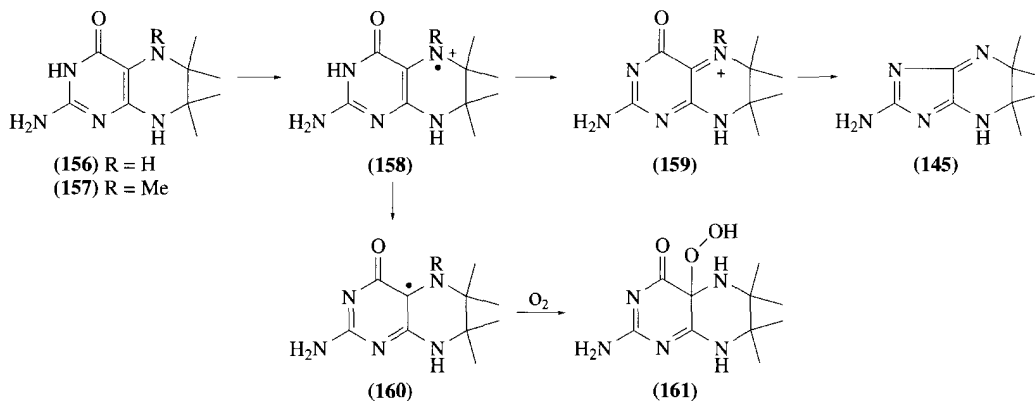
The synthesis of functionalized 7,7-dialkyl-7,8-dihydropterins and a 7-spirocyclopropane derivative have been performed to find new types of inhibitors for 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase and dihydrofolate reductase <85JCS(P1)2133, 85JCS(P1)2145, 89JCS(P1)1297>. An informative review on the chemical and biological reactions of reduced pterins is also available <84MI 718-08>.

7.18.6.2 Tetrahydro Derivatives

Tetrahydropterins are highly reactive in oxidation reactions and are even able to activate oxygen for hydroxylations, especially of aromatic compounds. The autoxidation is due to the electron-donating groups such as amino and hydroxy functions, whereas removal of such substituents enhances the stability of the reduced pteridine nucleus tremendously <59JA2464>. In view of these aspects it is not surprising that 2-substituted ethyl 5,6,7,8-tetrahydropteridine-4-carboxylates (**155**) obtained by NaBH₄ reduction from the corresponding ethyl pteridine-4-carboxylates (**154**) are easy to handle and stable in air (Equation (11)) <85JOC388, 89JCR(S)282>. There is resonance between the *N*(5)-H and the ester function converting the nucleophilic *N*(5)-H group into an amide-type stabilization.



The 6,6,7,7-tetramethyl-5,6,7,8-tetrahydropterin (**156**), its 5-methyl- (**157**), and 6,7,8-dihydro- (**145**) derivatives have been investigated as models for the biopterin center of aromatic amino acid mixed function oxidases <84JA7916>. Compound (**159**) is obtained by a 2e⁻ oxidation of (**156**), as also is (**157**), due to a rapid demethylation reaction (Scheme 24). The semiquinone (**160**), achieved by mixing (**156**) and (**146**) in 1 N HCl, is less stable than are flavin radical species but 1e⁻ oxidation of (**157**) forms a radical cation (**158**) stable enough to be observed by cyclic voltammetry (Scheme 24). Oxidation by O₂ occurs by 1e⁻ transfer to oxygen and coupling of the resultant species to form unstable peroxides (**161**). The great instability of the pteridinium cation (**159**) does not allow the synthesis of a 4a-hydroperoxy adduct (**161**) (Scheme 24). The quinonoid species rearrange in a general base-catalyzed reaction to 7,8-dihydropterins. The 6,6-dimethyl-substituted analogues cannot undergo such a tautomerism but show instead a ring contraction followed by decarboxylation to imidazo[4,5-*b*]pyrazines (**146**). There is also evidence from model studies that the hydroxylation of phenylalanine by 6,7-dimethyl-5,6,7,8-tetrahydropterin under aerobic conditions is caused by hydroxyl radicals formed during autoxidation of the cofactor <84CPB752>.

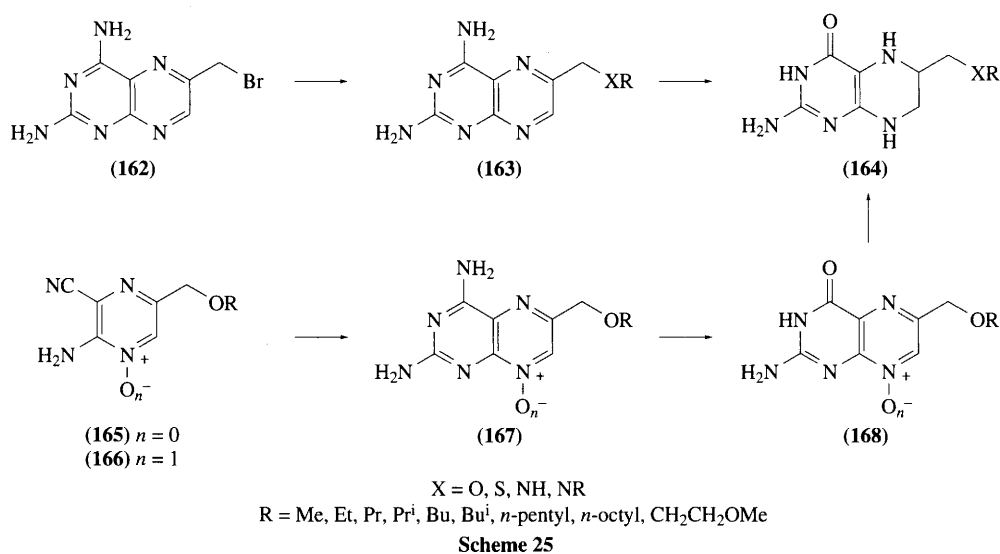


Scheme 24

Catalytic reduction of biopterin in TFA leads, after acetylation, to a 1:3 mixture of (6*S*)- and (6*R*)-tetraacetyl-5,6,7,8-tetrahydrobiopterin whereas the same procedure starting from *N*²,1',2'-triacylbiopterin in EtOH gave a 3:1 mixture <84AJC355>. However, catalytic hydrogenation of biopterin over platinum oxide at pH 11.4 proceeded highly stereoselectively and gave, after subsequent crystallization from HCl/EtOH, unexpectedly, the pure (6*R*)-isomer as a dihydrochloride salt (67% isolated yield) <84CL735>. Other 6-hydroxyalkylpterins also show stereoselective hydrogenation forming one stereoisomer in preference, according to the adjacent chiral center <85H(23)3115>.

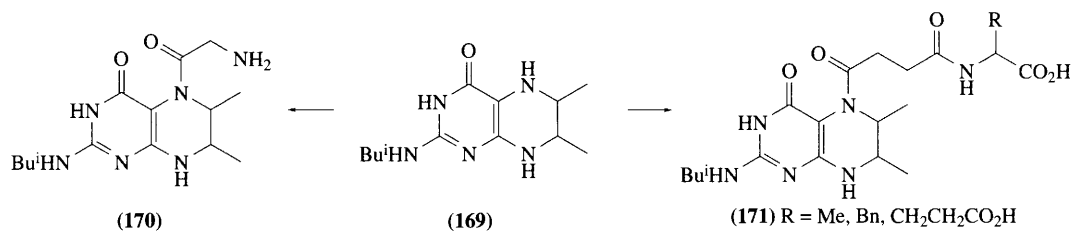
Several efforts have also been undertaken to synthesize various 6-substituted 5,6,7,8-tetrahydropterins as simplified analogues of tetrahydrobiopterin with potential cofactor activity. A

valuable starting material for such studies is found in the 6-bromomethyl-2,4-diaminopteridine (**162**) <79JHC537, 77JOC208> which can be substituted in the sidechain by *O*-, *S*-, and *N*-nucleophiles. Direct catalytic reduction forms the tetrahydro derivatives and hydrolysis to the corresponding pterins (**163**) yielded in TFA with Pt/H₂ the 6-substituted-tetrahydropterins (**164**) (Scheme 25) <B-85MI 718-07>. A series of 6-alkoxymethyl-5,6,7,8-tetrahydropterins (**164**) was also prepared by the Taylor approach starting from 6-alkoxymethyl-3-aminopyrazine-2-carbonitriles (**165**) and their corresponding 4-oxides (**166**) (Scheme 25). Cyclization with guanidine leads to the 6-alkoxyalkyl-2,4-diaminopteridine derivatives (**167**) which can be hydrolyzed to the pterins (**168**) used for further catalytic reduction to (**164**) (Scheme 25) <87JMC40>. Several lipophilic 6-alkyl-5,6,7,8-tetrahydropterins have been synthesized unambiguously by the Polonovski–Boon approach and have turned out to be good substrates for mammalian hydroxylases <87MI 718-07>.



Scheme 25

New amino acid-tetrahydropterin conjugates were synthesized from *N*²-isobutyryl-6,7-dimethyl-5,6,7,8-tetrahydropterin (**169**) by either direct acylation (**170**) or via a succinate linker (**171**) followed by removal of protecting groups and ammonia treatment to deblock selectively the isobutyryl group (Scheme 26) <89MI 718-08>.

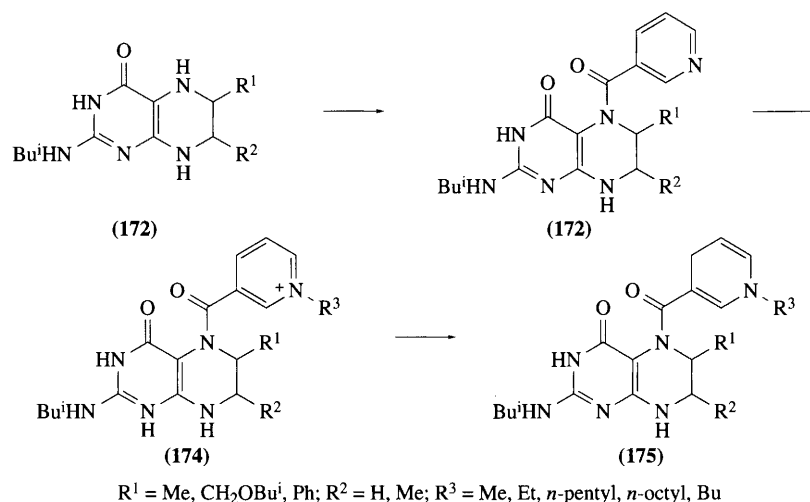


Scheme 26

In order to improve cell and blood–brain-barrier permeability of the polar tetrahydropterins model studies were performed by applying the concepts of the Bodor system. 6-Mono- and 6,7-disubstituted 5,6,7,8-tetrahydropterins (**172**) have been acylated with nicotinoyl chloride at N-5 (**173**) followed by quaternization of the pyridine moiety by various alkyl and aralkyl halides (**174**), respectively (Scheme 27). Reduction of the pyridinium residue to its 1,4-dihydro stage afforded new types of potentially active conjugates (**175**) (Scheme 27) <90MI 718-07, 91MI 718-03>.

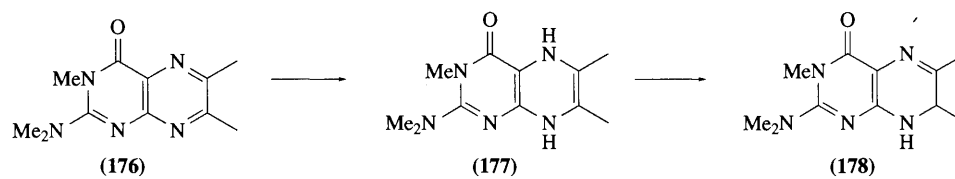
A series of unsubstituted, 6-methyl-, *cis*-6,7-dimethyl-, *cis*-2,6,7-trimethyl-, *cis*-6,7-dimethyl-2(1*H*)-thioxo-, and *cis*-6,7-dimethyl-2-methylthio-5,6,7,8-tetrahydro-4(3*H*)pteridineones were successfully prepared by NaBH₄ reduction since catalytic hydrogenations failed, not unexpectedly, in these cases <86AJC31>.

Electrochemical reductions of pteridines have been studied quite extensively <B-77MI 718-01> showing that a large number of pterins and related pteridines are reduced on a hanging mercury



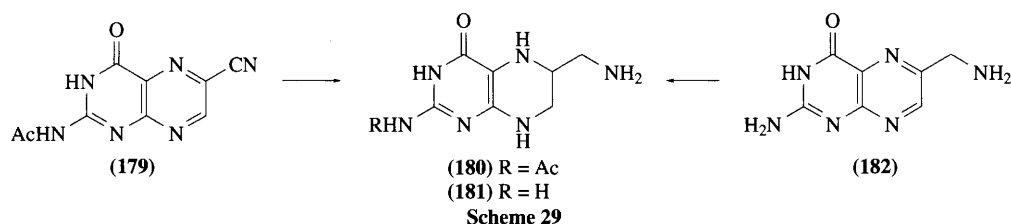
Scheme 27

drop electrode in a $2e^-/2H^+$ process to an unstable 5,8-dihydro derivative which quite rapidly rearranged in a pH-dependent reaction into the corresponding 7,8-dihydro compound <73BBA(297)285>. During the course of the reduction of 2-dimethylamino-3,6,7-trimethyl-4(3*H*)-pteridone (176) at a pyrolytic graphite electrode it was found that the primarily formed 5,8-dihydro derivative (177) is stable enough to be observed by thin-layer spectroelectrochemistry for the first time (Scheme 28) <83MI 718-03>. Slow tautomerism leads to the 7,8-dihydro derivative (178).



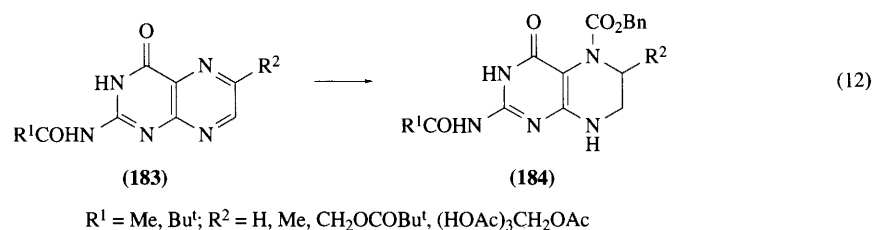
Scheme 28

Catalytic reduction of *N*²-acetyl-6-cyanopterine (179) proceeded well in TFA to the 2-acetamino-6-aminomethyl-5,6,7,8-tetrahydro-4(3*H*)pteridone (180) which was hydrolyzed by aqueous HCl to 6-aminomethyl-5,6,7,8-tetrahydropterin trihydrochloride salt (181) (Scheme 29) <88AJC667>. The same compound resulted also from the PtO_2/H_2 hydrogenation of 6-aminomethylpterine (182) (Scheme 29).



Scheme 29

Reduction has also been achieved by sodium cyanoborohydride which converted *N*²-acetyl- and *N*²-pivaloylpterine (183) in the presence of benzyl chloroformate into the corresponding 5-benzyloxycarbonyl-5,6,7,8-tetrahydropterine derivatives (184) (Equation (12)) <92JCS(P1)1245>.



Less soluble pteridines are converted, in the form of their soluble trimethylsilyl derivatives, by Pt/H_2 in benzene into the tetrahydro derivatives from which the silyl groups are cleaved by mild hydrolysis <88T5179>.

Tetrahydropterins are sensitive to autoxidation whereby in the first step the involvement of a trihydropterin radical was postulated <74Cl(L)233>. Such radicals have been produced in strongly acidic media by chemical oxidizing agents <67HCA411> and by photochemical methods in acetonitrile <89CL35>. More effective is the oxidation by the azide radical $\text{N}_3\cdot$ which can be generated conveniently through oxidation of N_3^- by $\cdot\text{OH}$ radicals, produced in the pulse radiolysis of N_2O -saturated solutions <90CJC1974>.

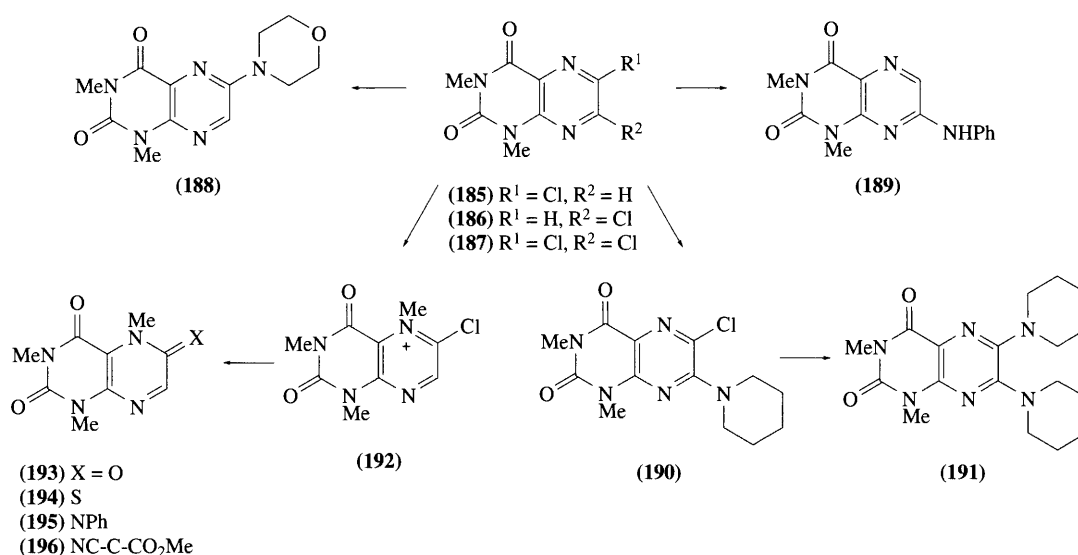
7.18.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.18.7.1 General Survey of Substituents on Carbon

The differences in the reactivities of the same substituents on a heteroaromatic nucleus and on benzene rings is a measure of the influence of the heteroatoms. The sp^2 -hybridized N-atom attracts electrons away from the carbon atoms of the ring. The influence for the α - and γ -positions is largest, for reasons of resonance. Good leaving groups are displaced easily by a two step addition–elimination mechanism which is most common with π -electron-deficient six-membered nitrogen heterocycles.

7.18.7.2 Nucleophilic Displacement

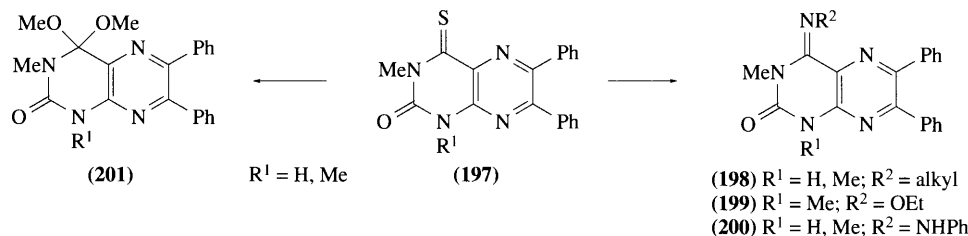
Nucleophilic displacement reactions at π -deficient nitrogen heterocycles can be regarded as the most versatile synthetic reactions for a broad variety of modifications. Good leaving groups facilitate this type of reaction. 6-Chloro- (185), 7-chloro- (186), and 6,7-dichlorolumazines (187) react with a large number of *N*-nucleophiles (Scheme 30) <89MI 718-07>. The 7-chloro group is much more reactive than the 6-chloro substituent: compound (187) is selectively substituted at position 7 (190) while prolonged heating affords disubstitution (191) (Scheme 30).



Scheme 30

Quaternization of compound (185) at N-5 by trimethyloxonium tetrafluoroborate increases reactivity to a large extent allowing displacement of the chlorine atom by *O*-, *S*-, *N*-, and *C*-nucleophiles in the 6-position (193)–(196) under mild conditions (Scheme 31) <86HCA704>. 3-Methyl- and 1,3-dimethyl-4-thiolumazines (197) also show easy substitutions of the thioxo function. Ammonia

and primary amines lead to the corresponding 4-imino derivatives (**198**) and hydroxylamine and hydrazines, respectively, form amidoximes (**199**) and amidrazones (**200**) (Scheme 31). Treatment of (**197**) with sodium methoxide in the presence of HgBr_2 results in amidacetal formation (**201**) (Scheme 32) <86MI 718-06>.



Scheme 31

The less reactive halogen in 6-chloro-1,3-dimethylumazine and 2-amino-6-chloro-4-(*n*-pentyl-oxy)pteridine, respectively, shows smooth nucleophilic displacement by NaSH to form 1,3-dimethyl-6(5*H*)lumazinethione <86HCA708> and *O*⁴-*n*-pentyl-6-thioxanthopterin <92HCA2317>.

7.18.7.3 Electrophilic Attack

Diazotization reactions of aminopteridines are initiated by an electrophilic attack of the nitrosonium ion at amino functions. The resulting diazonium derivatives are very unstable and are converted into the corresponding pteridinones. It is interesting to note that in the pteridine series the 2-amino group can be displaced by a hydroxy group whereas the 4-amino function is stable under these conditions. 2,4-Diaminopteridine reacts with nitrous acid to form isopterin (4-amino-pteridin-2-one). Similar treatment of 2,6-diamino-7-methyl-4(3*H*)-pteridin-4-one gave 7-methyl-2,4,6(1*H*,3*H*,7*H*)-pteridinetrione <55JCS1113>.

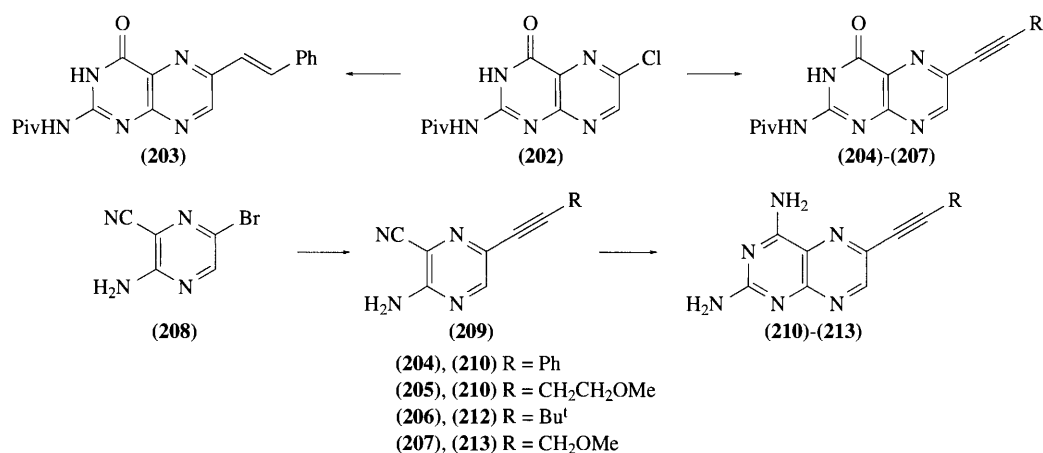
The acylation of primary and secondary aminopteridines proceeds quite readily leading mainly to monoacyl derivatives. Acetylation has been, by far, the most common process yielding from 2-, 4-, and 7-aminopteridine the corresponding 2-, 4-, and 7-acetaminopteridine, respectively. Pterin (**2**) reacted to form *N*²-acetylpterin which easily hydrolyzes back to pterin due to activation of the amino group by the vinylogously located 4-oxo function <60CB2015>. 2,4-Diaminopteridine gave on heating in Ac_2O 2,4-bis-acetaminopteridine <70CB722> and the diuretic triamterene was transformed into 2,4,7-tris-acetamino-6-phenylpteridine.

7.18.7.4 Metal Catalyzed Substitutions

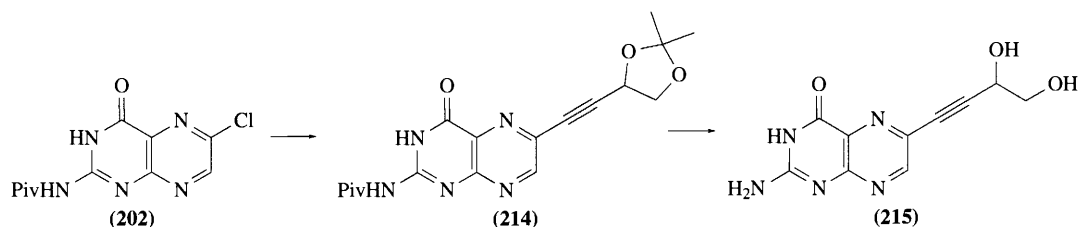
The Heck coupling reaction was found to work very well in the heterocyclic series, especially for converting halo-nitrogen heterocycles into the corresponding ethylene and alkyne derivatives, respectively. 6-Chloro-*N*²-pivaloylpterin (**202**) reacted to give *N*²-pivaloyl-6-styrylpterin (**203**) in 76% yield under palladium catalysis <87SC1865> (Scheme 32). Similarly, a new and unequivocal route to 6-substituted pteridines is available from compound (**202**) <87JOC3997> and 2-amino-6-chloro-4-pentyloxypteridine <90MI 718-09>, respectively, using alkynes as carbon source (**204**)–(**207**) (Scheme 32).

The C—C coupling reaction has also been performed with halopyrazine derivatives (**208**) which are converted into the 2-amino-3-cyano-5-ethynylpyrazines (**209**) in good yield and subsequent cyclization with guanidine gives the 2,4-diamino-6-ethynylpteridines (**210**)–(**213**) (Scheme 32). The synthesis of the dephospho form A, derived from the molybdenum cofactor on oxidative degradation, followed the same principle by reacting (**202**) with (*S*)-3,4-dihydroxybutyne acetonide to give (**214**) and its subsequent hydrolysis to (*S*)-6-(3,4-dihydroxybut-1-ynyl)pterin (**215**) (Scheme 33) <89JA7664, 91TL7357>.

Palladium-effected synthesis of 5,10-dideazafoolic acid and its 5,6,7,8-tetrahydro derivative



Scheme 32



Scheme 33

<89JOC3618> as well as of 10-deazafolic acid and 10-deazaaminopterin <88JOC35> underline the high synthetic efficiency of the Heck reaction in C—C bond formations.

7.18.7.5 Oxidation Reactions

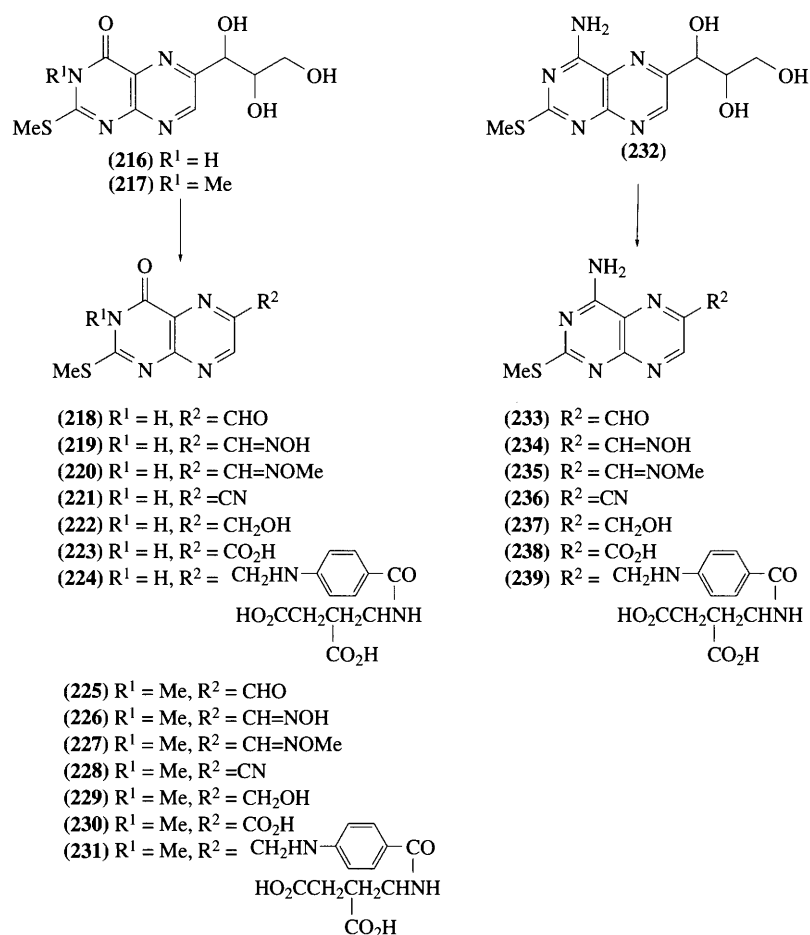
Pteridines carrying a polyhydroxyalkyl sidechain are valuable synthons for the synthesis of functionalized derivatives. Various 6-(1,2,3-trihydroxypropyl)pteridines (**216**, **217**, **232**) have been oxidized by periodate to the corresponding pteridine-6-carbaldehydes (**218**, **225**, **233**) which are further substrates for the interconversion into oximes (**219**, **220**, **225**, **226**, **234**, **235**), carbonitrile (**221**, **228**, **236**), hydroxymethyl (**222**, **229**, **237**) and carboxy derivatives (**223**, **230**, **238**) as well as folic acid analogues (**224**, **231**, **239**) (Scheme 34) <90MI 718-08>.

Oxidation reactions at the sulfur atom of thioamides reveal an interesting approach to reactive intermediates. 3-Methyl- and 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (**240**) can be oxidized to the corresponding sulfoxes (**241**) by H₂O₂ <86MI 718-06> and 1,3,5-trimethyl-6(5*H*)pteridinethione reacts analogously on treatment by *m*-chloroperbenzoic acid (Scheme 35) <86HCA704>. Aerobic photolysis forms the oxo derivatives (**242**) (Scheme 35).

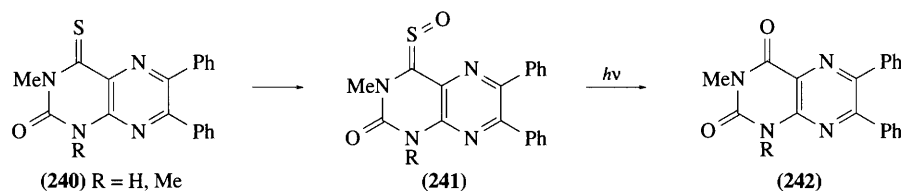
Oxidations of 1,3-dimethyl-6(5*H*)lumazinethione (**243**) and 1,3,6-trimethyl-7-thiolumazine by activated MnO₂ and KMnO₄ lead to the corresponding sulfinic (**244**) and sulfonic acids (**245**), respectively (Scheme 36).

Similarly, 2-thiolumazines (**246**) <89MI 718-09>, 6- and 7-hydroxy-2-thiolumazines <89MI 718-10> and 2-thio-6,7(5*H*,8*H*)lumazinediones <89MI 718-11> can be oxidized by H₂O₂ to the 2-sulfinates (**248**) and by KMnO₄ to the 2-sulfonates (**249**) (Scheme 37). Treatment of 6,7-diphenyl-2-thiolumazine with one equivalent of H₂O₂ gave the unstable 2-sulfenic acid which could be isolated as a silver salt (**247**). Oxidative desulfurization of (**246**) takes place in HCOOH with H₂O₂ forming first the sulfinic acid which eliminates SO₂ to give (**250**) (Scheme 37). The sulfinic and sulfonate groups are also prone to nucleophilic displacements when heated with amines, for example (**251**) and (**252**) (Scheme 37). In the 4-thiolumazine series the sulfinates and sulfonates are very reactive and cannot be isolated but their intermediate formation is obvious from mild displacements with amines <89MI 718-09>.

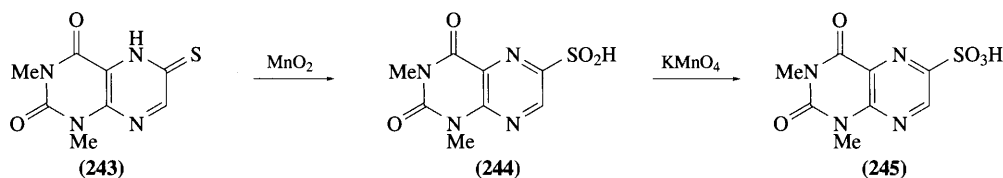
1,3-Dimethyl-6-methylthiolumazine reacted with *m*-chloroperbenzoic acid to give either the *S*-oxide or the corresponding 6-methylsulfone <86HCA708>.



Scheme 34



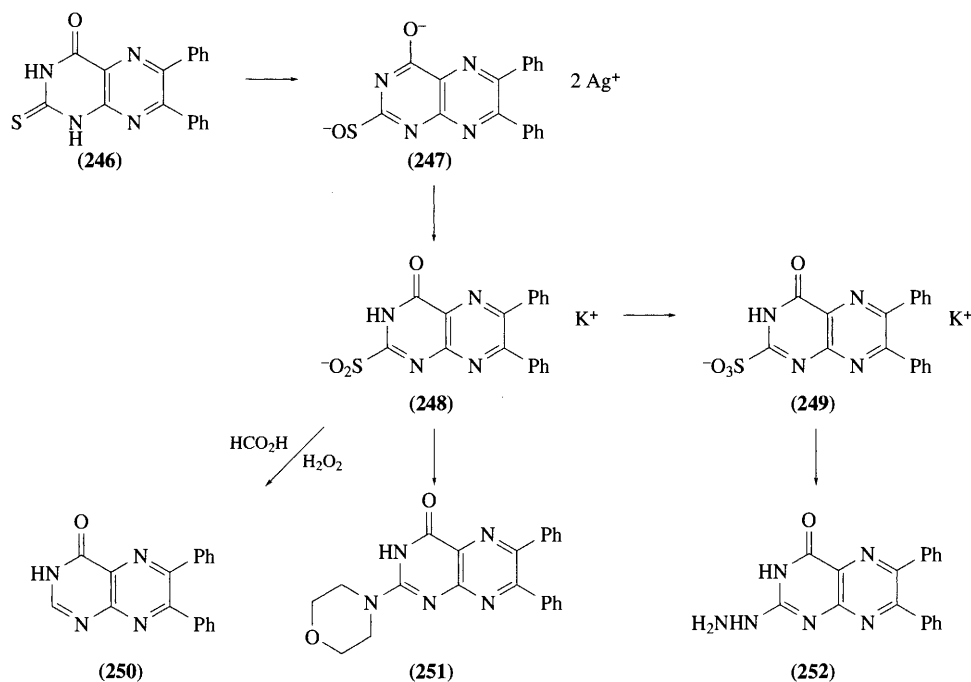
Scheme 35



Scheme 36

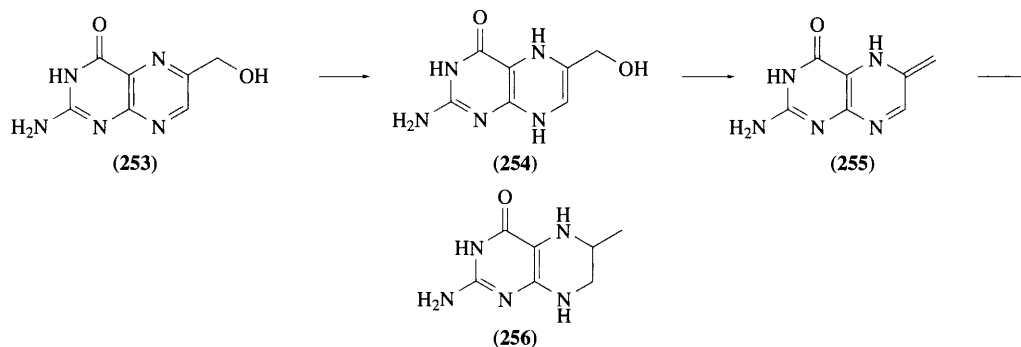
7.18.7.6 Reductive Cleavage

The reductive cleavage of thioamide and alkylthio groups by Raney nickel is a versatile method in nitrogen heterocyclic chemistry for indirect removal of oxo functionalities. Unfortunately, Raney nickel desulfurization of thiopteridines <70JOC4154> has so far not been achieved. However, attempts under milder conditions using Raney cobalt, copper/aluminum alloy or aluminum amalgam are successful as found with 2,4-diamino-7-methylthio-6-propionylpteridine and the corresponding 7-methylthio-6-propionylpterin <88HCA531>.



Scheme 37

Unusual sidechain reductions have been observed during catalytic hydrogenations of 6- and 7-hydroalkylpterins (**253**) leading finally to alkyl derivatives (**256**) (Scheme 38). It is assumed that no direct reductive cleavage of OH groups takes place but H_2O elimination gives (**255**) from the intermediate 5,8-dihydro species (**254**) and subsequent reduction of the $\text{C}=\text{C}$ bonds (Scheme 38) [B-89MI 718-02].

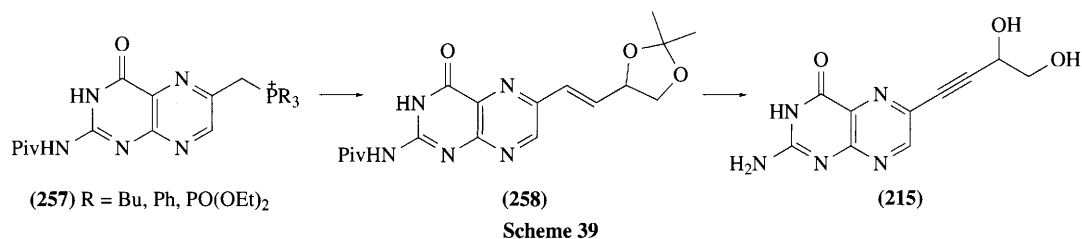


Scheme 38

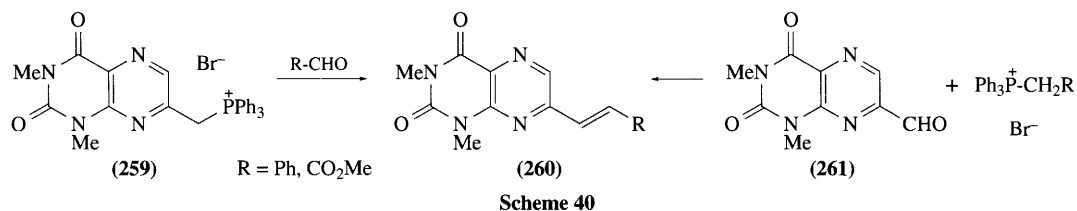
7.18.7.7 Side Chain Reactions

Structural modifications of the sidechain of heterocycles have a large synthetic potential which often has its counterpart in aliphatic chemistry. The Wittig alkenation was applied to pteridines for the first time by Piper and Montgomery in 1980 [80JMC320] using the intermediary pteridine ylide for the synthesis of 10-deaza-9,10-dehydroaminopterin, a structural analogue of 4-amino-folic acid. A similar approach was performed with N^2 -pivaloylpterin-6-ylmethyl-tributyl- and -triphenylphosphonium salts (**257**), respectively, and (*R*)-glyceraldehyde acetonide (Scheme 39). This led to the corresponding alkene (**258**) which gave, on bromination and subsequent dehydrobromination

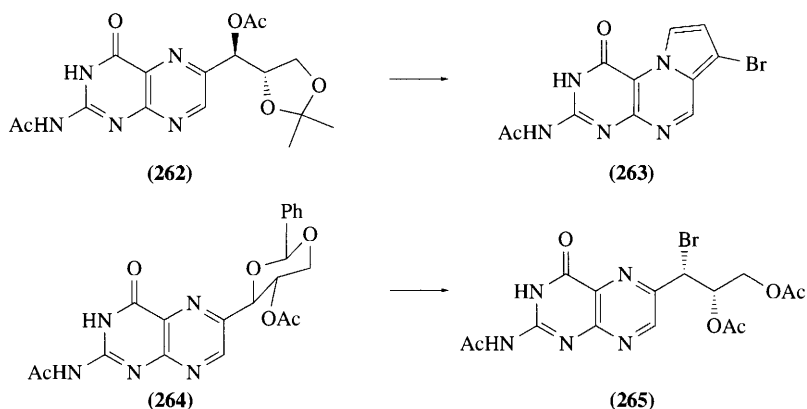
by dbu and hydrolysis, dephospho-form A (**215**), identical to the oxidative breakdown product of the molybdenum cofactor (Scheme 39) <92TL3371>.



Wittig condensations have also been successful with 1,3-dimethylumazin-6- or 7-ylmethyl-triphenylphosphonium salts (**259**) and benz- or pyridinecarbaldehydes leading to the corresponding styrene derivatives (**260**) (Scheme 40). The same products are obtained when 1,3-dimethylumazine-6- or 7-carbaldehydes (**261**) are reacted with benzyl-triphenylphosphonium bromide (Scheme 40) <B-92MI 718-03>. A normal aldol-type condensation is possible between 1,3,7-trimethylumazine and benzaldehyde under sodium methoxide catalysis but the isomeric 6-methyl derivative is not activated enough for this reaction. Similar reactions take place to form methyl β -(1,3-dimethylumazin-6- and 7-yl)acrylates, respectively.



Oxidative modifications of 6- and 7-alkylpteridines, respectively, can be regarded as an interesting possibility for the functionalization of carbon side chains. *N*²-Acetylpterin was oxidized by lead tetraacetate to form *N*²-acetyl-6-acetoxymethylpterin in 84% yield <85AJC629>. Furthermore, folic acid was oxidatively degraded with bromine in 48% HBr to 6-formylpterin which gave *N*²-acetyl-6-diacetoxymethylpterin on treatment with Ac₂O <84JHC909>. Side chain activation of neopterin was initiated from *N*²,1'-*O*-diacetyl-2'3'-*O*-isopropylidene-L-neopterin (**262**), yielding on bromination with HBr/AcOH *N*²-acetyl-3-bromo-pyrrolo[1,2-*f*]pterin (**263**) (Scheme 41). The corresponding six-membered ring benzylidene acetal (**264**) reacted with NBS with ring opening to give an L-monapterin derivative (**265**) (Scheme 41) <87HCA766>.

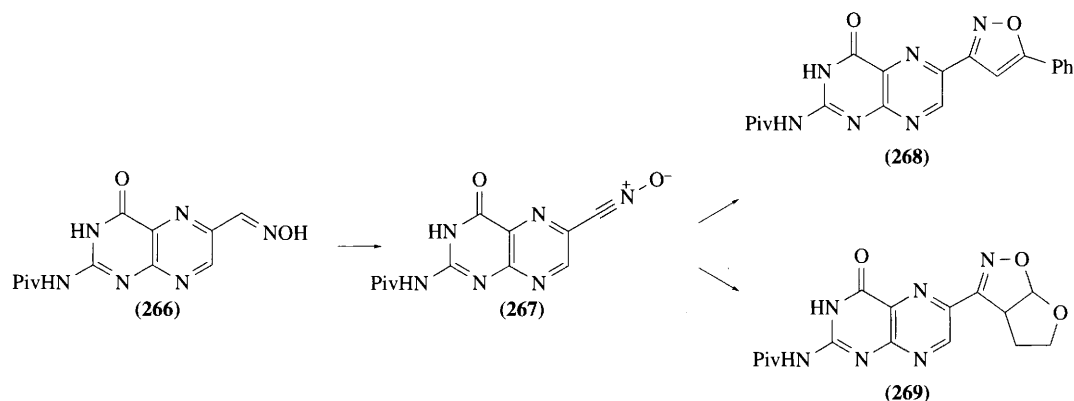


Scheme 41

Furthermore, the side chain of biopterin can be modified to 6-(L-threo-2-acetoxy-1-chloropropyl)pterin by treatment with α -acetoxyisobutyric chloride <84LA1815>.

Acylation influences the solubility of the less soluble pterins to a large extent allowing reactions which are otherwise not possible, for solubility reasons. *N*²-Pivaloyl-6-hydroxyiminomethylpterin (**266**) can be converted to its respective nitrile oxide (**267**) and gives, in the presence of

1,3-dipolarophiles, sidechain isoxazoles (**268**) and isoxazolines (**269**) by 1,3-dipolar cycloaddition reactions (Scheme 42) <91JOC1812>.



Attempts towards a chemical synthesis of molybdopterin include the introduction of the endithiole functionality by dithiolation of the appropriate alkyne. However, 1-(2-(pivaloylpterin-6-yl)-3-[(*t*-butyldimethylsilyl)oxy]but-1-yn-1-yl)-3-[(*t*-butyldimethylsilyl)oxy]but-1-yn-1-yl (**270**) reacted via the betainic tributylphosphine–carbon disulfide complex (**271**) and the heteroanalogous Wittig reaction using nitrosobenzene to give only a minute yield of the anticipated 2-(phenylimino)-1,3-dithiole derivative (**272**) (Scheme 43). Activation of the sidechain by a keto group (**274**) was more successful leading to (**275**) or, in a Wittig reaction with diethyl mesoxalate, to the corresponding dithiole (**273**) (Scheme 43) <91JOC1816>.

An interesting disulfide cleavage is performed with 7,7'-dithio-bis[1,3,6-trimethylumazine] (**276**) in basic medium yielding the relatively stable silver 7-sulfenate (**277**) and thiol (**278**) (Scheme 44). The free 1,3-dimethylumazine-7-sulfenic acid (**279**) has been prepared from 7-isopropylthio and 7-[2-(4-nitrophenyl)ethylthio]-1,3-dimethylumazine first by oxidation to the corresponding sulfoxides (**282**, **283**) then by a modified Cope elimination and dbu treatment, respectively (Scheme 44).

In acid medium (**279**) disproportionates into (**276**) and 1,3-dimethylumazine-7-sulfenic acid (**280**) and reaction with ethylthiol gave ethyl-(1,3,6-trimethylumazin-7-yl)disulfide (**281**) (Scheme 44).

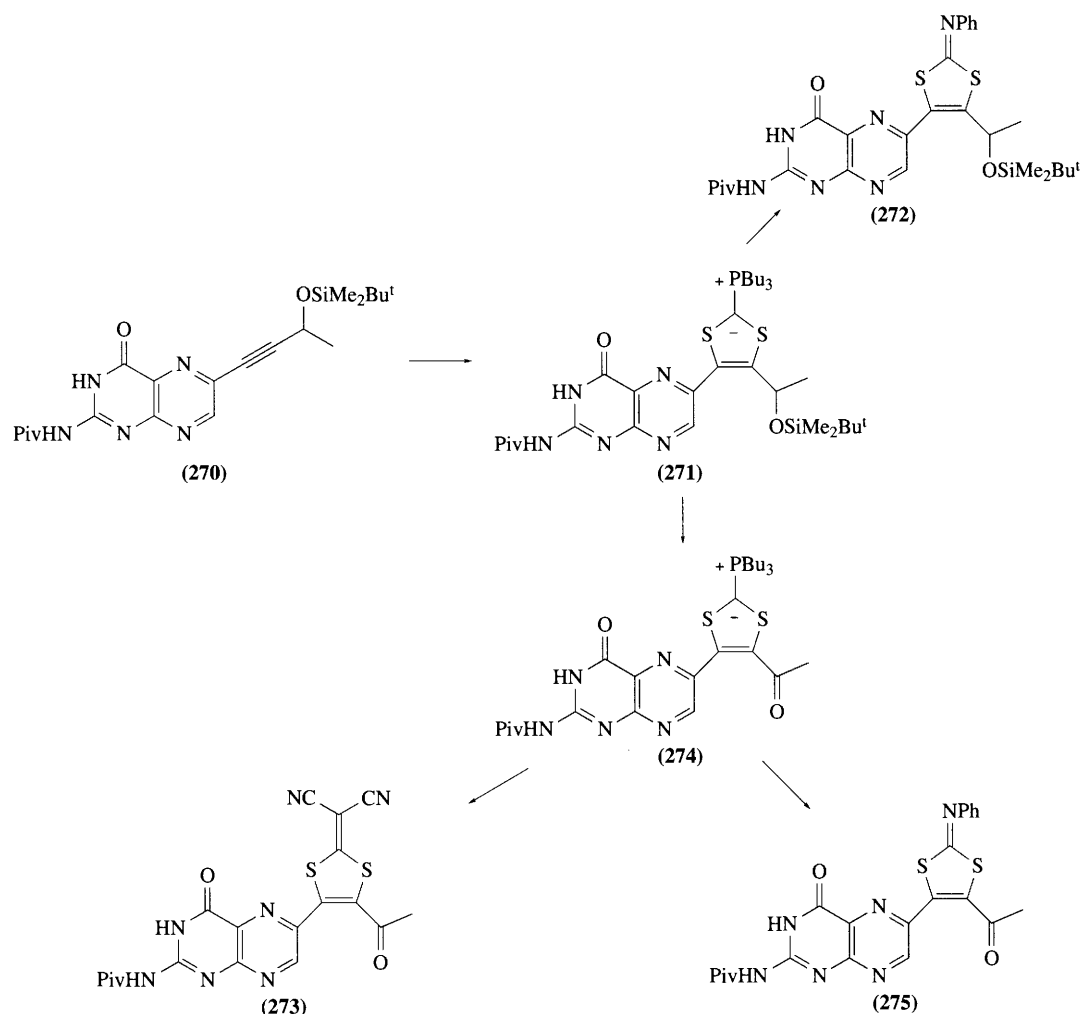
A series of carbonyl reactions have been performed with 1,3-dimethyl-6- and 7-carbaldehyde to give oximes, acetals, dithioacetals, and amins as well as the hydroxymethyl derivatives on NaBH_4 reduction, and the carboxylic acids on KMnO_4 oxidation <87JHC597>.

7.18.7.8 Photochemical Reactions

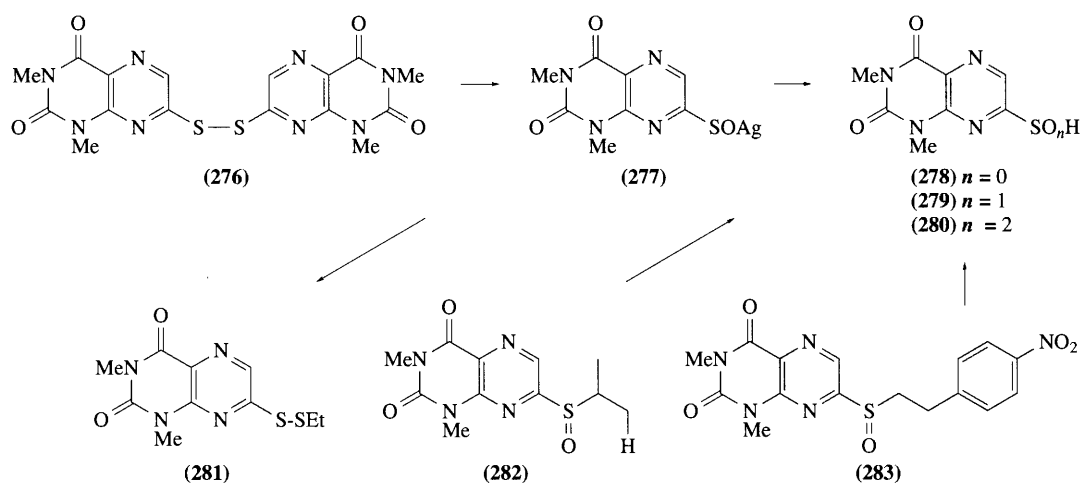
Photophysical properties of oxidized pteridines are not well documented in the literature despite the fact that fluorescence and phosphorescence emissions are characteristic features of this heterocyclic ring system. The room temperature fluorescence quantum yield of pterin was found to be low ($\Phi = 0.057$) and is maximum at pH 10. The 77 K phosphorescence emission is complex and consists of two overlapping emissions originating from π, π^* triplet states. The longer lived triplet reacts with the solvent forming the semireduced pterin. The photosensitizing properties indicate that photoreactions cause the formation of singlet oxygen <81MI 718-02>. The autooxidative chemiluminescence appears to be a general feature of 8-substituted pterins and lumazines (**284**) bearing a methyl group at the 7-position. In alkaline media the 7-oxo derivatives (**287**) are formed in the excited state by cleavage of the intermediate dioxetane (**286**) (Scheme 45) <81T833>.

8-Alkylumazines (**288**) are extremely photolabile if the β -position of the alkyl residue is substituted by an oxygen or nitrogen function (Scheme 46). 8-(2-Hydroxyethyl)-lumazine is cleaved on irradiation in a Norrish-type II reaction with a half-life of 25 seconds to lumazine (**289**) (Scheme 46). The 8-(2-hydroxyethyl)-6,7-diphenylumazine reacts more slowly with $\tau = 5 \frac{1}{2}$ minutes while the 8-(2-methoxyethyl) analogue ($\tau = 2$ minutes) and especially 8-(2-morpholinoethyl)-6,7-diphenylumazine ($\tau = 6$ seconds) are much more labile. Conversion of the electron-donating group into an acceptor, as in 8-(2-acetoxyethyl)-6,7-diphenylumazine, increases the photostability ($\tau = 40$ minutes) substantially <82LA762>.

Thioxopteridines are also an interesting class of photoactive compounds. Under aerobic conditions, various types of photooxidations take place. 1,3,5-Trimethyl-6(5*H*)-lumazinethione



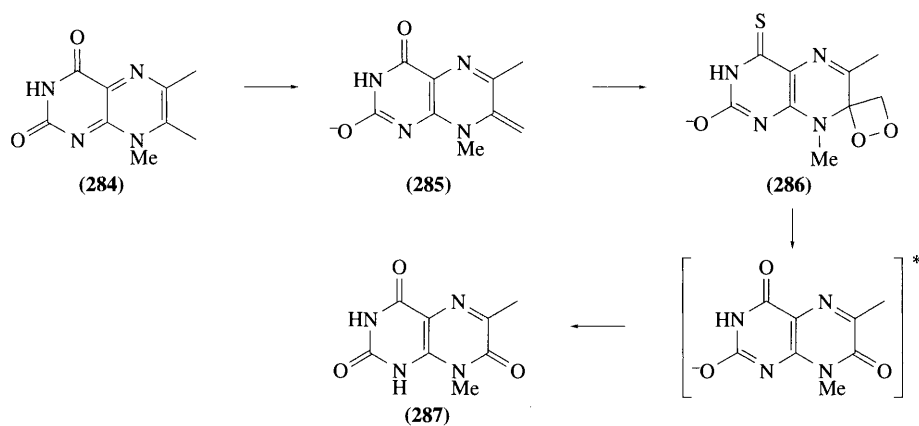
Scheme 43



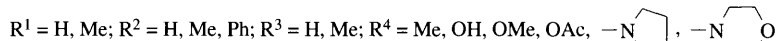
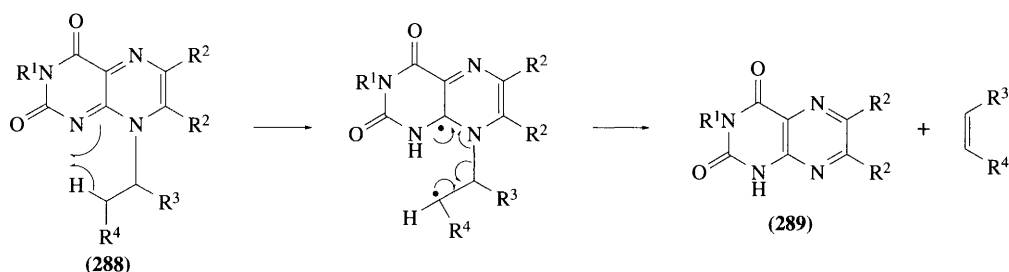
Scheme 44

(290) is converted via a dioxathietane intermediate (291) into 1,3,5-trimethyl-6(*H*)-lumazinone (292) (Scheme 47) <86HCA704>.

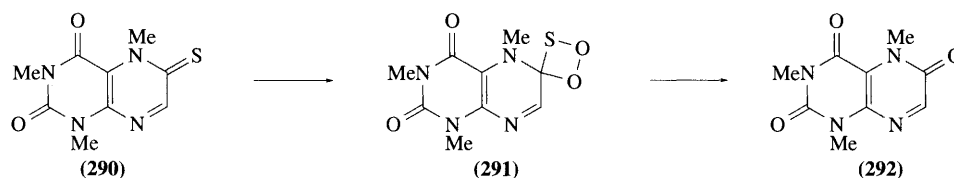
Irradiation of 1,3-dimethyl-6(5*H*)lumazinethione (293) led in an acidic medium to 6,6'-dithio-bis[1,3-dimethyl-lumazine] (294) while photooxidation at pH 9 formed first 1,3-dimethyl-lumazine-6-



Scheme 45



Scheme 46

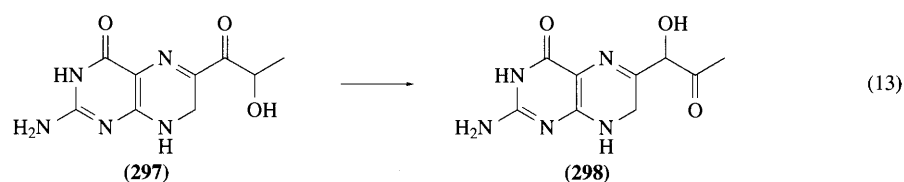
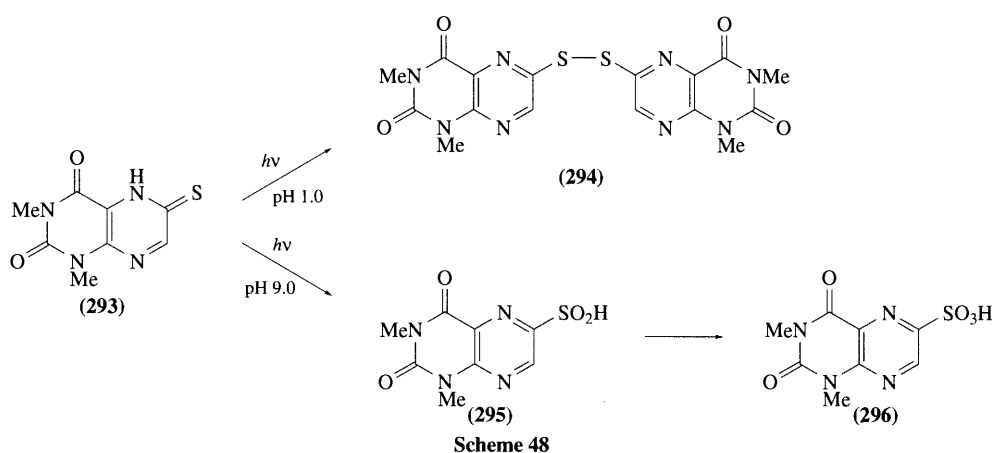


Scheme 47

sulfinic acid (**295**) and on prolonged irradiation the 6-sulfonic acid (**296**) (Scheme 48). The isomeric 7-thiol-1,3-dimethylumazine again afforded at pH 1 the corresponding 7,7'-disulfide and at pH 13 the 7-hydroxy-1,3-dimethylumazine derived via the 7-sulfinic and 7-sulfonic acids and subsequent hydrolysis $\langle 86\text{HCA}708 \rangle$. The mechanisms of these photooxidations consist of singlet oxygen, superoxide radical anion, and radical chain reactions, respectively $\langle 86\text{HCA}1088 \rangle$.

7.18.7.9 Enzymatic Reactions

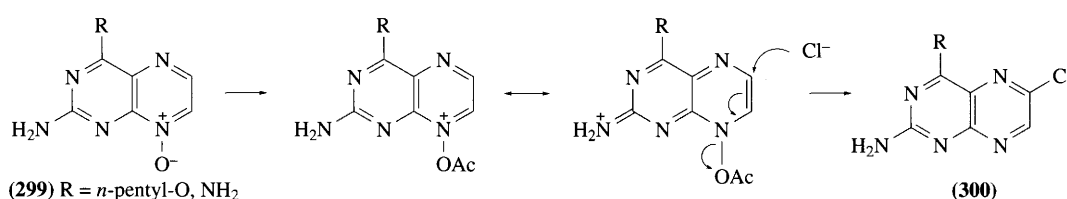
Enzymatic reactions in the side chains of pteridines are recommended for such cases where the chemical transformations are difficult and nonselective. A convincing example of this approach is the enzymatic isomerization of sepiapterin (6-lactoyl-7,8-dihydropterin) (**297**) into 6-(1-hydroxy-2-oxopropyl)-7,8-dihydropterin (**298**) which had been believed to be too labile to actually exist (Equation (13)) $\langle 89\text{MI} 718-06 \rangle$. This product, which was formed by the isomerase activity of sepiapterin reductase, was detectable electrochemically at 500 mV and fluorometrically on HPLC analysis.



7.18.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO NITROGEN

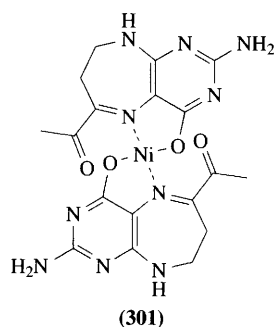
7.18.8.1 Reactivity of *N*-Oxides

Pteridine *N*-oxides are commonly used in Katada–Boeckelheide rearrangements in order to modify the adjacent ring C-atom by nucleophiles. 1,3-Dimethylumazine 5-oxide reacts with AcCl in TFA at -40°C to give 6-chloro-1,3-dimethylumazine (82LA2135). 2-Amino-4-(*n*-pentyloxy) pteridine 8-oxide (299) and 2,4-diaminopteridine 8-oxide show, analogously to pterin 8-oxide (78JOC680), an anomalous Katada-type *tele*-substitution leading with AcCl/TFA to the corresponding 6-chloro derivatives (300) (Scheme 49) (92HCA2317).



7.18.8.2 Metal Complexes

An interesting possibility for stabilization of sensitive structures in solution can be seen in the formation of metal complexes involving some of the ring N atoms. Several pterins, including sepiapterin (297), have been studied in presence of Ni^{2+} ions indicating an interaction between the heterocycle and the metal ion by a bathochromic shift of the absorption maximum to a wavelength close to the maximum found at pH 12. Detailed structural assignments, however, are not available and await further investigation. The labile 6-acetyldihydrohomopterins (337), a natural precursor of the eye pigments of *Drosophila melanogaster*, can be stabilized by Ni^{2+} causing a red shift of 53 nm. A chelate with structure (301) is most likely, from IR studies (85MI 718-02).



The condensed 1,3-dimethyl-phenanthro[5,6-*f*]lumazine forms ruthenium(II) polypyridyl complexes which are in principle capable of being reduced by up to 6 H-atoms, making them potential electrochemical mediators <93IC5591>. Charge transfer has been noticed in complexes of 1,3-dimethylalumazine with low-valent metals such as Cu⁺, Re⁺, and Ru²⁺ revealing absorption bands in the visible region <89IC4645, 89ZAAC(577)39>.

7.18.9 RING SYNTHESSES

7.18.9.1 Syntheses from Pyrimidines

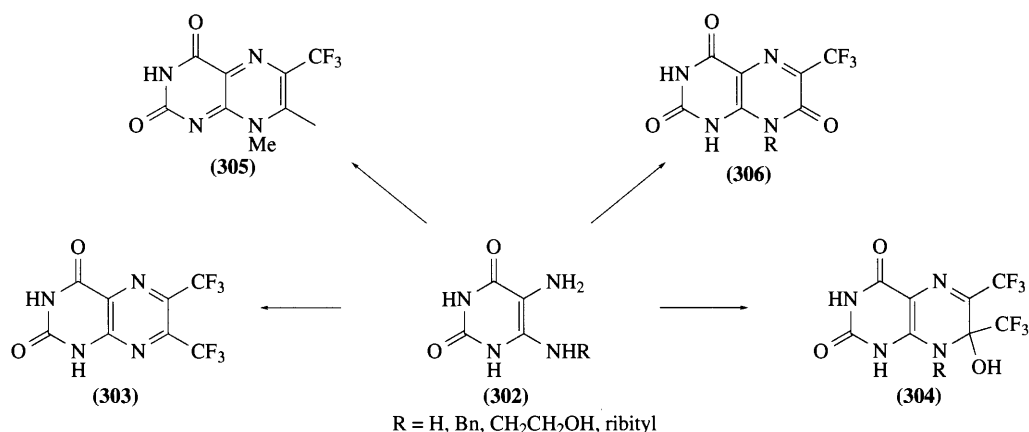
Pteridine syntheses from pyrimidine intermediates <B-88MI 718-07> have been applied very frequently since the 5,6-pyrimidinediamines and 5-nitroso-6-pteridinamines are easily available by Traube synthesis and can be condensed with 1,2-dicarbonyl compounds and ketones and aldehydes, respectively, in a very effective manner. There is also a series of regioselective approaches leading towards 6- and 7-substituted pteridine derivatives carrying a broad variety of substituents in these positions.

7.18.9.1.1 Gabriel–Isay condensations

The Gabriel–Isay condensation reaction belongs to the oldest approaches for the synthesis of pteridines from 5,6-pyrimidinediamines with 1,2-dicarbonyl compounds. Despite the fact that numerous pteridines have been synthesized by this method the condensations with unsymmetrical 1,2-dicarbonyl compounds still present a problem of regioselectivity towards 6- or 7-substituted pteridine derivatives. Reaction of 2,5,6-triamino-4(3*H*)pyrimidone sulfate with methylglyoxal at 0–5°C and in the presence of a large excess of sodium sulfite leads in 80% yield to a 6-/7-methylpterin mixture of 9/1 from which the pure 6-methyl isomer can be obtained by acetylation to *N*²-acetylpterin, recrystallization, and hydrolysis <85AJC629>. Condensations of various 5,6-diaminopyrimidines (302) with perfluorobutane-2,3-dione were performed to obtain information about the formation and stabilization of covalent hydrates at the pyrazine moiety of these molecules (303) (Scheme 50) <86JCS(P1)1043>. Furthermore, 8-substituted 6,7-bis-trifluoromethylalumazines were prepared in an analogous manner, existing as stable 1,7-hydrates (304) (Scheme 50) <86JCS(P1)1051, 91JOC4603>. Reactions with 2,2-dibromo-1,1,1-trifluoro-2-butanone and methyl trifluoropyruvate, respectively, proceed regiospecifically to give the corresponding 6-trifluoromethyl derivatives (305) and (306) (Scheme 50).

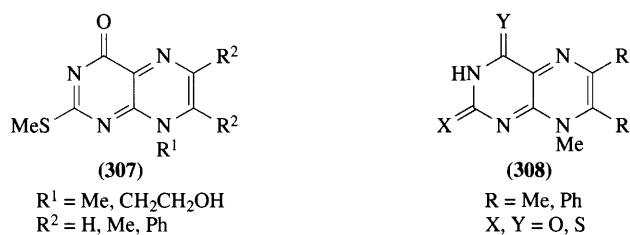
The isomer distribution in the condensations of 2,5-diamino-6-alkylamino-4(3*H*)-pyrimidone and methylglyoxal giving the 6- and 7-methyl-8-alkyl-pterins is also affected by the alkyl substituent <92MI 718-06, 92MI 718-10>. Detailed studies of the mechanism give more information about this seemingly simple reaction <93JCR(S)349, 93JCR(M)2359>.

Similar condensations of 5-amino-6-substituted anilino-3-methyluracils with glyoxal, diacetyl and benzil led to the corresponding 3-methyl-8-substituted phenyllumazines of which the 8-(4-chlorophenyl)- and 8-(3,5-dimethylphenyl)-3-methylalumazines showed activity against cultured *Plasmodium falciparum* <90AJC1449>. 5-Amino-6-methylamino- and 6-β-hydroxyethyl-2-methylthio-4(3*H*)pyrimidone also condense with glyoxal, diacetyl, and benzil to the corresponding 8-substituted

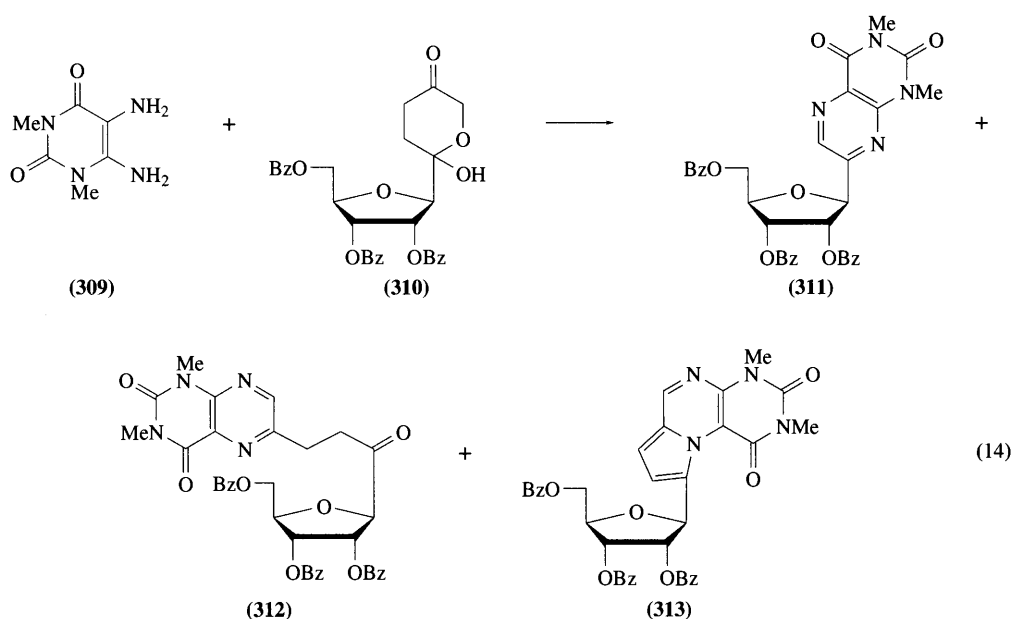


Scheme 50

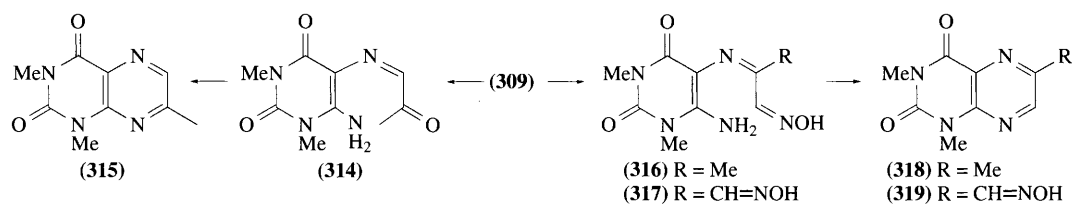
2-methylthio-4(8*H*)pteridones (**307**) which are yellow compounds with the typical cross-conjugated π -electron system giving rise to pH-dependent adduct formation or intramolecular additions $\langle 88\text{HCA}1379 \rangle$. 6,7,8-Trimethyl-4-thiolumazine $\langle 89\text{HCA}738 \rangle$ and 8-substituted 2,4-dithiolumazines (**308**) are available by analogous condensation reactions but the starting materials are more difficult to synthesize $\langle 89\text{HCA}744 \rangle$.



An interesting pyrazine ring formation was detected between 5,6-diamino-1,3-dimethyluracil (**309**) and 6-hydroxy-6-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-2*H*-pyran-3(6*H*)-one (**310**) leading to a mixture of 1,3-dimethyl-7-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)lumazine (**311**), 1,3-dimethyl-6-[3-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-3-oxopropyl]-lumazine (**312**), and 6,8-dimethyl-1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)pyrrolo[1,2-*f*]pteridine-7,9-dione (**313**) (Equation (14)) $\langle 89\text{JOC}3927 \rangle$.



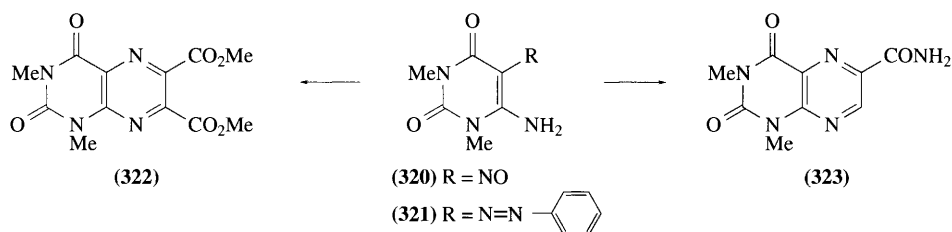
The problems regarding regioselective condensations again become obvious during the reaction of 5,6-diaminopyrimidine with ethyl pyruvate. 6-Methyl-7(8*H*)pteridone synthesis can be achieved in a regioselective manner but the isomeric 7-methyl-6(5*H*)-pteridone is only formed in poor yield <92JHC1279>. An effective regioselective approach was found by separating the two subsequent condensation steps. 5,6-Diamino-1,3-dimethyluracil (**309**) reacts with methylglyoxal and methylglyoxalmonoaldoxime, respectively, to give the Schiff's bases (**314**) and (**316**) which were cyclized in weak acid to compound (**315**) and in 80% H_2SO_4 to the isomers (**318**) (Scheme 51). Analogously, propane-1,3-dioxime condenses first to the orange colored product (**317**) and on treatment with 5% NaHCO_3 to the oxime (**319**) (Scheme 51).



Scheme 51

7.18.9.1.2 Timmis reaction

The Timmis reaction makes use of the regioselective condensations of 6-amino-5-nitroso-pyrimidines with aldehydes, ketones, esters, and nitriles under base catalysis. An extension of this principle is seen in the condensation reaction of 6-amino-5-nitroso-(**320**) and 6-amino-5-phenylazo-1,3-dimethyluracils (**321**) with dimethyl alkenedicarboxylate and propiolamide, respectively, leading by a Michael addition mechanism to 6,7-bis(methoxycarbonyl)- (**322**) and 6-carbamoyl-1,3-dimethyluracine (**323**) (Scheme 52) <82JHC949>.

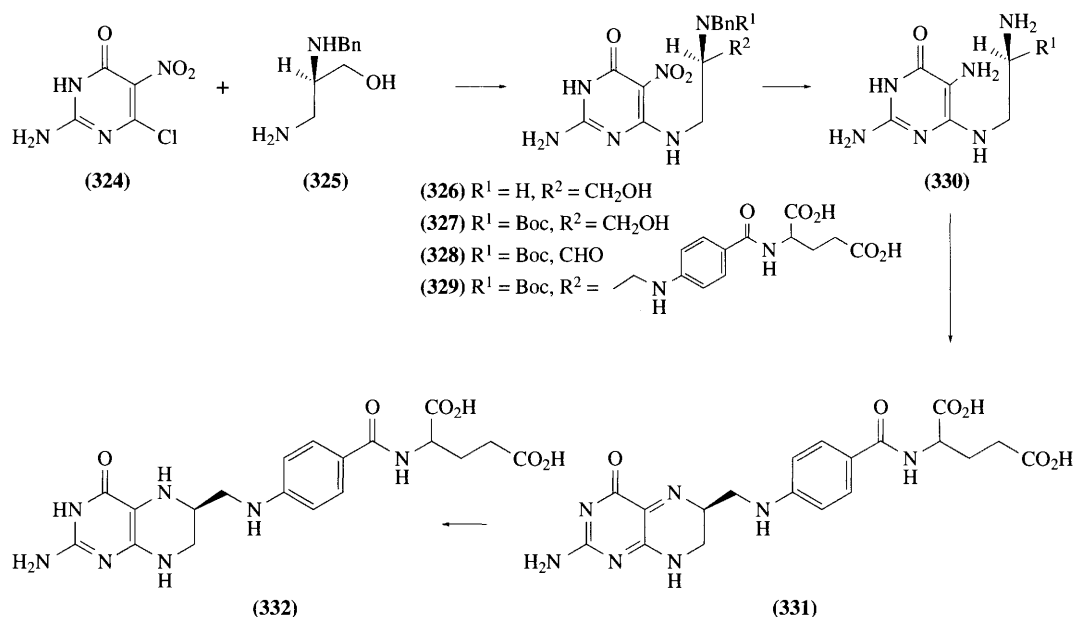


Scheme 52

7.18.9.1.3 Polonovski–Boon cyclization

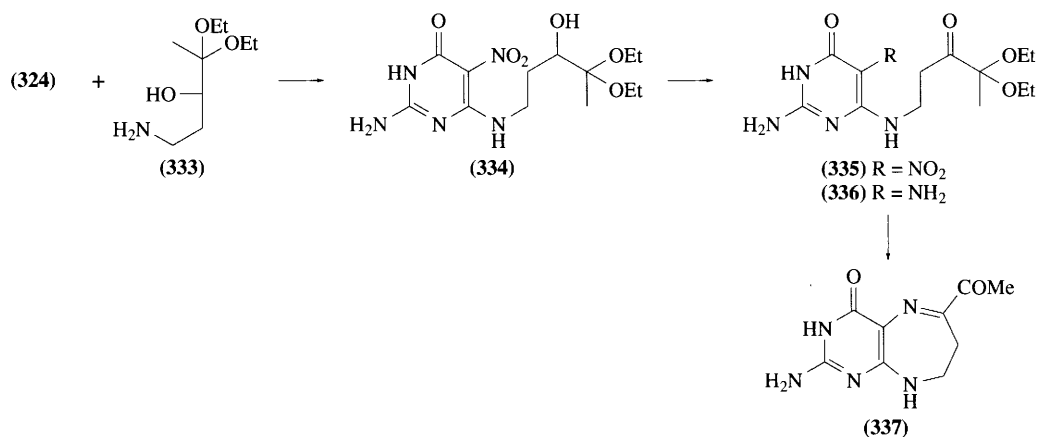
An unambiguous regioselective approach to 6- and 7-substituted pteridines has been performed for the first time by Polonovski <50CR(230)392> and Boon <51JCS96> in reacting 6-chloro-5-nitro- and 6-chloro-5-arylazo-pyrimidines, respectively, with α -aminocarbonyl compounds followed by reduction to the 5-amino derivative and subsequent cyclization <84CHEC-I(3)315>. A somewhat similar route was applied to synthesize (6*R*)- or (6*S*)-tetrahydrofolic acid from 2-amino-6-chloro-5-nitro-4(3*H*)pyrimidone (**324**) and D- or L-serine which were converted to the corresponding 3-amino-2(*R* and *S*)-(benzylamino)propan-1-ols (**325**) (Scheme 53). Nucleophilic displacements led to (**326**) which was further protected by the Boc group to (**327**). This was then oxidized by the Dess–Martin periodinane procedure to the aldehyde (**328**), condensed with *p*-aminobenzoyl-L-glutamic acid and subsequently reduced by NaBH_3CN to (**329**) (Scheme 53). Deprotection of the Boc group and catalytic reduction on Pd/C afforded the 5-aminopyrimidine (**330**) which was oxidized by iodine to the 5-imino derivative prone to immediate cyclization to the quinonoid-type (6*S*)-6,7-8*H*-dihydro-

folic acid (**331**) and finally $\text{Na}_2\text{S}_2\text{O}_4$ reduction to (6*S*)-5,6,7,8-tetrahydrofolic acid (**332**) (Scheme 53). The corresponding (6*R*)-isomer was prepared in an analogous manner from D-serine <92JOC4470>.



Scheme 53

The quinonoid 6,6,8-trimethyl-7,8-dihydro-(6*H*)pterin was synthesized from the pyrimidone (**324**) and *N*-methyl(2-methyl-2-nitropropyl)amine by a similar sequence of reactions <85MI 718-09>. Furthermore, 6-acetyl-7,8(9*H*)dihydrohomopterin (**337**), a precursor in the biosynthesis of the drosopterins, could be obtained from (**324**) and 1-amino-4,4-diethoxypentan-3-ol ((**333**)). These formed first the pyrimidine (**334**) which was oxidized to the ketone (**335**), followed by reduction of the nitro group (**336**), ring closure and subsequent hydrolysis of the acetal function yielding (**337**) (Scheme 54) <90JCS(P1)2071>. The 4-amino derivative was prepared analogously showing that the Polonovski-Boon approach works also in the synthesis of pyrimido-diazepines <91T5259>.



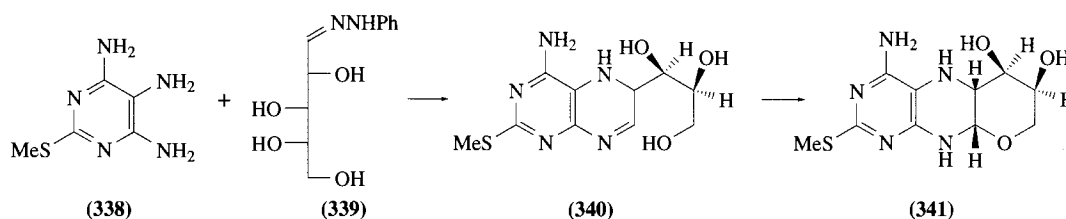
Scheme 54

7.18.9.1.4 Viscontini reaction

Viscontini has demonstrated in an elegant synthesis of neopterin that sugar-phenylhydrazones condense under slightly acidic conditions regioselectively to 6-substituted pterins <70HCA1202>. The mechanism involves two Amadori rearrangements to guarantee regioselectivity which is quite surprising in this complex condensation reaction <84CHEC-I(3)312>. The high yield in the neopterin

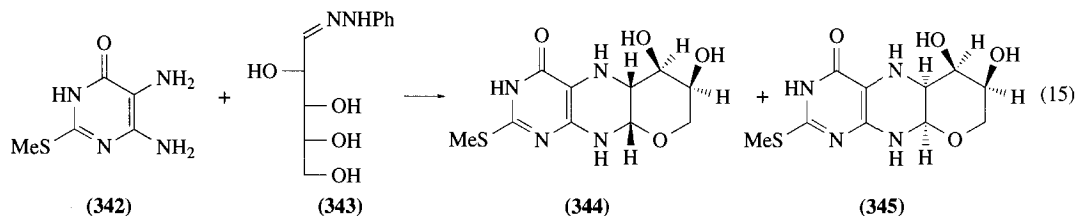
and monapterin syntheses could not, however, be achieved with the phenylhydrazone of 5-deoxy-L-arabinose <72HCA570> or its triacetate <77HCA211, 85HCA1639> to form biopterin. A small improvement of the Viscontini procedure to give 56% of *N*²,1',2-triacetyl-biopterin resulted from the condensation of 2,5,6-triamino-4(3*H*)pyrimidine and 5-deoxy-L-ribose phenylhydrazone, but deacetylation yielded only 70% of biopterin <89LA1267>. The 5-deoxy-L-ribose was therefore prepared from D-ribose in four steps. Another approach from ethyl (*S*)-lactate to (2*RS*,3*S*,4*S*)-2,3-diacetoxy-4-hydroxypentanal is much too long and gives only a 32% yield in the final condensation reaction to biopterin <89LA963>.

More information about the mechanism of the Viscontini reaction has been collected from model studies condensing 4,5,6-triamino-2-methylthiopyrimidine (**338**) in a similar manner with the phenylhydrazones of L- (**339**) and D-arabinose and omitting the iodine oxidation step (Scheme 55). Under these conditions an interesting intermediate, consisting of a tricyclic pteridine ring system (**341**), was formed by intramolecular adduct formation of the trihydroxypropyl sidechain on to the 7-position of the 5,6-hydropteridine precursor (**340**) (Scheme 55). The main reaction product could be crystallized and the structure unambiguously proven by an x-ray analysis <90HCA808>.



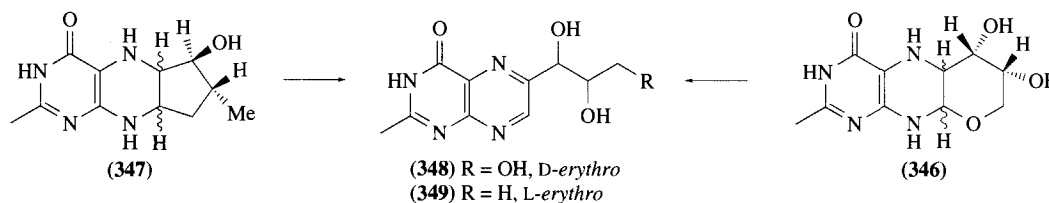
Scheme 55

The ¹H NMR spectra of the pyrano[3,2-*g*]pteridine (**341**) and its enantiomer derived from the phenylhydrazone of D-arabinose (**343**) show a time-dependent change due to the formation of an equilibrium involving the isomeric furo[3,2-*g*]pteridines. Analogous results were obtained with 5,6-diamino-3-methyl-2-methylthio- and 5,6-diamino-2-methylthio-4(3*H*)-pyrimidone (**342**), respectively, leading in the latter case even to a separation of the two enantiomers (**344**) and (**345**) with respect to the chiral centers at the 6- and 7-position of the pteridine moiety (Equation (15)).



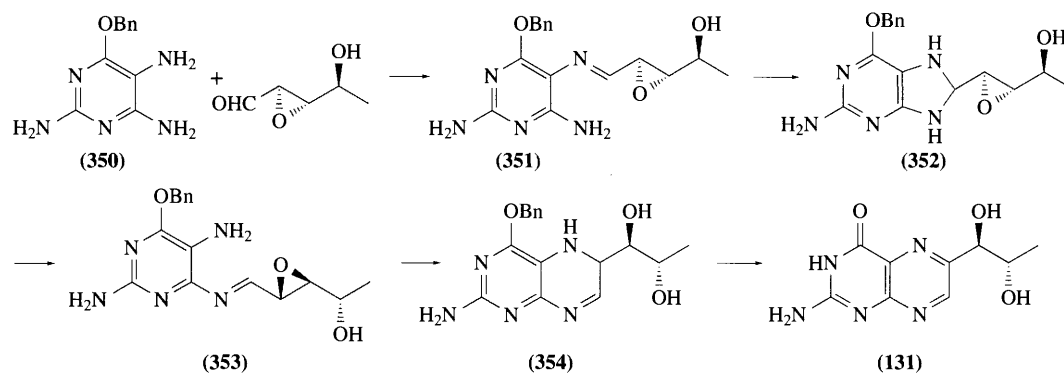
The condensation of 2,5,6-triamino-4(3*H*)-pyrimidone with L-arabinose-phenylhydrazone leads to analogous tricyclic adducts which are, however, more sensitive to oxidation and more difficult to handle. The same type of adducts have also been observed during the condensation of 5,6-diamino-2-methyl-4(3*H*)pyrimidone with the phenylhydrazones of D-arabinose (e.g., (**346**)) or 5-deoxy-L-arabinose (e.g., (**347**)) (Scheme 56) <89MI 718-05>. The various hydrofuro- and hydropyrano[3,2-*g*]pteridine derivatives are expectedly valuable intermediates for the synthesis of 6-substituted pteridines which were obtained by air oxidation in alkaline medium or more directly by treatment with *p*-benzoquinone <90MI 718-08> and iodine/H₂O₂, respectively (**348**) and (**349**) (Scheme 56).

A novel regio- and stereoselective synthesis of biopterin and various 6-substituted pteridines



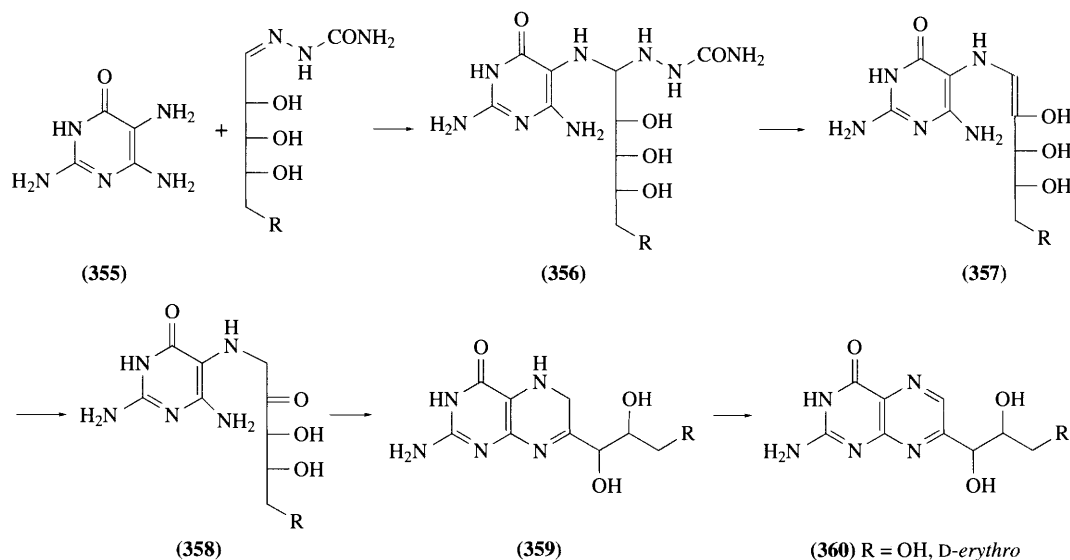
Scheme 56

was derived from the condensation of 2,5,6-triamino-4-butoxypyrimidine (**350**) with appropriately substituted 2-formyloxiranes followed by subsequent oxidation with iodine. The mechanism of this reaction involves first Schiff's base formation (**351**), cyclization to an aminal (**352**), ring opening in a reverse manner (**353**), and then attack of the more nucleophilic 5-amino group at the oxirane C-atom leading to the intermediate 5,6-dihydro derivative (**354**) which is easily oxidized and hydrolyzed to the corresponding pterin derivative (**131**) (Scheme 57). The same approach was also applied to obtain various other 6-substituted pterins <92S303>.



Scheme 57

Furthermore, a regioselective condensation leading to 7-substituted pterins was found using the semicarbazones of pentoses and 2,5,6-triamino-4(3*H*)-pyrimidinone (**355**) to give 7-(D-erythro-1,2,3-trihydroxypropyl)pterin (*Anapterin*) (**360**) and 7-(L-erythro-1,2-dihydroxypropyl)pterin (*Primapterin*) (**361**), respectively, at pH 3.5–4 (Scheme 58) <90HCA337>. It is assumed that the more stable semicarbazones do not exhibit an Amadori rearrangement favoring an addition to an intermediary aminal (**356**) which eliminates semicarbazide via (**357**) to give a ketose derivative (**358**) for further condensation (**359**) and final oxidation (Scheme 58).

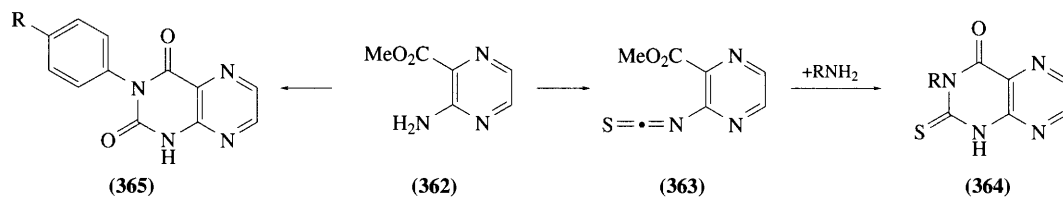


Scheme 58

7.18.9.2 Synthesis from Pyrazines

Pteridine synthesis from pyrazine precursors are usually applied in such cases where the formation of special derivatives cannot be achieved easily by the pyrimidine approach. Methyl 3-amino-2-pyrazinecarboxylate (**362**) reacts with thiophosgene to give the corresponding 3-isothiocyanato derivative (**363**) which cyclizes with primary amines, arylalkylamines, aminoalcohols, amino acids,

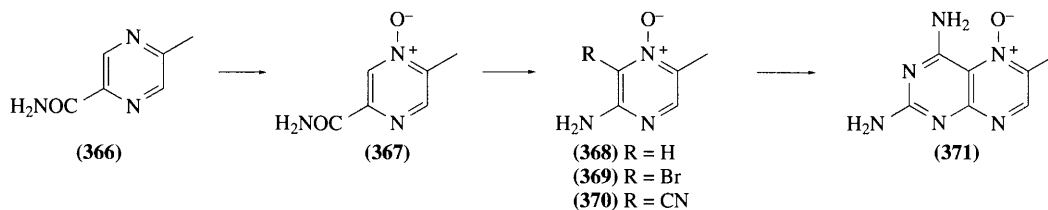
and hydrazine, respectively, to 3-substituted 2-thiolumazines (**364**) under mild conditions and in good yield (Scheme 59) <90JHC433>. Similarly arylisocyanates react with the amine (**362**) directly to give 3-aryl-lumazines (**365**) (Scheme 59) <93H(35)949>.



Scheme 59

Acylation of the amine (**362**) and subsequent cyclization afforded 2-arylpyrazino[2,3-d]-1,3-oxazin-4-ones which react with primary amines under ring transformation to give 2,3-disubstituted 4(3*H*)pteridones <94S405>.

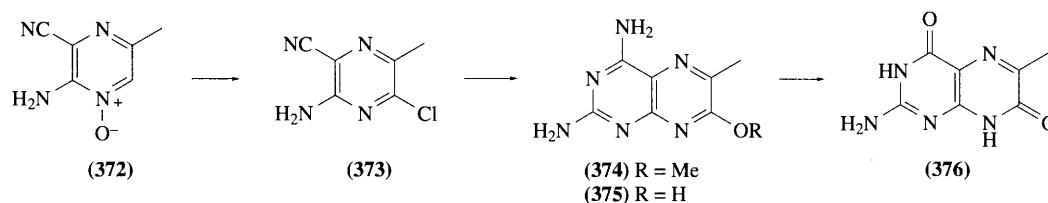
Another key intermediate for pteridine synthesis was also seen in 2-amino-3-ethoxycarbonyl-5-phenylpyrazine 1-oxide which reacts with various amines to form the corresponding amides followed by cyclization with triethyl orthoformate giving 3-alkyl-6-phenyl-4(3*H*)pteridinone 8-oxides <87JHC1109>. The synthesis of 2,4-diamino-6-methylpteridine 5-oxide (**371**) was achieved from 5-methyl-pyrazine-2-carboxamide (**366**) via the 4-oxide (**367**), a Hofmann degradation (**368**), bromination (**369**), and cyanation (**370**) followed by cyclization with guanidine to give (**371**) (Scheme 60) <93JHC841>.



Scheme 60

7.18.9.2.1 Taylor synthesis

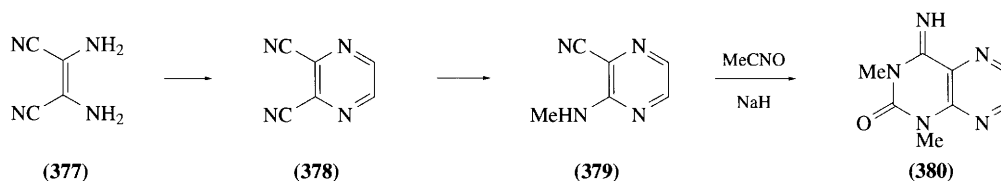
The Taylor approach to pteridines from pyrazine precursors offers a valuable alternative to the commonly applied condensation reactions between 5,6-diaminopyrimidines and dicarbonyl compounds <68JA2424>. Aminomalononitrile reacts with 2-oxopropanal 1-oxime to give 2-amino-3-cyano-5-methylpyrazine-1-oxide (**372**). Subsequent POCl_3 treatment forms the rearranged 6-chloro derivative (**373**) which cyclizes with guanidine in sodium methoxide solution in high yield to 7-methoxy-6-methyl-2,4-pteridine-diamine (**374**) (Scheme 61). Weak hydrolysis cleaves the methoxy group to give (**375**) whereas treatment with strong base under prolonged heating leads to 6-methylisoxanthopterin (**376**) <87JHC1621>.



Scheme 61

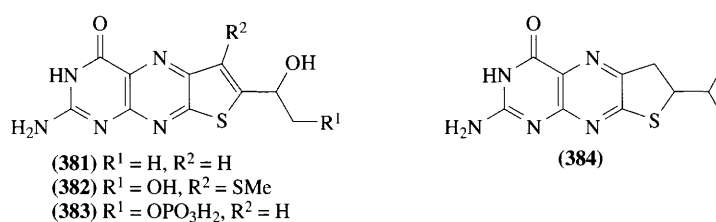
Starting from diaminomaleonitrile (**377**), condensations with 1,2-dicarbonyl compounds lead to pyrazine-2,3-dicarbonitriles (**378**) which allow a nucleophilic displacement of one cyano group by

amines to give, for example, 2-methylaminopyrazine-3-carbonitrile (**379**) (Scheme 62). Ring closure to various lumazine derivatives (**380**) proceeds under standard conditions <86JHC1299>.

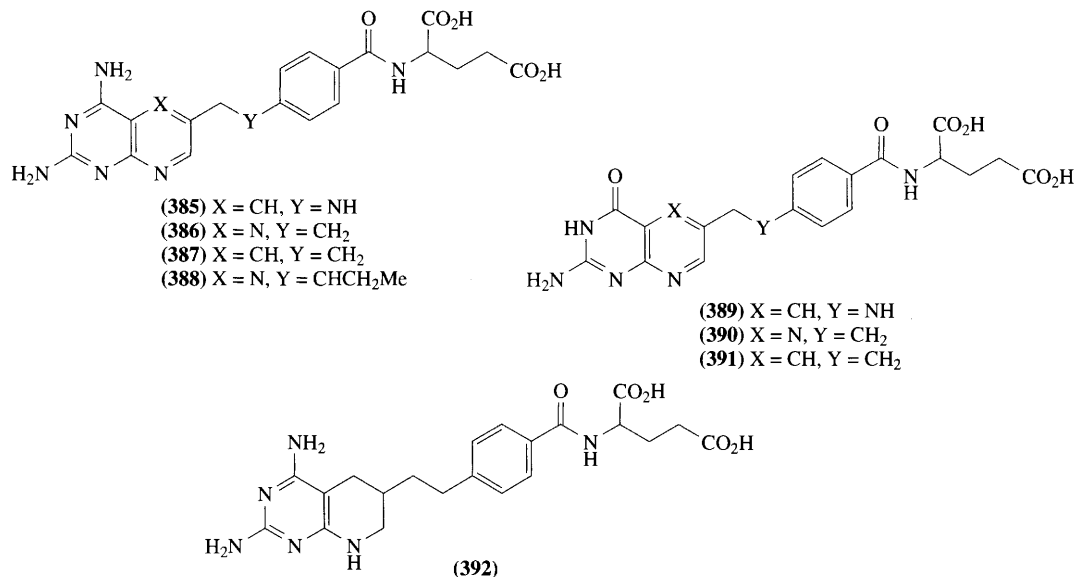


Scheme 62

The Taylor route is also very useful in the synthesis of more complex structures as demonstrated in the total synthesis of deoxyurothione (**381**), ($\pm$)-urothion (**382**) <89JA285>, and analogous 6,7-dihydrothieno[3,2-*g*]pterins (**384**) which are model substances of the oxidative breakdown product (**383**), termed form B of the molybdenum cofactor (**399**) <88JOC5839>.



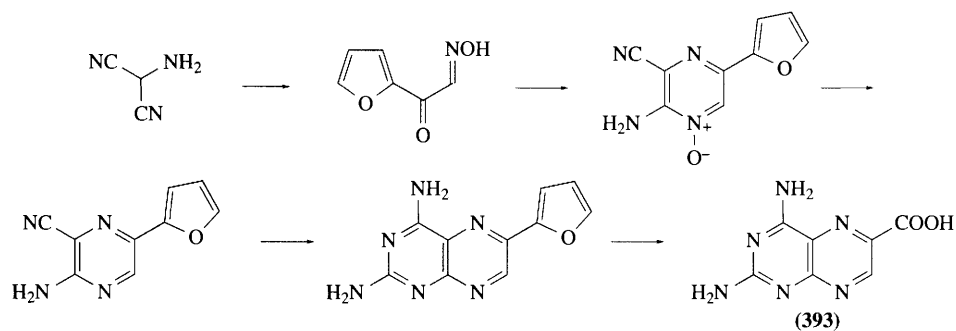
Various antileukemic agents related to methotrexate, such as 5-deazaaminopterin (**385**), 5-deaza-folic acid (**389**) <83JOC4852>, 10-deazaaminopterin (**386**), 10-deazafolic acid (**390**) <88JOC35>, 5,10-dideaza-folic acid (**391**), 5,10-dideazaaminopterin (**387**), and its 5,6,7,8-tetrahydro derivative (**392**) <85JMC914> are also synthetically available by this method. This route is even successful in the preparation of polyglutamate derivatives of antifolates <91JOC3386>.



More simple transformations to highly functionalized pyrazines and pteridines have been documented by the syntheses of xanthopterin and isoxanthopterin <75JOC2341>, pterin-6-carboxaldehyde <80JOC2485>, pteridine-6-carboxylic acids (**393**) <88JHC1737>, biopterin <74JA6781>, and euglenapterin (Scheme 63) <81JOC5416>.

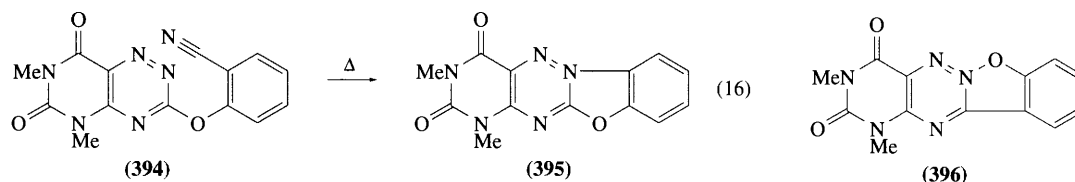
7.18.9.3 Intramolecular Cyclizations

Intramolecular hetero-Diels–Alder reactions provide a novel approach to polycyclic pyrazines and lumazines if 1,2,4-triazines contain the dienophilic component in a side chain tethered to the



Scheme 63

azadiene. Cycloaddition then proceeds with remarkable ease as a consequence of the entropic assistance inherent in intramolecular reactions. 7-(2-Cyanophenoxy)-1,3-dimethyl-6-azalumazine (394) gave on prolonged heating in nitrobenzene 1,3-dimethyl-benzofuro[2,3-*g*]lumazine (395) <87T5159> and its corresponding isomer (396) from 6-(2-cyanophenoxy)-1,3-dimethyl-6-azalumazine (Equation (16)) <88JOC3568>.

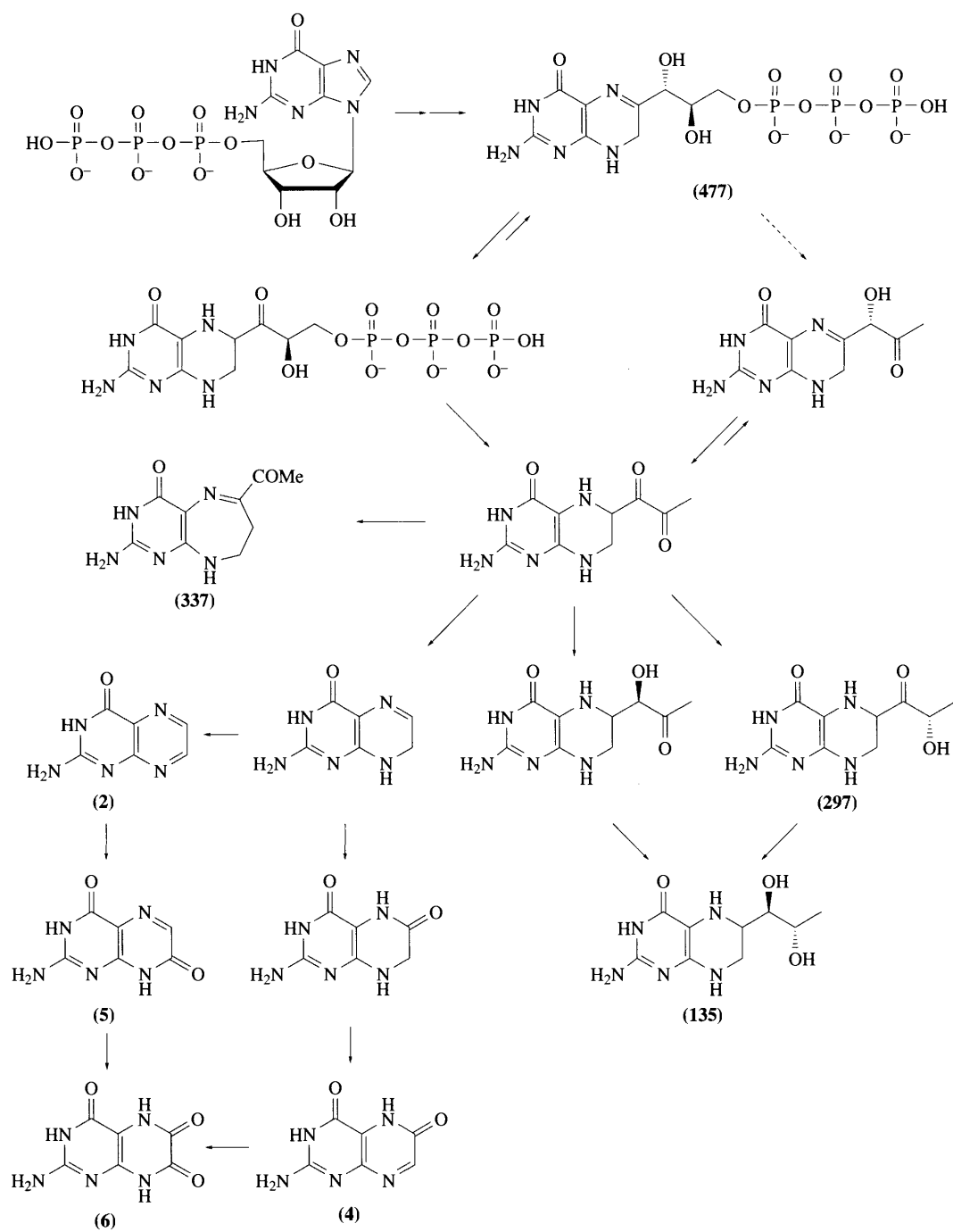


7.18.10 RING SYNTHESIS BY TRANSFORMATIONS OF OTHER RINGS

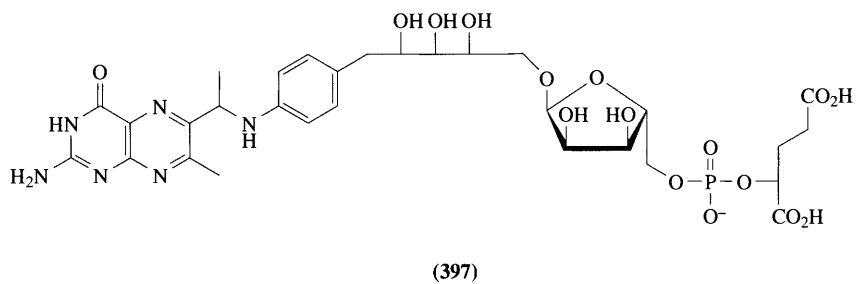
7.18.10.1 Biosynthesis of Pteridines

One of the most interesting and spectacular ring transformations in nature is achieved by the enzyme GTP-cyclohydrolase which converts the purine derivative guanosine-5'-triphosphate into 7,8-dihydroneopterin-3'-triphosphate (477), the mother substance of all naturally occurring pterins. The uniqueness of this interconversion is seen first in the ring-opening of the thermodynamically very stable imidazole ring and second by taking advantage of the ribosyl moiety in the pyrazine ring formation. The subsequent step in the biosynthesis of the butterfly and *Drosophila* pigments as well as tetrahydrobiopterin (135) is the elimination of the triphosphate function coupled with an intramolecular redox reaction to give 6-pyruvoyl-5,6,7,8-tetrahydropterin <86MI 718-08> as a key intermediate from which branches lead to either sepiapterin (297) and (135) or by cleavage of the carbon side chain to 7,8-dihydropterin and its oxidation products pterin (2), xanthopterin (4), isoxanthopterin (5), and leucopterin (6) (Scheme 64). 6-Pyruvoyl-tetrahydropterin can also undergo a ring enlargement reaction to 6-acetylhomopterin (337) which then couples in a nonenzymatic reaction with 7,8-dihydropterin to the enantiomeric drosopterins (450) <B-86MI 718-09>. Most enzymes catalyzing these interconversions have been isolated and characterized proving the present picture of the biosynthetic pathway as represented in Scheme 64. Further details are found elsewhere <B-85MI 718-05>.

Biosynthetic evidence indicates that methanopterin (397), a coenzyme involved in C-1 metabolism in the methanogenic archaeobacteria <87MI 718-02>, is the first example of a naturally occurring, structurally modified folic acid <86JA6434> that functions as a cofactor in cells. Since these bacteria lack folic acid, methanopterin performs all the normal functions of folic acid and serves as a C-1 carrier for serine hydroxymethyltransferase <86MI 718-03>, 5,10-methylenetetrahydromethanopterin dehydrogenase <85BBR(133)884> and 5,10-methenyltetrahydromethanopterin cyclohydrolase <85MI 718-01>. Labeling experiments provided information about the biosynthesis of methanopterin (397) <86JA344> and confirmed that 6-hydroxymethyl-7,8-dihydropterin is the precursor of the pterin portion of methanopterin and that the two additional methyl groups C-11 and C-12 originate from methionine <90B5397>. The attachment of the side chain follows a pathway analogous to the biosynthesis of folic acid.

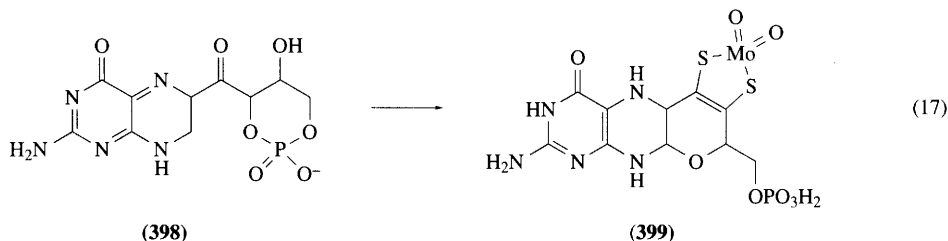


Scheme 64



(397)

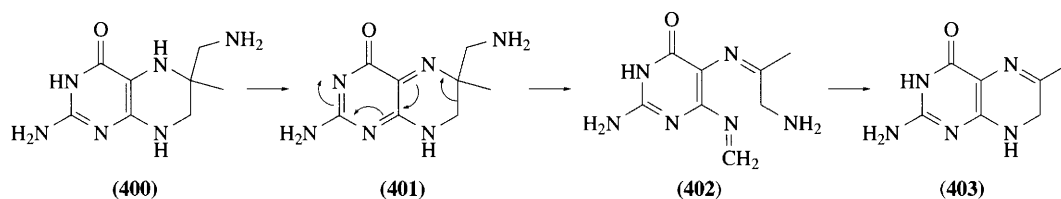
Information about a late step of the molybdenum cofactor biosynthesis was achieved from *in vitro* experiments converting the precursor **Z** (**398**) into Moco (**399**) (Equation (17)) <93JBC(268)13506>. The conversion is accomplished by transfer of sulfur to produce the 2,1,3-molybdadithiolene ring structure.



The enzymatic interconversion of 7,8-dihydroneopterin-5'-triphosphate into tetrahydrobiopterin consists of a series of reactions of which each step has now been unraveled and characterized. In the *de novo* biosynthesis of tetrahydrobiopterin it was noticed that the C(6)-H is derived from H₂O whereas NADPH is used in the conversion from sepiapterin <85JBC(260)5221>.

7.18.10.2 Pteridine–Pteridine Transformations

Strange reactions associated with ring transformations are often made apparent in labeling experiments. 6-Aminomethyl-6-methyl <71HCA2287> (**400**) and 6-aminomethyl 6,7-dimethyl-5,6,7,8-tetrahydropterin <71HCA1125>, respectively, lose their aminomethyl sidechains under oxidative conditions. It is likely that the intermediary quinonoid dihydropterin (**401**) is labile since it can undergo a retro-aldol reaction with ring-opening (**402**) followed by nucleophilic attack of the amino group at C-8a to give 6-methyl-7,8-dihydropterin (**403**) (Scheme 65) <85MI 718-09>.



Scheme 65

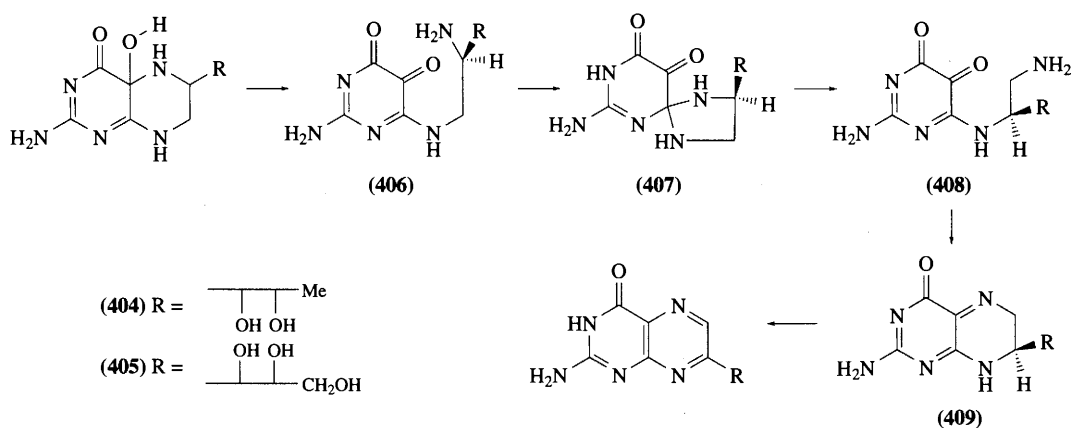
The interconversions of biopterin (**131**) into 7-biopterin (primapterin) (**361**) and of neopterin (**468**) into 7-neopterin (anapterin) (**360**) <90JBC(265)3923> are best explained by a rearrangement on the quinonoid level. The covalent 4a-OH adducts (**404**) and (**405**) are prone to ring-opening (**406**) followed by nucleophilic attack of the terminal amino group at C-8a forming an intermediary spiro derivative (**407**) (Scheme 66). Ring-opening in the opposite direction leads to (**408**) which will cyclize and dehydrate to (**409**) for further oxidation to the final products (**361**) and (**360**), respectively (Scheme 66) <90BBR(172)1060>.

7.18.10.3 Ring Transformations

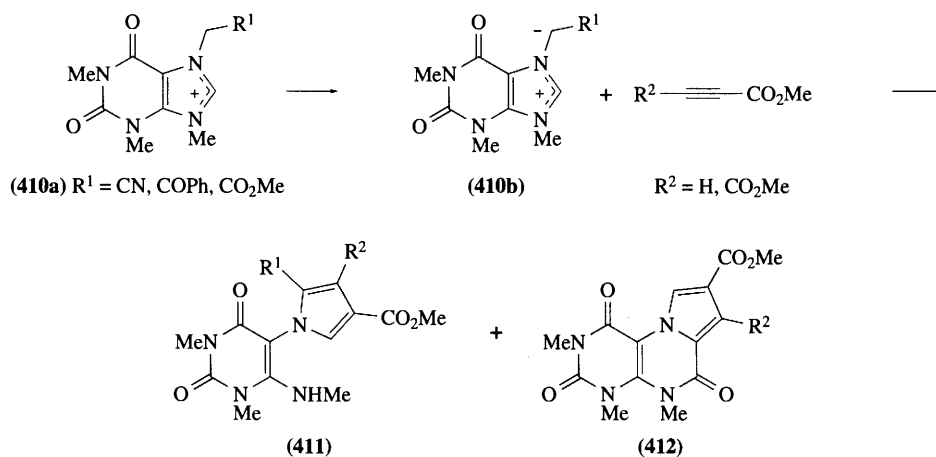
Ring transformation reactions are a potential alternative to the open-chain condensation reactions forming new heterocyclic ring systems. Ring enlargements of purines into pteridines follow the biogenetic pathway of pteridines, using guanosine-5'-triphosphate (GTP) as the only precursor. GTP cyclohydrolase is responsible for the formation of 7,8-dihydroneopterin-3'-triphosphate, the mother substance of all naturally occurring pterins.

Treatment of 7,9-dialkylxanthinium cations (**410a**) with *n*-butyllithium forms the corresponding ylide (**410b**) which reacts in a 1,3-dipolar addition with alkyne compounds to give 5-pyrrolouracils (**411**) and/or pyrrolo[1,2-*f*]pteridines (**412**) (Scheme 67) <82H(19)1845>.

An unusual ring contraction proceeded on treatment of 6-alkyl-7-methoxy-1,3-dimethylumazines (**413**) with activated aluminum in methanolic ammonia to give 8-substituted theophyllines (**416**)

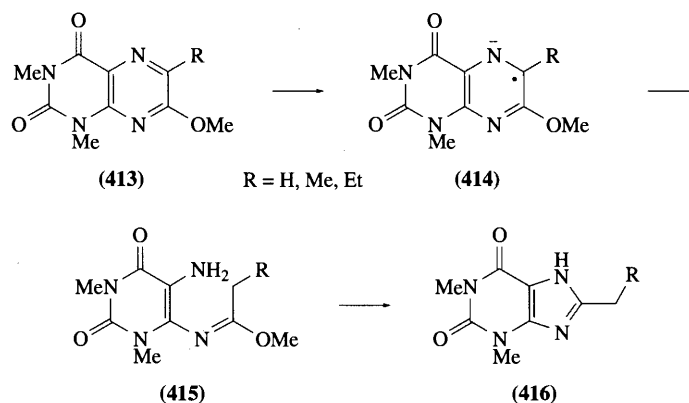


Scheme 66



Scheme 67

(Scheme 68) <86H(24)1565>. The most likely mechanism of this reaction involves radical anion formation (414), cleavage, successive electron addition, and cyclization of the intermediary imido-ester (415) to an imidazole derivative (416) (Scheme 68).



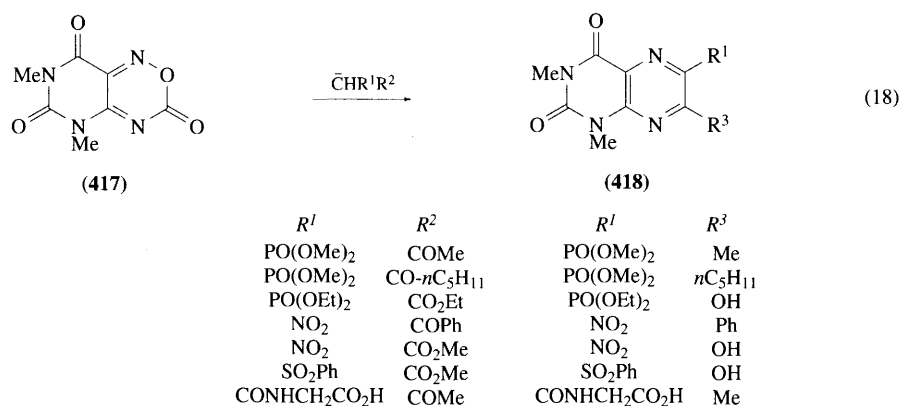
Scheme 68

Similarly, 7-alkoxy- and 7-methylthiopterins react with activated aluminum to 8-substituted guanines and smaller amounts of the demethoxylated pterins <87H(26)2091>.

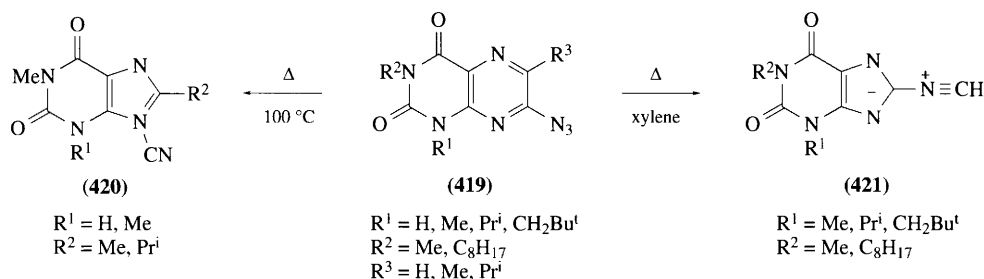
Another ring contraction is observed during 1,3-dipolar cycloadditions of 6-aryl-1,3-dimethyl-lumazine 5-oxides with dimethyl alkynedicarboxylate, forming 8-aryltheophyllines and 1,3-

dimethyl-5-methoxycarbonyl-6-methoxalyl-pyrrolo[2,3-*d*]-uracil together with a deoxygenated lumazine derivative <85H(23)2317>.

Pyrimido[5,4-*c*]-1,2,5-oxadiazinones (**417**) are suitable starting materials to construct annulated pyrazines. Reaction with carbanions derived from CH-acidic compounds, activated by two different electron-withdrawing functions, proceed in a regioselective manner by initial attack at the N—O bond. Triethyl phosphonoacetate, β -ketophosphonates, nitro ketones, nitro esters, sulfonylacetates, and *N*-acetoacetyl glycine have been applied to form 6,7-disubstituted lumazines (**418**) (Equation (18)) <91H(32)79>.



1,3-Disubstituted 7-azidolumazines (**419**) also show ring-contraction reactions, giving 1,3-dialkylxanthines on heating. 7-Azido-1,3-dimethylumazine and its 6-alkyl derivatives are converted on drying at 100°C in a solid state reaction without change of habit into 9-cyano- and 8-alkyl-9-cyanotheophyllines (**420**), respectively, via an intermediate nitrene or zwitterido mechanism (Scheme 69) <79ACR125>. Heating of the derivatives (**419**) in boiling xylene resulted in the formation of resonance stabilized 1,3-dialkylxanthin-8-yl nitrilium ylides (**421**) (Scheme 69) <89H(28)203>.



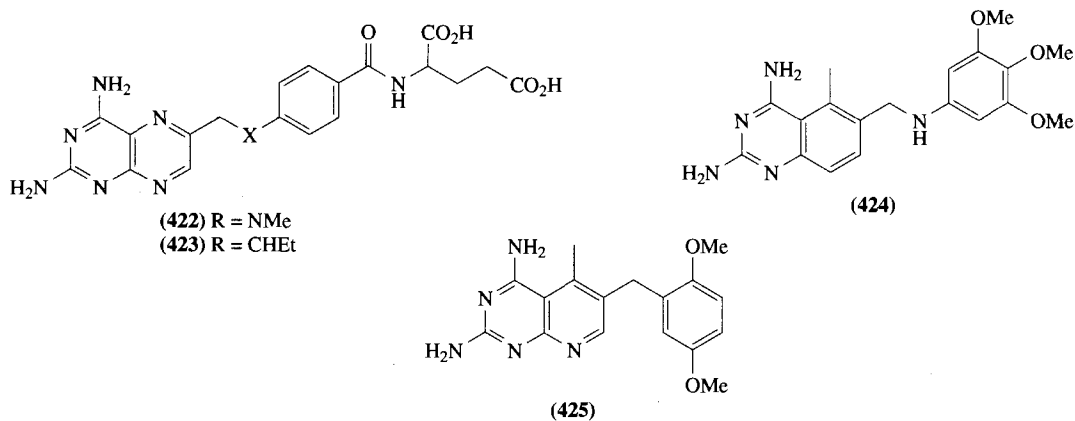
Scheme 69

7.18.11 SYNTHESIS OF PARTICULAR CLASSES OF PTERIDINE DERIVATIVES

7.18.11.1 Folic Acid Derivatives

During the 1980s and 1990s the role of folic acid analogues, especially methotrexate (MTX) (**422**), in cancer chemotherapy has been intensively studied <B-84MI 718-04>. The enzyme dihydrofolate reductase (DHFR) has been the primary target of this effort. The introduction of 10-ethyl-10-deazaaminopterin (10-EDAM) (**423**), piritrexim (PTX) (**424**) and trimetrexate (TMX) (**425**) into clinical trials attests to the continued interest in this field <87MI 718-06>.

Leucovorin or folinic acid, a mixture of the 6*R*- and 6*S*-diastereomers of 5-formyltetrahydrofolic acid, is an important clinical agent which may be used as a remedy for megaloblastic anemia and as an antidote for inadvertent overdoses of antifolates in patients with cancer, parasitic diseases, or autoimmune disorders such as psoriasis and rheumatoid arthritis. In view of these applications it is surprising that few significant improvements in the manufacture of leucovorin have occurred



since the 1950s. Leucovorin and 5-formyl-5,6,7,8-tetrahydrohomofolic acid are new antifolates with specific biochemical effects directed against the *de novo* biosynthetic pathway to purines and can be prepared from folic acid and homofolic acid, respectively, directly by reduction with $\text{BH}_3 \cdot \text{HNMe}_2$ in HCO_2H as a solvent [85JOC2582]. The separation of the (6*R*)- and (6*S*)-diastereoisomers of tetrahydrofolic acid (332) by derivatisation on N-5 with chiral auxiliary reagents was successful using (–)-menthyl chloroformate. The resulting carbamates can be separated, converted to the 5,10-methenyl-tetrahydrofolic acids by $\text{HBr}/\text{HCO}_2\text{H}$ treatment and are finally hydrolyzed [93JCS(P1)87]. Diastereoselective hydrogenation of folic acid with immobilized rhodium(I)-diphosphorane catalysts gave only a small diastereomeric excess [92CB2085].

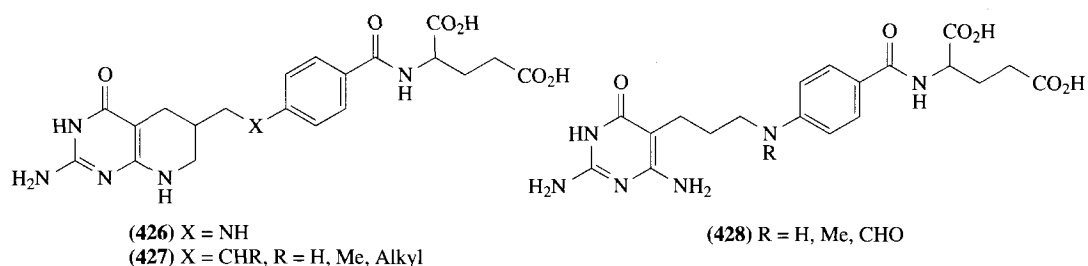
Methotrexate (MTX) (422) and aminopterin (AMT) have also been modified at the glutamic acid moiety by esterification to enhance cell penetration [85JMC660] or by replacement of the amino acid moiety by the ornithine and lysine residues [87JMC1463, 88JMC1332] as well as by long-chain 2-aminoalkanedionic acids [88JMC1338]. The shift of the carboglutamate sidechain from *para* to *ortho* or *meta* positions, respectively, caused loss of cell growth inhibitory potency relative to MTX [88JMC763]. Furthermore, the terminal carboxyl group was changed to phosphonates and sulfates [88JMC1326]. Other examples are the modifications at the benzoyl moiety and substitutions of the glutamic acid residue [94JMC2167]. Substitution at N-5 in tetrahydrofolic acid by various types of carbamoyl residues to prepare multisubstrate analogues of the substrate-cofactor adduct in the reactions catalyzed by the folate-mediated one-carbon transfer reactions did not lead to biological activity [88JMC697]. The 2-desamino- and 2-desamino-3-methyl analogues of MTX and AMT were also synthesized and show inhibition of the growth of tumor cells, but were very poor inhibitors of dihydrofolate reductase (DHFR) [91JMC227, 91JMC1594].

In 1994 the synthesis of (6*S*)-*N*⁵-formyl-5,6,7,8-tetrahydropteroyl-di-, -tri-, -tetra-, and -penta-*g*-L-glutamic acids was achieved for the first time leading to a stereochemical purity of >99% [94JCS(P1)897].

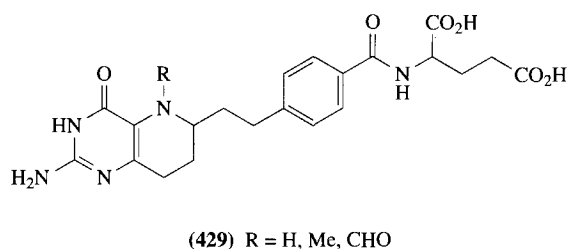
7.18.11.2 Folic Acid Analogues

Research for new therapeutic targets has focused on the folate-utilizing enzymes in *de novo* purine and pyrimidine synthesis. Two enzymes of the purine biosynthetic pathway, glycylamide ribonucleotide transformylase (GAR-Tfase) and aminoimidazolecarboxamide ribotide transformylase (AICAR-Tfase) utilize 10-formyl-5,6,7,8-tetrahydrofolate as a cofactor [84MI 718-10]. It was found that 5-deaza-5,6,7,8-tetrahydrofolic acid (5-DATHF) (426) [89JMC1517] and 5,10-dideazatetrahydrofolic acid (DDATHF) (lometrexole) (427) [85JMC914, 89JBC(264)328] inhibit *de novo* purine biosynthesis at the GAR-Tfase step and show potent *in vitro* and *in vivo* antitumor activity. Several synthetic routes to DDATHF and analogues, including a stereospecific approach [89TL6291], have been reported. 5,10-Dideazaaminopterin and its tetrahydro derivative as well as 5-deaza- and 10-deazaaminopterin and -folic acid were also prepared [83JOC4852, 85JMC914, 92JMC1578]. Several analogues thereof [92JMC1399] additionally modified at the 2- and 10-positions [92JMC1399], the 10-methyl-DDATHF and 10-alkyl-5,10-dideaza-tetrahydrofolic acids [90JMC673] (427) as well

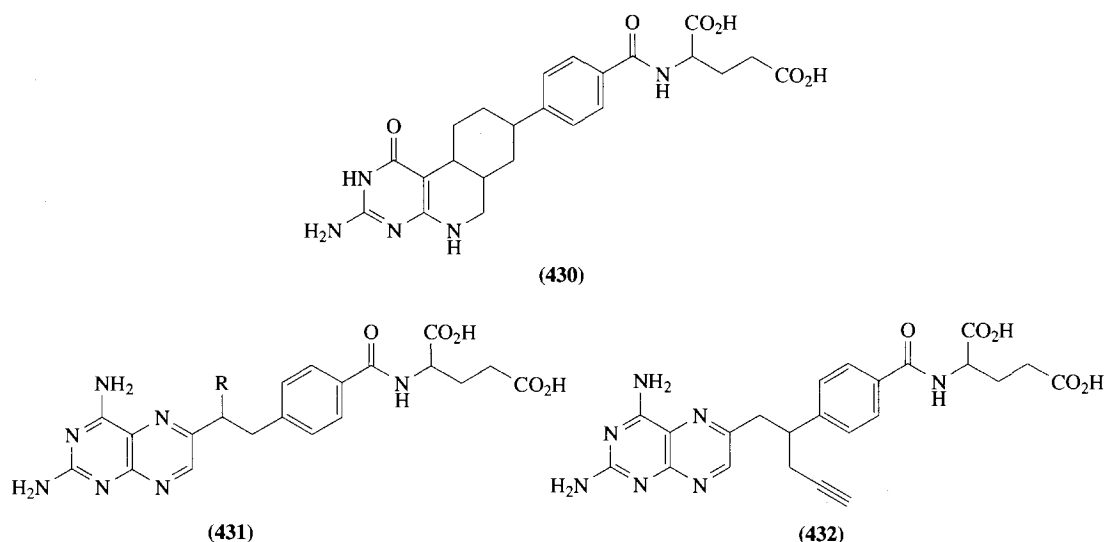
as the ring-opened derivative of DDATHF (**428**) <89H(28)1169, 90JMC561>, and their chemistry and synthesis have also been described <90JHC1>.



Furthermore the syntheses of 8,10-dideazatetrahydrofolic acid and its 5-methyl- and 5-formyl derivatives (**429**) have been reported <93H(35)755>. The 5-*N*-methyl derivative turned out to be more potent than 5,10-DDATHF as an inhibitor of growth for L1210 cells in culture but the locus of action is apparently unrelated to inhibition of GAR-Tfase. Unfortunately, 5-methyl-8,10-DDATHF was not active *in vivo* against an L1210 challenge in mice.

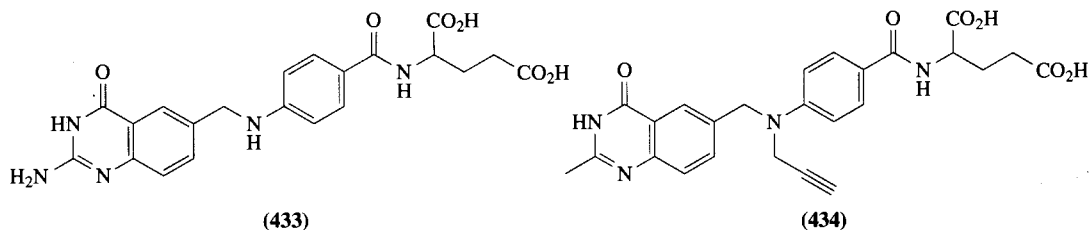


Other structural modifications have been realized by the synthesis of 5,10-ethano-5,10-dideazaaminopterin (**430**) <92JMC320>, 7,10-ethano-5-deazaaminopterin <85JOC1005>, 10-deazaaminopterin, its 9-alkyl- (**431**) <90JMC212>, and 10-ethyl derivatives <85JOC1879>. 9-Methyl-10-deazaaminopterin revealed a 21 times more potent activity than MTX as an inhibitor of cell growth in L1210 cells. 10-Propargyl-10-deazaaminopterin (**432**) is transported inward very effectively in L1210 cells showing a 10-fold advantage over MTX <93JMC2228>.



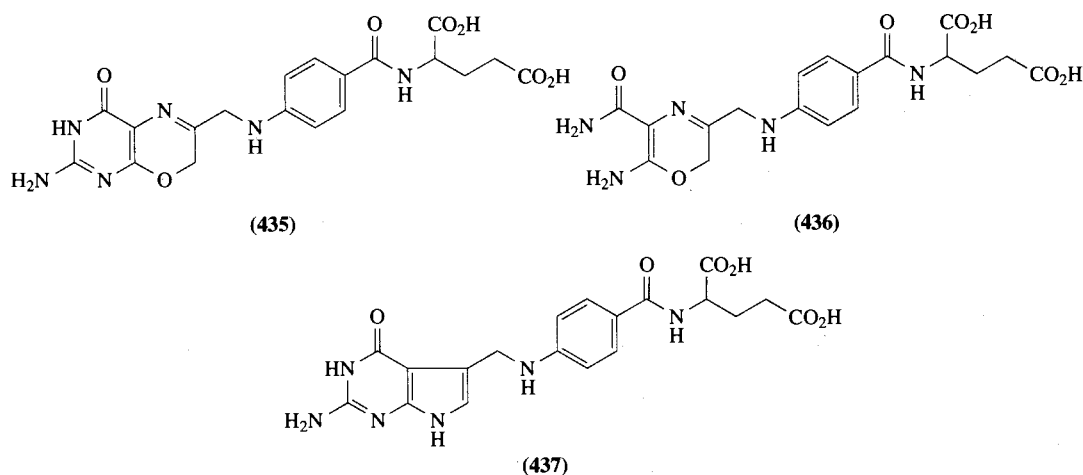
Chinazoline analogues (**433**) are also powerful antifolates, inhibiting thymidylate synthase <81MI 718-01, 88MI 718-04, 89JMC1284, 94JMC1616>. Reduction to the tetrahydro form and introduction of a 10-propargyl group lowered the activity <87JMC1256>. Striking biological results, however, were obtained when the 2-amino group of the potent TS inhibitor *N*(10)-propargyl-5,8-dideazafolic acid (PDDF) was replaced by a methyl group (**434**). High activity was also found if γ -L-linked dipeptides and L- γ -amide analogues have been synthesized <94JMC3294>. Furthermore, the benzene ring was

replaced by a broad variety of heterocyclic rings revealing an enhanced cytotoxicity <91JMC1594>. These results led to the evaluation of 1-deaza-, 3-deaza-, and bridge-elongated analogues of PDDF <91JMC2746>. On the other hand, 5,8,10-trideaza-5,6,7,8-tetrahydrofolate and its L-ornithine analogue showed no activity <89JMC709>.



Another potent candidate is 5,10-dideaza-5,6,7,8-tetrahydrohomofolic acid (HDDATHF) <90JOC3222> whose mechanism of action again involves inhibition of GAR-Tfase in *de novo* purine biosynthesis.

More severe structural changes are obvious in *N*-[(2-amino-7,8-dihydro-8-oxa-4(3*H*)pteridon-6-yl)benzoyl]-L-glutamic acid (435) <83JMC1164>, in *N*-(4-[(5-amino-6-carbamoylpyrazin-2-yl)methyl]methylamino)benzoyl)-L-glutamic acid (436) <85JHC5>, *N*-(4-(2-(2-amino-4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl)benzoyl)-L-glutamic acid (437) <92T8089, 91JMC555>, *N*-(4-[*O*-(2-amino-4-substituted-6,7-dihydrocyclopenta[*d*]pyrimidin-5-yl)alkyl]benzoyl)-L-glutamic acids <94JMC1616>, 2,4-diaminofuro[2,3-*d*]pyrimidin-5-yl analogues <94JMC1169>, and [4-(2-guanin-8-yl)benzoyl]-L-glutamic acid <91JOC6937>.



A review on the potent inhibitors of *de novo* pyrimidine and purine biosynthesis summarizes the developments in this field <90MI 718-04> and another report is concerned mainly with the synthetic approaches to the various types of inhibitors of folate-dependent enzymes <B-93MI 718-07>.

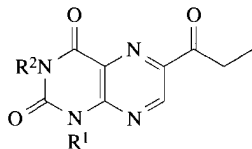
7.18.12 IMPORTANT PTERIDINES AND APPLICATIONS

7.18.12.1 Naturally Occurring Pteridines

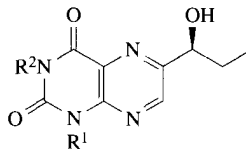
Pteridines are widely distributed in nature and function as pigments, biological markers, and cofactors of enzymatic reactions. The oxidized heteroaromatic forms show a characteristic fluorescence which allows easy detection even in low concentrations. However, the more active 5,6,7,8-tetrahydro derivatives are nonfluorescing and oxidizable and create experimental problems in handling this type of compound. So far, all naturally occurring pteridines have turned out to be derivatives of pterin (2) and lumazine (3) which are modified by different substituents and functional groups in the 6- and/or 7-position.

A series of new lumazine derivatives has been isolated from the luminescent marine polychaete *Odontosyllis undecimdonata* and identified as 6-propionyllumazine (438), its 3-methyl- (439), and 1,3-

dimethyl derivatives (**440**) <90CL367> as well as (*S*)-6-(1-hydroxypropyl)-3-methyl- (**441**) and -1,3-dimethyl- (**442**) <94H(38)971> indicating that marine products are richer in lumazines than pterins. The structure of leucettidine was revised from 3-methyl- to 1-methyl-6-(1-hydroxypropyl) lumazine (**443**) on synthetic and spectroscopic evidence <88T3373>.

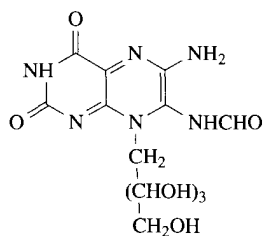


(**438**) $R^1 = H, R^2 = H$
 (**439**) $R^1 = H, R^2 = Me$
 (**440**) $R^1 = Me, R^2 = Me$

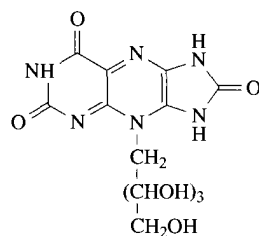


(**441**) $R^1 = H, R^2 = Me$
 (**442**) $R^1 = Me, R^2 = Me$
 (**443**) $R^1 = Me, R^2 = H$

Interesting lumazine derivatives have been isolated from *Russulae* as yellow, fluorescing pigments, called russupteridine-yellow I and IV. It has been suggested that the proposed structures be represented by the more likely tautomers (**444**) and (**445**) <84HCA550, 84HCA570>.

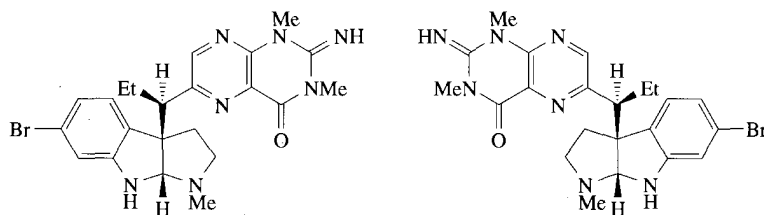


(**444**)

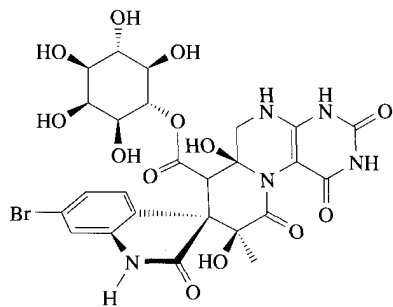


(**445**)

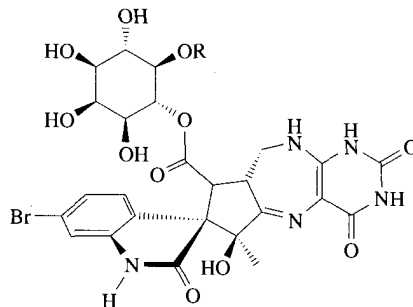
An uncommon lumazine structure was found in the tunicate *Ciona savigny*. The enantiomeric urochordamines A and B (**446**) can be considered as pteridine-containing bromophysostigmine alkaloids, the constitutions of which have been determined by extensive spectral analysis <93TL4818>. Even more complex structures are presented in surugatoxin (**447**), prosurugatoxin (**448**), and neosurugatoxin (**449**), isolated from the toxic Japanese ivory shell, *Babylonia japonica*, and chemically confirmed by total synthesis <88TL1547, 94T2729, 94T2753>. Biological studies revealed that surugatoxin (**447**) containing a tetrahydrolumazine ring is nontoxic but ring enlargement to the pyrimido[4,5-*f*]-1,4-diazepine system in (**448**) and (**449**) causes high toxicity, as for atropine.



(**446**)

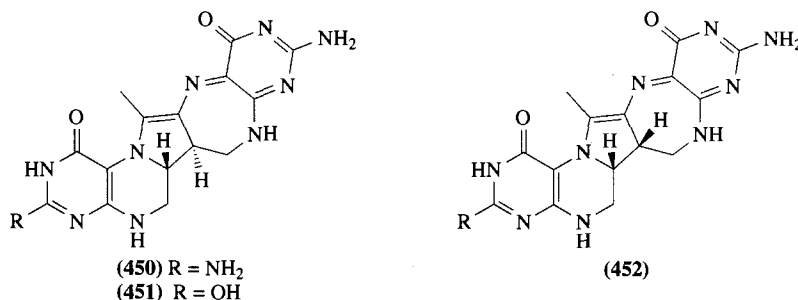


(**447**)

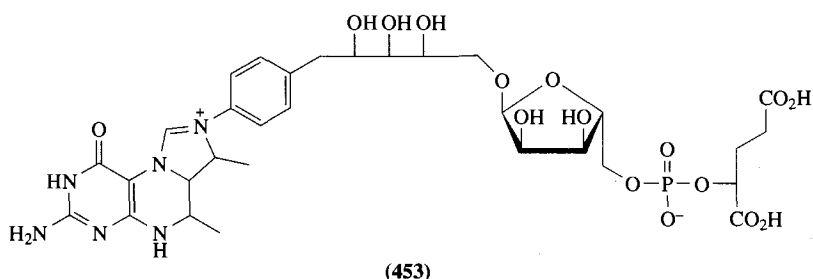


(**448**) $R = H$
 (**449**) $R =$

The pyrimido[4,5-*f*]-1,4-diazepine ring system is also present in 6-acetylhomopterin (**337**) <81JBC(256)10399, 82B5700>, isolated from the head of *Drosophila melanogaster*, and functions as a chemical precursor in a nonenzymatic reaction to form with 7,8-dihydropterin the enantiomeric drosopterins (**450**) <B-86MI 137-04> and with 7,8-dihydrolumazine the corresponding auro-drosopterins (**451**) <93HCA1970>. The stereochemistry of droso- and neodrosopterin (**452**) has not yet been settled unambiguously but from detailed NMR studies it is assumed that (**452**) is the *cis*- and (**450**) the *trans*-isomer regarding the two chiral centers <B-93MI 718-04>.



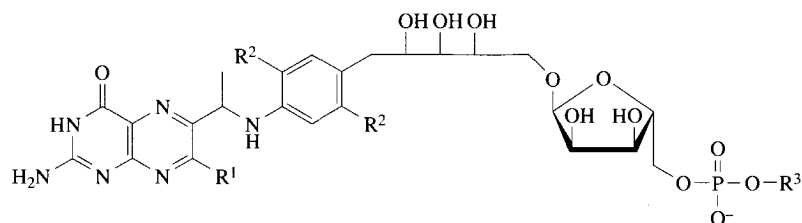
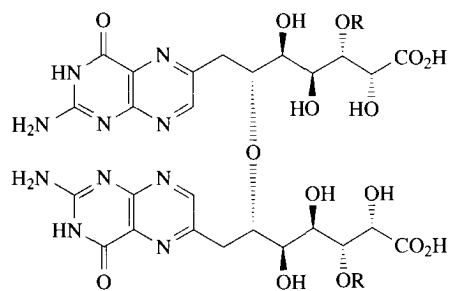
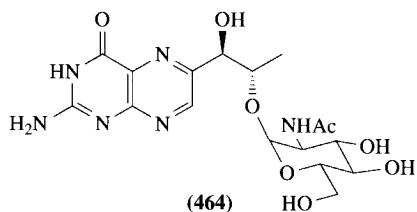
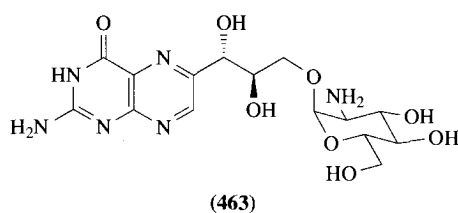
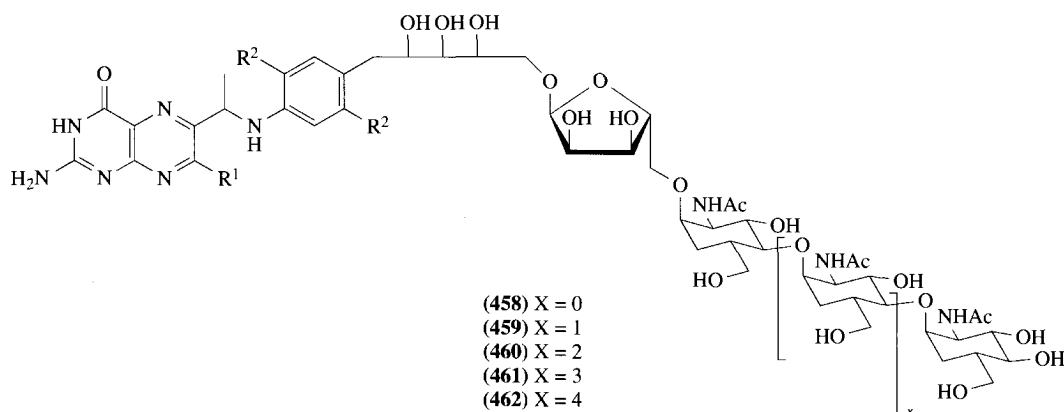
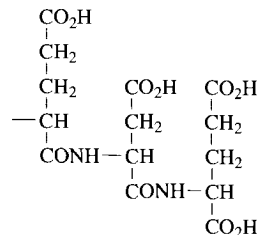
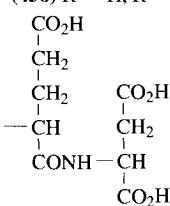
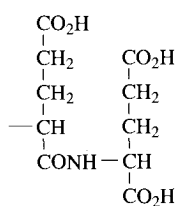
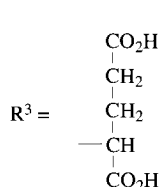
A new type of modified folic acid derivative was found in methanogenic bacteria belonging to the kingdom of the archaeobacteria <78MI 718-01>. These are separately classified, like other organisms living in extreme environments such as the halobacteria, the thermoacidophiles, and the thermophilic anaerobes *Thermoproteus* and *Desulfurococcus*. Methanopterin (**397**) was first identified <83MI 718-01, 84MI 718-01, 84MI 718-02> as the metabolic precursor of the yellow fluorescent compound, now called 5,10-methenyl-5,6,7,8-tetrahydromethanopterin (**453**) <84B4448>.



Often associated with methanopterin (**397**) is 7-methylpterin which has so far not been found in nature <83MI 718-06, 88MI 718-02>. *Methanosarcina barkeri* and other methylotrophic methanogens contain sarcinapterin (**454**), a closely related derivative of (**397**) which carries an additional L-glutamyl residue bound via an amide linkage to the α -carboxylic group of α -hydroxyglutarate <84MI 718-01>. Further modification of the methanopterin structure was encountered in tatiopterin 0 (**455**) and tatiopterin 1 (**457**) which were isolated from *Methanogenium tationis* and identified as the aspartyl and aspartylglutamyl derivatives <91MI 718-03> of the 7-nor-sarcinapterin (**454**). A dihydroxy derivative of (**455**) was found in *Methanoculleus thermophilum* and was named thermopterin (**456**) <91MI 718-01>.

Furthermore, various thermophilic archaeobacteria show some structural modifications at the terminal end of methanopterin by the substitution of the α -hydroxyglutaric acid residue. In *Pyrococcus furiosus* 1-3 *N*-acetylglucosamine molecules are attached through glycosidic linkages to the 5'-OH group of the ribosyl moiety (**458–460**) <93MI 718-02> and in *Thermococcus litoralis* the poly-*N*-acetyl-glucosamine sidechain is even extended to four or five sugar units (**461**) and (**462**) <93MI 718-13>.

Analogous studies and separation procedures of other nonmethanogenic archaeobacteria revealed that *Sulfolobus solfataricus* exhibits solfapterin (1-*O*-(erythro-neopterin-3'-yl)-2-deoxy-2-amino-D-glucopyranosid) (**463**) <88MI 718-06> and various *Halobacteria* contain sulfohalopterin 2 (**465**) and phosphohalo-pterin 1 (**466**) <87B6211, 88MI 718-05>, respectively, for which unusual dimeric structures have been proposed by indirect degradation experiments. This new type of natural pterins, however, afford further structural proof.

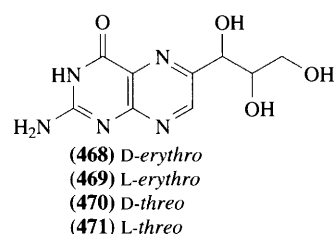
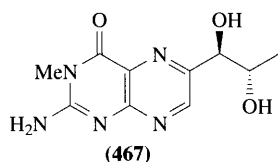
(397) $R^1 = \text{Me}, R^2 = \text{H}$ (454) $R^1 = \text{Me}, R^2 = \text{H}$ (455) $R^1 = R^2 = \text{H}$ (457) $R^1 = R^2 = \text{H}$ 

A pteridine glycoside closely related to (463) was isolated from *Chlorobium limicola* f. *thio-sulfatophilum* NCIB 8327 and identified, by spectral means and chemical degradations, as 1-(bio-pterin-2'-yl)-N-acetyl- β -D-glucosamine (95HCA600). The native form of limipterin (464) is the 5,6,7,8-tetrahydro derivative.

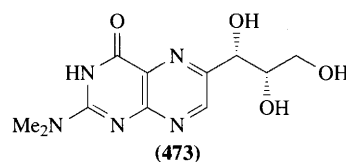
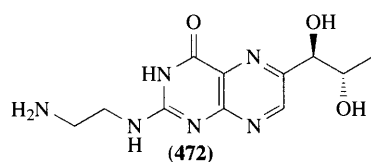
New 7-substituted biopterin (L-primapterin) (**361**) and neopterin (anapterin) (**360**) analogues were discovered in 1988 as excretion products in the urine of patients suffering from a new form of atypical phenylketonuria <88BBR(153)715, 88MI 718-03>. This interconversion proceeds most probably on the quinonoid dihydrohydropterin level and is due to a 4a-carbinol-amine dehydratase defect allowing isomerization via an intermediary spiro-compound <90BBR(172)1060>.

3-Methylbiopterin (**467**), the first N-3 substituted naturally occurring pterin derivative has been found in the marine anthozoan *Astroides calycularis* Pallas <87E950> and shows some cell-growth inhibiting activity. Another new natural pterin, called "umanopterin" (**470**), was isolated from the urine of cancer patients and its structure elucidation revealed that it is the last one of the four possible stereoisomeric 6-(1,2,3-trihydroxypropyl)pterins (**468–471**) found in nature and possessing the D-threo configuration in the sidechain <92TL1341>. The major pterin in *Tetrahymena pyriformis* is identical with (**471**) and its assignment as ciliapterin <68JBC(243)826> has to be corrected <91MI 718-04>. Neopterin (D-erythro) (**468**) is one of the major pteridine compounds found in urine, serum, and many other biological samples <B-85MI 718-04>. Since the early 1980s, particular interest has been focused on neopterin, since its urinary concentration has been found to increase in various kinds of neoplasia, viral infections including acquired immunodeficiency syndrome (AIDS), and allograft rejections. All these diseases are associated with the activation of the cellular immune system <B-92MI 718-01> and it has been shown that neopterin is produced by macrophages on activation with interferon-gamma derived from T-cells <84MI 718-09>.

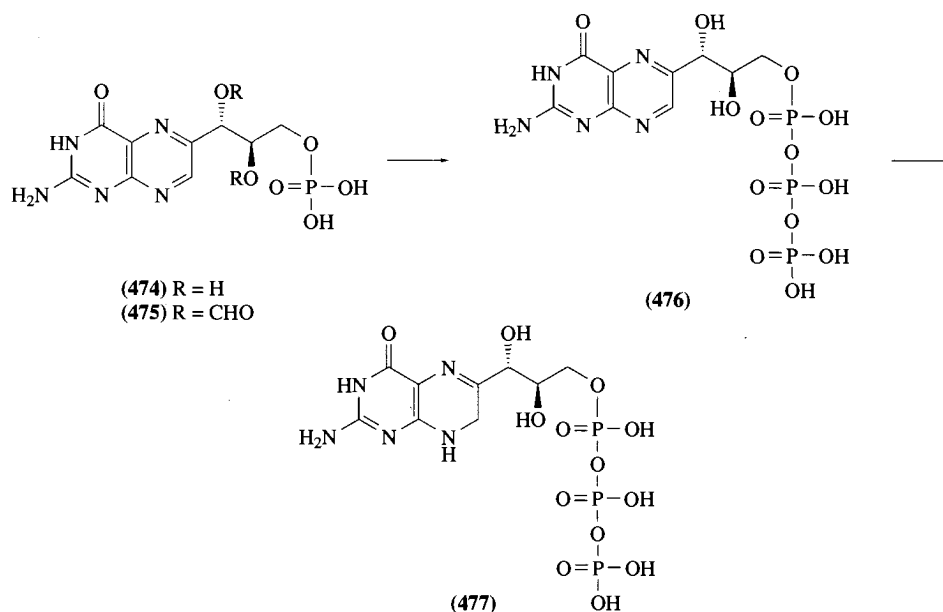
Thus, neopterin is a hopeful candidate as a nonspecific biochemical marker to investigate an activation state of cell-mediated immunity and to monitor the diseases discussed above. The enantiomer of neopterin, named bufochrome (L-erythro) (**469**), has been found in toad skin <58E182, 63MI 718-01>. Monapterin (L-threo) (**471**), the enantiomer of umanopterin, is more widely distributed and is found in various microorganisms <68HCA1548, 69JBC(244)142, 71ZPC1271>, germinating potatoes <80N610>, and in plasma <86MI 718-07> but not in human urine <B-93MI 718-06>. The enantiomeric separation of biopterin and neopterin stereoisomers <93MI 718-08> and the determination of the stereoconfiguration of the sidechains have been solved by chiral HPLC techniques <92MI 718-05> alleviating the problems of identification and characterization greatly. A natural isomer of biopterin has been found in *Dictyostelium discoideum* possessing the D-threo configuration and is called dictyopterine <90MI 718-05>.



Oncopterine (**472**), another natural pterin derivative from the urine of cancer patients, was identified as N²-(3-aminopropyl)biopterin <93MI 718-19>, showing again an unusual substitution at the 2-amino group as first noticed for euglenapterin (**473**) <86LA1705>.



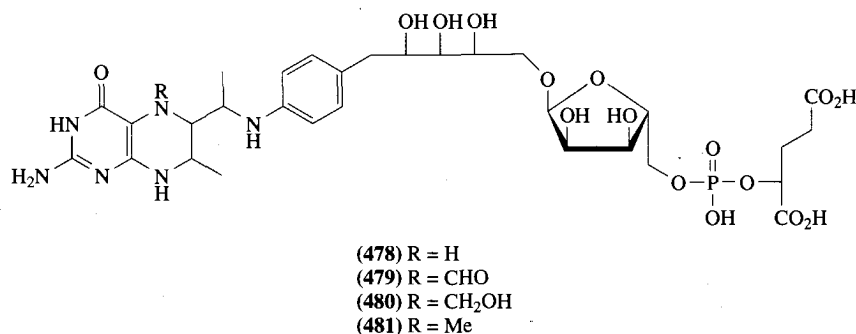
The first chemical synthesis of 7,8-dihydroneopterin-3'-triphosphate (**477**), the biosynthetic precursor of all naturally occurring pterin derivatives, has been achieved from neopterin-3'-monophosphate (**474**) by formylation of the two hydroxy groups (**475**) followed by coupling with pyrophosphate to (**476**). Chemical or catalytic reduction resulted in the 7,8-dihydro derivative (**477**), which was fully active as a substrate in enzymic reactions <88BBR(152)1193>.



Scheme 70

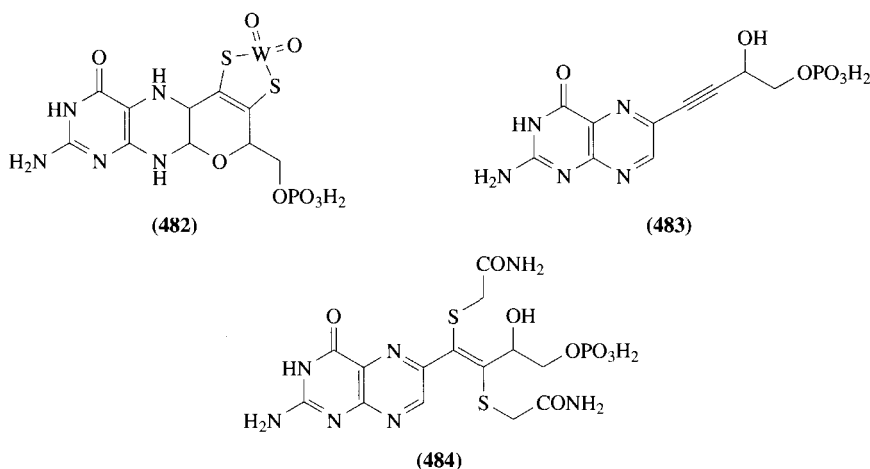
7.18.12.2 Pteridine Cofactors

In archaeobacteria the folic acid pathway for C-1 transformations is based upon methanopterin as an ancient precursor of these important cellular interconversions. Tetrahydromethanopterin (478) has been identified as the active coenzyme and carbon carrier (479–481) in methanogenesis [84JBC(259)9447] and functions *et alia* as formaldehyde activation factor [84PNA(81)1976].



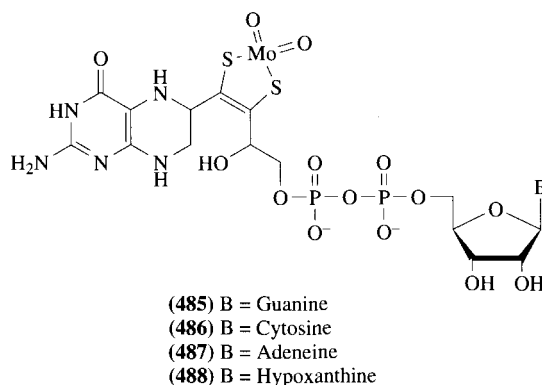
Another very important coenzyme is seen in the molybdenum cofactor (399) [B-93MI 718-09] which is present in sulfite oxidase, xanthine dehydrogenases, and nitrate reductase and was identified and structurally characterized by conversion into an oxidized inactive form [80JBC(255)1783] showing the composition of a metal complex of molybdenum with a unique pterin derivative. The elucidated structures of two oxidized fluorescent breakdown products (383) and (483) can be regarded as corroborative evidence for the unusual molybdenum stabilized endithiol function in the C-6 side chain of the pterin nucleus. The cofactor itself has not yet been isolated due to its extreme lability when released from its protective protein environment. More definite proof of the structure of molybdopterin was derived by conversion to the dicarboxamidomethyl derivative (484) and structural characterization of the latter [87JBC(262)16357]. However, it should also be taken into account that the native structure is a covalent adduct of the hydroxy group of the side chain on to a 5,6-dihydropterin (399) analogous to some more simple model substances proven by x-ray analysis [90HCA808]. Furthermore, studies on the structure of (383) and its chemical relationship to urothion (382) [82PNA(79)6856], isolated as early as 1940 from urine by Koschara [40ZPC(263)78, 43ZPC(277)284]

and later synthesized in racemic form <89JA285>, make the proposed basic constitution even more plausible.



Synthetic and structural aspects about the extremely labile molybdenum cofactor (Moco) have been summarized <93H(35)1551> and indicate fundamental difficulties in building up the molybdenum enedithiole complex.

Isolation of molybdopterin from DMSO reductase revealed that this coenzyme is even more complex in structure, consisting of molybdopterin guanine dinucleotide (485) <90PNA(87)3190>. Furthermore the cofactor of another prokaryotic enzyme, CO dehydrogenase from *Pseudomonas carboxydoflava* was shown to contain molybdopterin cytosine dinucleotide (486) (bactopterin) <86MI 718-04, 87BBA(912)357, 90MI 718-01> and in the early 1990s dinucleotide variants containing guanine (485) <90MI 718-03> cytosine (486), adenine (487), and hypoxanthine (488) have been discovered <91MI 718-02>. Interestingly enough, all of the eukaryotic enzymes analyzed so far contain only molybdopterin and the dinucleotides have been found only in eubacteria and methanogens.

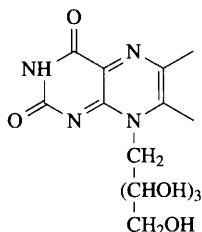


Several hyperthermophilic organisms require tungsten for growth instead of molybdenum which is bound in an analogous manner to the enthiol function of the same tetrahydropterin moiety (482) whose structure was concluded from the conversion of the tungsten cofactor into the breakdown product (483) <93JBC(268)4848>. The presence of pterins in naturally occurring tungstoproteins has been inferred with both formate dehydrogenase <83JBC(258)1826> and carboxylic acid reductase <92MI 718-04> from *Clostridium thermoaceticum*.

7.18.12.3 Biologically Active Pteridines

Luminescent bacteria are found in various ecological niches, but most species are present in the ocean where some live in symbiosis with fish. Light emission can be switched on and off and it is the present thesis that bacterial bioluminescence goes by a "sensitized chemiluminescence" mechanism <B85MI 718-08>. Most of the luminescent bacteria are placed into two genera, *Vibrio* and

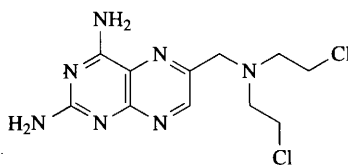
Photobacterium. The basic bioluminescence mechanism appears to be the same for all types of bacteria, but secondary features like color of light, temperature of maximum light intensity, and response to oxygen concentration are often different. There are two types of light emissions: the direct chemiluminescence and the indirect or "sensitized" chemiluminescence <77MI 718-02>. A novel protein called "lumazine protein" has been identified as a sensitizer in the cells <78PNA(75)833>. The noncovalently bound, natural fluorescent marker turned out to be 6,7-dimethyl-8-D-ribityllumazine (489) <85B1467, 85B1489>.



(489)

The synthetic 2,4-diamino-6-(bis-2-chloroethyl)aminomethylpteridine (490) was found to be highly potent against L-1210 mouse leukemia lymphoblasts. After tumor inoculation, it increased the lifespan of 50% of mice to more than 200%, while the other 50% of animals were cured <84MI 718-07>.

Unfortunately, most simple synthetic pteridines have turned out to be inactive in broad screening experiments indicating that the oxidized forms are less prone to interactions in cells than their tetra- and dihydro species.



(490)

7.19

Bicyclic 6-6 Systems: Other Four Heteroatoms 2 : 2

HEINRICH WAMHOFF, CHRISTIAN SATTLER and
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Universität Bonn, Germany

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7.19.1 INTRODUCTION

The properties, syntheses, and applications of the ring systems dealt with in this chapter have already been described in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(3)329>. In this chapter new reactions of known systems which have appeared in the literature since CHEC-I are described.

7.19.2 DIAZINODIAZINES

Thirteen diazinodiazines without bridged heteroatom are theoretically possible. All of these have been reported in the literature. There are: (i) four pyridazinopyridazines, namely pyridazino[4,3-*c*]pyridazine (**A**), pyridazino[3,4-*c*]pyridazine (**B**), pyridazino[4,5-*c*]pyridazine (**C**), and pyridazino[4,5-*d*]pyridazine (**D**); (ii) three pyrimidopyridazines, pyrimido[4,5-*c*]pyridazine (**E**), pyrimido[5,4-*c*]pyridazine (**F**), and pyrimido[4,5-*d*]pyridazine (**G**); (iii) two pyrazinopyridazines, pyrazino[2,3-*c*]pyridazine (**H**) and pyrazino[2,3-*d*]pyridazine (**I**); (iv) two pyrimidopyrimidines, pyrimido[4,5-*d*]pyrimidine (**J**) and pyrimido[5,4-*d*]pyrimidine (**K**); and, (v) only one pyrazinopyrazine: the pyrazino[2,3-*b*]pyrazine (**L**).

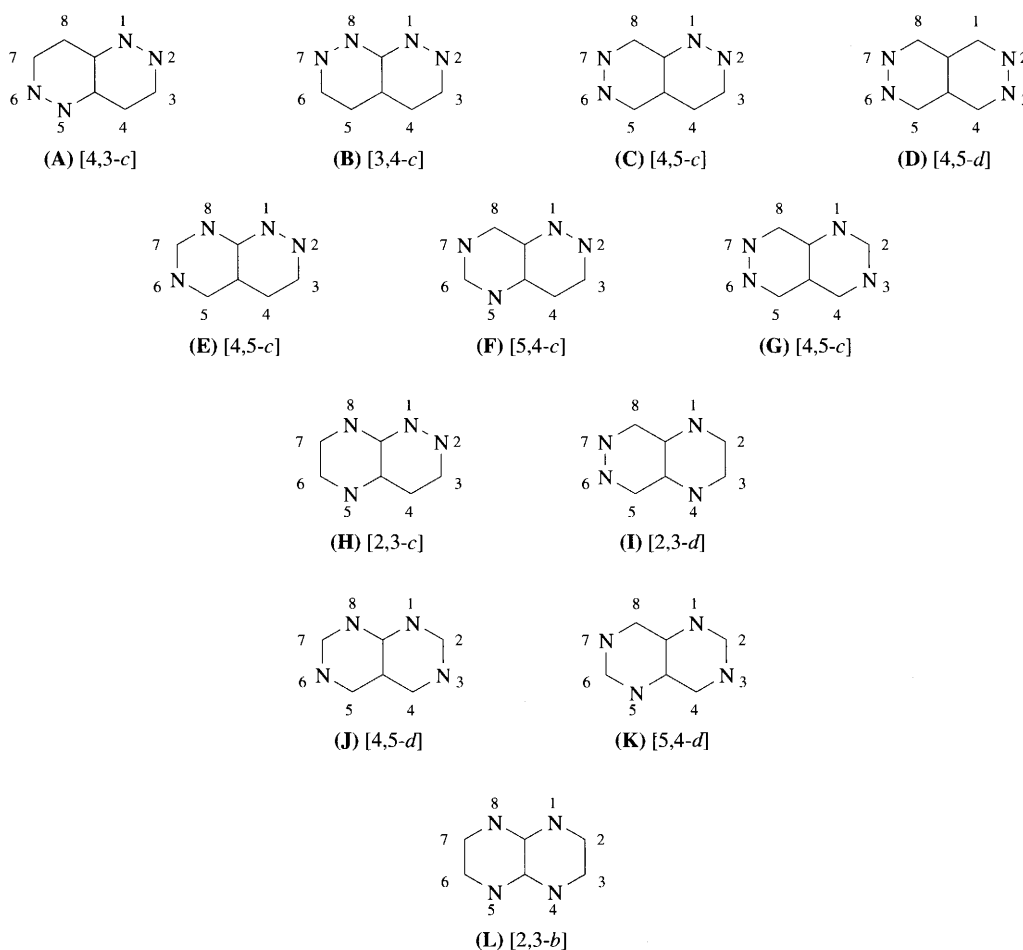
The pyrazino[2,3-*d*]pyrimidines (pteridines) are reviewed in Chapter 7.18.

7.19.2.1 Pyridazinopyridazines

7.19.2.1.1 Theoretical and experimental structural methods

(i) Pyridazino[4,3-*c*]pyridazines (**A**)

There are only a few experimental data available. One x-ray crystal structure determination and one Hückel MO calculation were reported in CHEC-I. Now there are more theoretical data available. With the AM1 SCF-MO method some pyridazino[4,3-*c*]pyridazine derivatives have been calculated <88JOC3900>. New quantum chemical calculations <90MI 719-01> and some more experimental data are reported <85KGS1428>.



(ii) *Pyridazino[3,4-c]pyridazines (B)*

One Hückel MO calculation was reported in CHEC-I. In some later publications new experimental and theoretical structure data are given. AM1 SCF-MO studies <88JOC3900> and ^1H NMR, ^{13}C NMR, mass spectrometry, and IR data for several substituted derivatives are available <82CJC1214, 89T1793, 90IJC(B)72>. In addition, some information about the conformational equilibrium are given <89T1793>.

(iii) *Pyridazino[4,5-c]pyridazines (C)*

Only a few experimental and theoretical structure data were reported in CHEC-I. Now some more NMR, NOE differential, mass, UV, and IR spectral data are available <90CC645, 91JCS(P1)991>. An AM1 SCF-MO calculation on pyridazino[4,5-c]pyridazine derivatives has been reported <88JOC3900>.

(iv) *Pyridazino[4,5-d]pyridazines (D)*

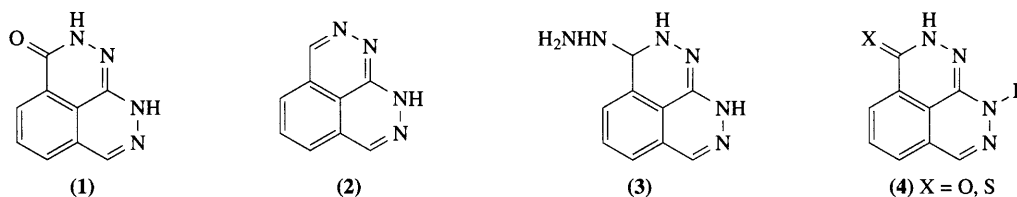
NMR, IR, UV, x-ray crystallographic data, and Hückel MO calculations were reported in CHEC-I. Now information about the torsional effects on the conformations of two diastereomeric pyridazino[4,5-d]pyridazines are available <91JA7882>. Additional x-ray crystal structure data and some photoelectron spectral analysis of the planar-parallel pyridazino[4,5-d]pyridazines has been given <82TL1251>. AM1 SCF-MO <88JOC3900> and fluorescence studies <85IJC839> are available. Special vicinal ^{13}C — ^{13}C coupling via $\text{N}=\text{N}$, $\text{N}=\text{O}$, and $\text{C}=\text{N}$ double bond paths <85TL4427> and a charge transport calculation in pyridazino[4,5-d]pyridazine as an organic solid are reported <86MI

719-01). Studies about the *exo* and *endo* isomers and the mechanism of the transformation of the thermodynamically less stable *exo*- into the *endo*-isomer upon heating of a solid sample are given <83JA3832>.

7.19.2.1.2 Reactivity

(i) Pyridazino[3,4-*c*]pyridazines (**B**)

Up to 1994, no reaction involving derivatives of pyridazino[3,4-*c*]pyridazines has been reported. Only some reactions and the synthesis of compound (1) as a key intermediate in the synthesis of pyridazino[3,4,5-*de*]phthalazine derivatives (2)–(4) has been described <82CJC1214>.



(ii) Pyridazino[4,5-*c*]pyridazines (**C**)

The most common reactions, nucleophilic displacements of dichloro derivatives, of this ring system have been reported in CHEC-I. The use of the azo-chromophore as a 2π -component in photo [2 + 2] cycloaddition reactions has now been described <84TL2459>.

(iii) Pyridazino[4,5-*d*]pyridazines (**D**)

1,4-Diarylpyridazino[4,5-*d*]pyridazine derivatives (5) have been found to undergo [4 + 2] cycloaddition reactions with a variety of electron-rich dienophiles like ketones or ketene acetals to afford phthalazine derivatives in good yields <91T3959>. Numerous examples of these ring transformations have been reported <91T3959> and only some representative examples can be described here (Scheme 1). The highly strained cycloadducts immediately eliminate nitrogen to afford cycloamino-substituted dihydrophtalazine derivatives. By using enamino reagents derived from cyclic ketones these primary reaction products (e.g. (6) and (8)) can be isolated. Attempts to aromatize these compounds by heating in toluene failed. Addition of TFA to the solutions effected smooth elimination of pyrrolidine to afford the condensed phthalazines ((7) and (9)) in high yields. Ketene *N,S*-acetals also react readily.

Alkylation of pyridazino[4,5-*d*]pyridazines is possible by electrochemical reduction in THF at -1.2 V in the presence of methyl iodide to afford the 4,5-dimethyl derivative quantitatively <89NJC579>.

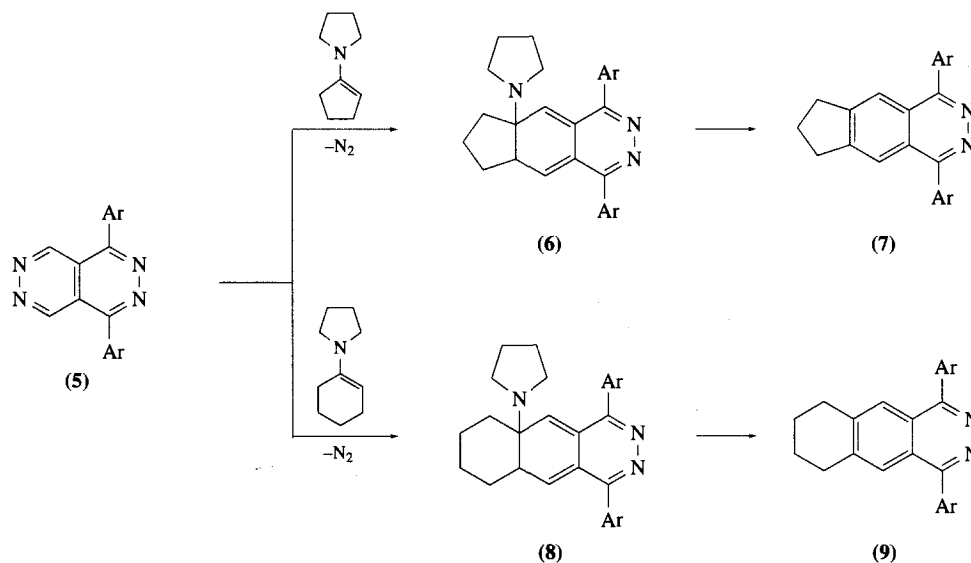
Some photochemical transformations of the azo-chromophore in pyridazino[4,5-*d*]pyridazines as 2π -components in photo [2 + 2] cycloaddition reactions have been described <82TL1251, 84TL2459>.

7.19.2.1.3 Ring Syntheses

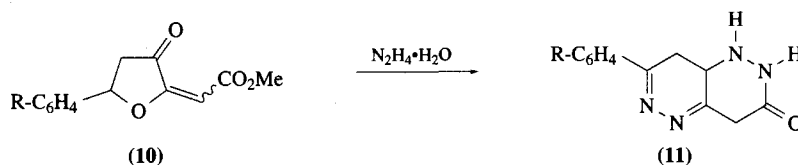
(i) Pyridazino[4,3-*c*]pyridazines (**A**)

In addition to the synthetic approaches already reported in CHEC-I, a new method for preparing pyridazino[4,3-*c*]pyridazines <85KGS1428> has been developed. Refluxing the furanylidene acetates (10) with 70% aq. N₂H₄ in ethanol gives pyridazino[4,3-*c*]pyridazines (11) in excellent yields.

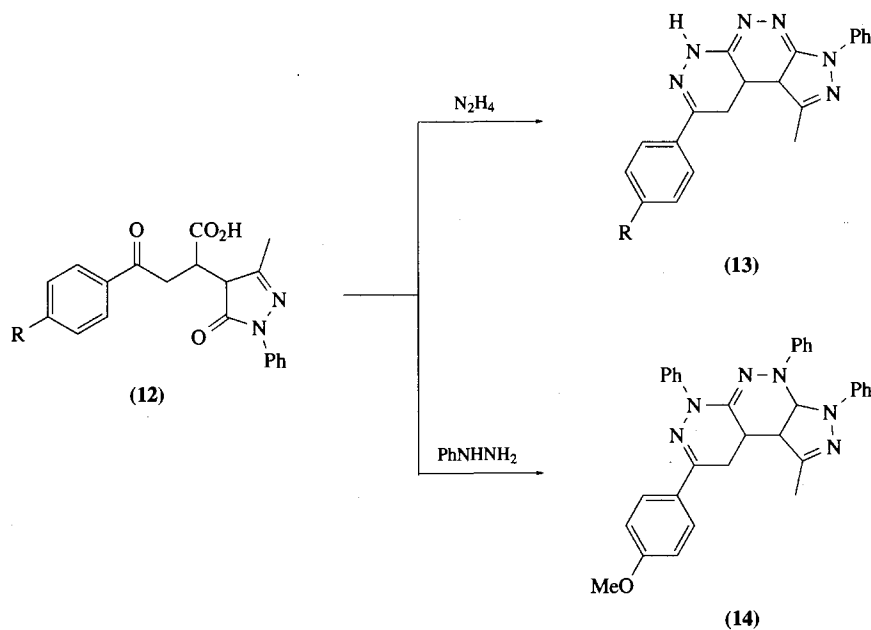
No applications of pyridazino[4,3-*c*]pyridazines have been reported.



Scheme 1

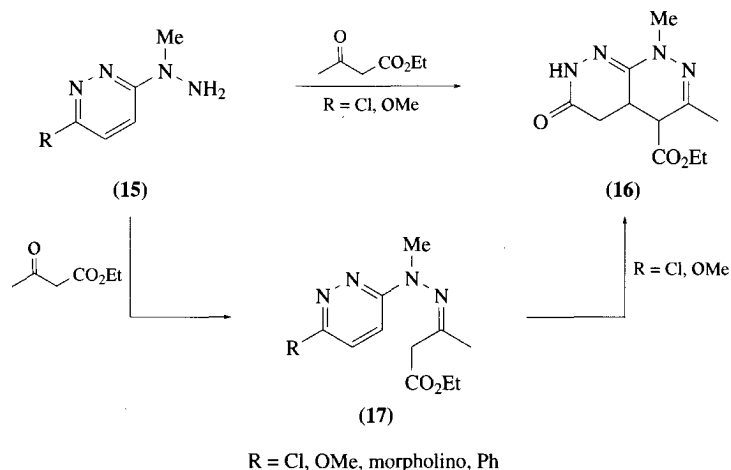
(ii) *Pyridazino[3,4-c]pyridazines (B)*

Some new approaches to the synthesis of pyridazino[3,4-*c*]pyridazines have been described. The pyrazolopyridazino[3,4-*c*]pyridazines (13; R = OMe, Me) and (14) are prepared by the reaction of β -aroyl- α -(3-methyl-5(4*H*)-oxo-1-phenyl-4-pyrazolyl)propionic acid (12) with hydrazine or phenylhydrazine in butanol (Scheme 2) <90JCB72>.



Scheme 2

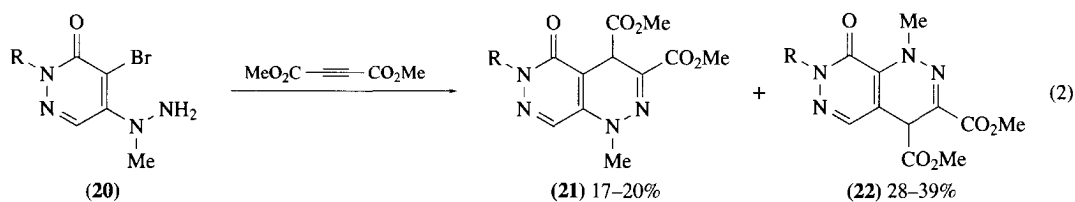
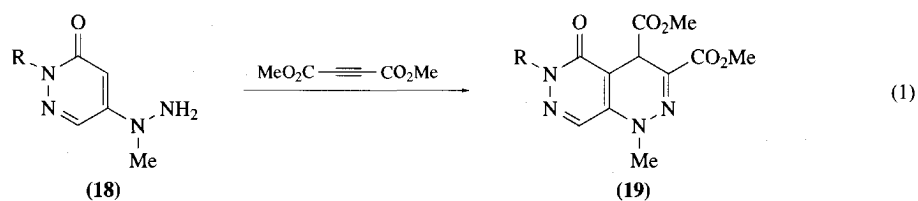
Heating of 1-methyl-1-(3-pyridazinyl)hydrazines (**15**) or their hydrazones at 240–250°C gives exclusively a pyridazino[3,4-*c*]pyridazine derivative (**16**). This reaction probably proceeds via a pyridazinone intermediate (**17**) which undergoes an intramolecular Michael addition leading to the pyridazino[3,4-*c*]pyridazine (**16**) (Scheme 3) <89T1793>.



Scheme 3

(iii) Pyridazino[4,5-*c*]pyridazines (**C**)

1,4-Dihydropyridazino[4,5-*c*]pyridazines (**19**), (**21**), and (**22**) are prepared by a novel cyclization and dehydrogenation reaction from 5-hydrazinopyridazin-3-ones (**18**) or the 4-bromo compounds (**20**) with DMAD (Equation (1)). These products are formed by a cyclization reaction between the enehydrazine moiety and the carbon-carbon triple bond of DMAD. When 4-bromo-5-hydrazinopyridazin-3-ones (**20**) are treated with DMAD at room temperature the expected 1,4-dihydropyridazino[4,5-*c*]pyridazines (**21**) and the regioisomers (**22**) are produced <90CC645, 91JCS(P1)991> (Equation (2)).

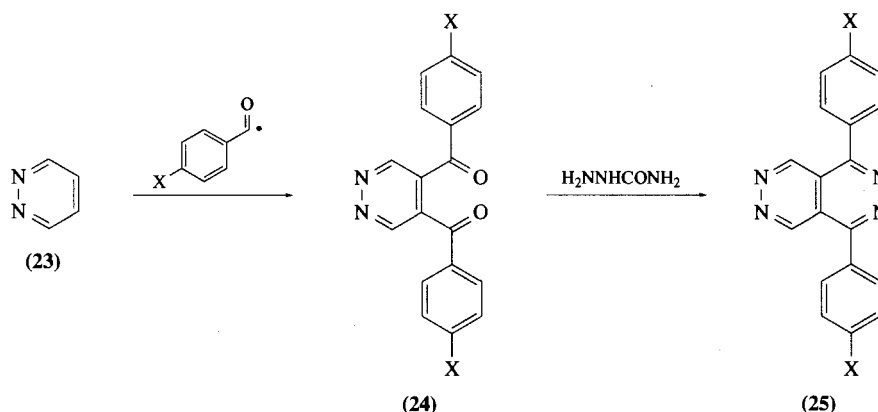


There are numerous approaches to fused pyridazines using 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in [4 + 2] cycloadditions. With this strategy a great number of heterocyclic compounds can be obtained, including some pyridazino[4,5-*c*]pyridazine derivatives. The conciseness does not

allow a full overview in this chapter and only some citations are presented <85JOC4378, 86CB2932, 89CB133, 90MI 719-02, 91BCJ3188, 91CC89>.

(iv) *Pyridazino[4,5-d]pyridazines (D)*

The most common synthetic approaches were reported in CHEC-I. Subsequently, some new strategies have been described. A synthesis of pyridazino[4,5-*d*]pyridazine derivatives (**25**) consists of radical arylation of pyridazine (**23**) and the cyclization of the resulting diketones (**24**) with semicarbazide (Scheme 4) <74M648>.

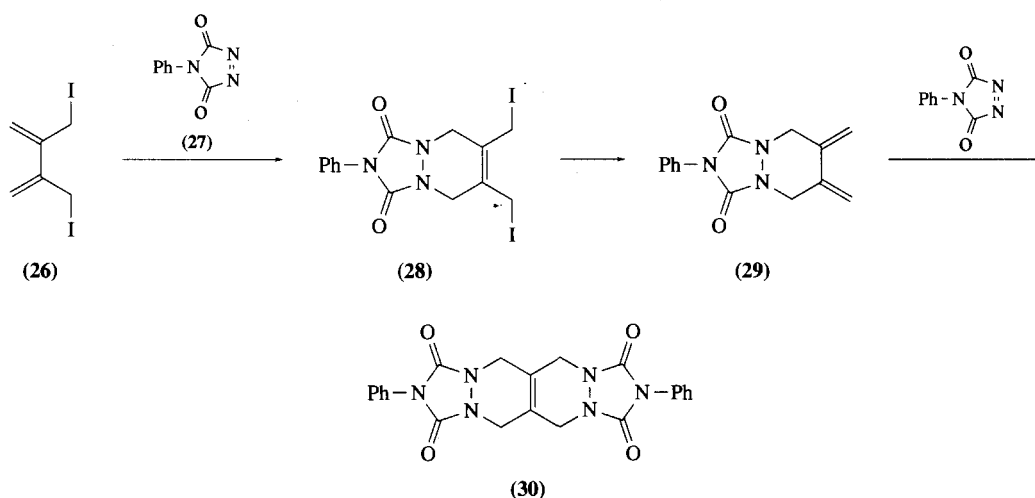


Scheme 4

Condensation of 5-bromo-1,3-diphenyl-2-thiobarbituric acid, which is readily available by bromination of 1,3-diphenyl-2-thiobarbituric acid, with ketomethylene compounds affords the amides. These are cyclocondensed to pyridazinopyridazines by treatment with 60% N_2H_4 and ammonium acetate in acetic acid <88IJC(B)902>.

Several syntheses of pyridazinopyridazines via Diels–Alder reactions of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) (**27**) with functionalized dienes have been described. One example is the reaction of the diene (**26**) with PTAD (**27**) to afford the tandem Diels–Alder adduct (**30**) (Scheme 5) <85JCS(P1)71>.

The cycloaddition of PTAD (**27**) is used in many synthetic approaches to pyridazino[4,5-*d*]pyridazine derivatives <83CB2355, 83HCA611, 83HCA615, 83NJC213>. Space restricts the description of these strategies and only some citations can be given.



Scheme 5

7.19.2.2 Pyrimidopyridazines

7.19.2.2.1 Theoretical and experimental structural methods

(i) *Pyrimido[4,5-c]pyridazines (E)*

The most important experimental data concerning NMR, IR, and UV spectroscopy have been reported in CHEC-I. Much information about structure, reactivity, and the most popular synthetic approaches to pyrimido[4,5-*c*]pyridazines has been reported in a review by Wamhoff, Dzenis, and Hirota (92AHC(55)129). In addition an AM1 SCF-MO study has been published (88JOC3900).

(ii) *Pyrimido[5,4-c]pyridazines (F)*

Only a few experimental and theoretical structures data were reported in CHEC-I. Additionally some new experimental data are available (84LA1390, 92JPS365). An AM1 SCF-MO study has been reported (88JOC3900).

(iii) *Pyrimido[4,5-d]pyridazines (G)*

The most important experimental data about NMR, IR, and UV spectroscopy have been reported in CHEC-I. In addition, an AM1 SCF-MO study has been published (88JOC3900). The relaxed reaction profile for aromatic nucleophilic substitution of some chloropyrimido[4,5-*d*]pyridazine has been investigated using the MNDO procedure (90JST(63)45). Kinetic measurements and MNDO calculations show that the C-8 position of the pyridazine ring is more reactive than C-5 in nucleophilic substitution reactions, and these follow a two-step S_NAr mechanism (89T4485).

7.19.2.2.2 Reactivity

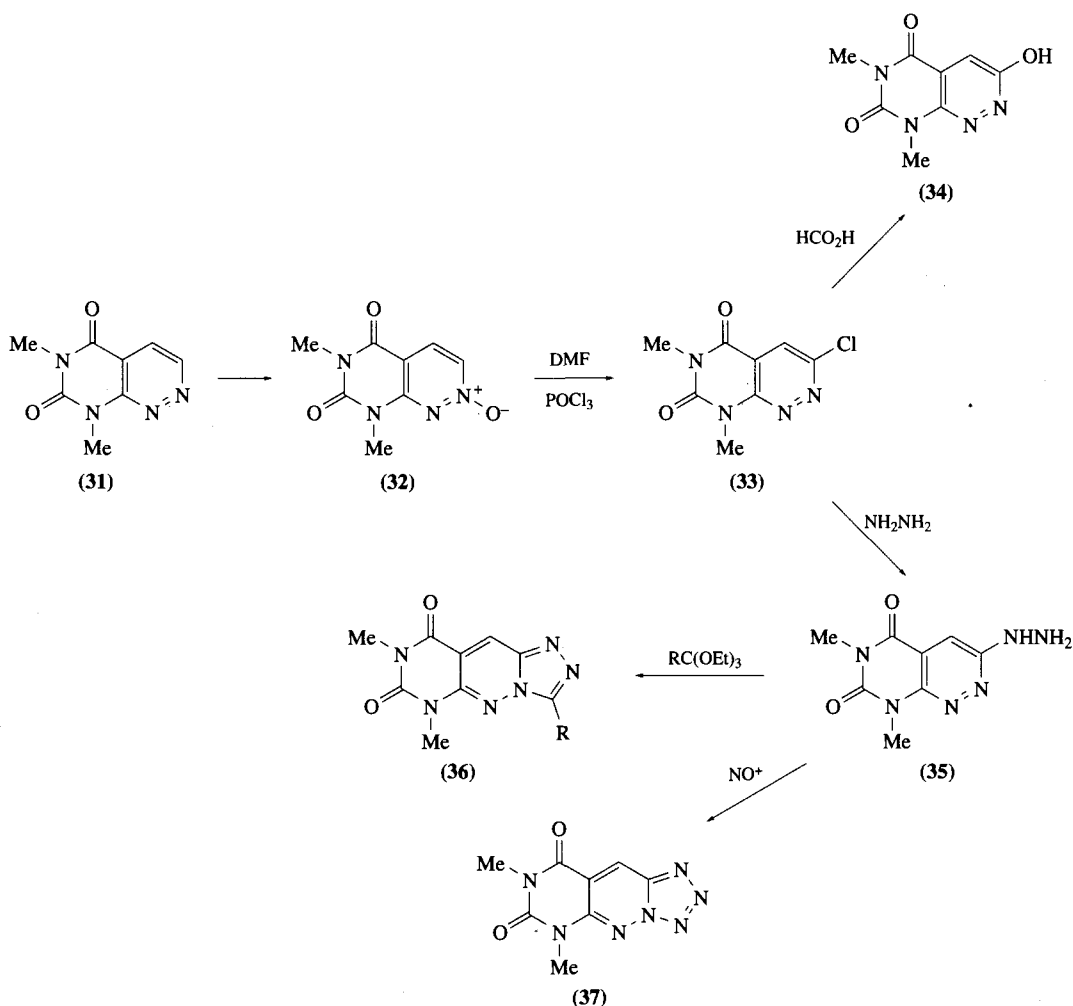
(i) *Pyrimido[4,5-c]pyridazines (E)*

Some basic reactions of pyrimido[4,5-*c*]pyrimidines were reported in CHEC-I. Much information about the reactivity of pyrimido[4,5-*c*]pyridazines is available in the review by Wamhoff *et al.* (92AHC(55)129). In addition, some new investigations have been published.

Treatment of 6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione (31) with peroxyformic acid gives 6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione 2-oxide (32) (83JOC1628). The position of *N*-oxidation is confirmed by comparison of the chemical shift. Only *N*-oxidation at N-2 and not at N-1 has been found. Treatment of 6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione 2-oxide with a mixture of phosphoryl chloride and DMF gives 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione (33) which is useful for many nucleophilic displacements (Scheme 6) (83JOC1628). Exchange of the chlorine atom with formic acid yields 3-hydroxy-6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione (34) and with hydrazine the 3-hydrazino-6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione (35) is obtained. Heating of the latter with ortho esters affords the triazolopyrimidinopyridazines (36). Some other new heterocyclic systems synthesized by use of 3-hydrazino-6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione or 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7-dione have been reported (83JOC1628).

(ii) *Pyrimido[5,4-c]pyridazines (F)*

In CHEC-I a few reactions involving pyrimidino[5,4-*c*]pyridazines were described and no further reactions have been reported.



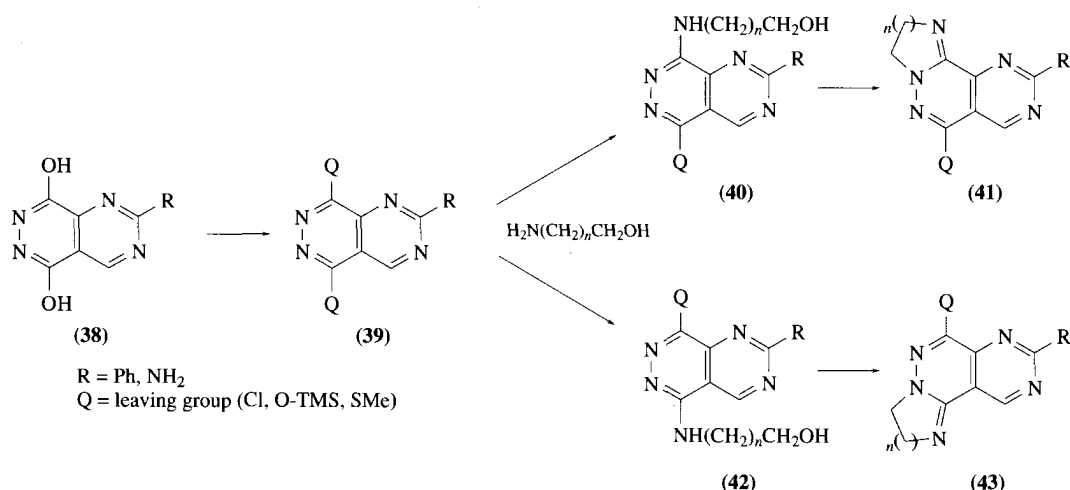
Scheme 6

(iii) *Pyrimido[4,5-d]pyridazines (G)*

The nucleophilic displacement of hydroxy groups or better leaving groups at positions C-5 and C-8 represents a new approach to the synthesis of novel heterocyclic ring systems. The two hydroxy groups at C-5 and C-8 of 2-phenyl and 2-aminopyrimido[4,5-*d*]pyridazines (38) are replaced by superior leaving groups like chloro, trimethylsiloxy, or thiol to groups (Scheme 7). These compounds are substituted by aminoalkanols. Cyclization of the 5- and 8-mono(*o*-hydroxyalkylamino) derivatives leads to new tricyclic compounds in which the pyrimidopyridazine skeleton is fused with a partially saturated imidazole or pyrimidine ring. The preparation of imidazo[1,2-*b*]pyrimido[5,4-*d*]pyridazines, dipyrimido[1,2-*b*:5',4'-*d*]pyridazine (41), and dipyrimido[1,2-*b*:4',5'-*d*]pyridazine derivatives (43) has been described <89T4485>.

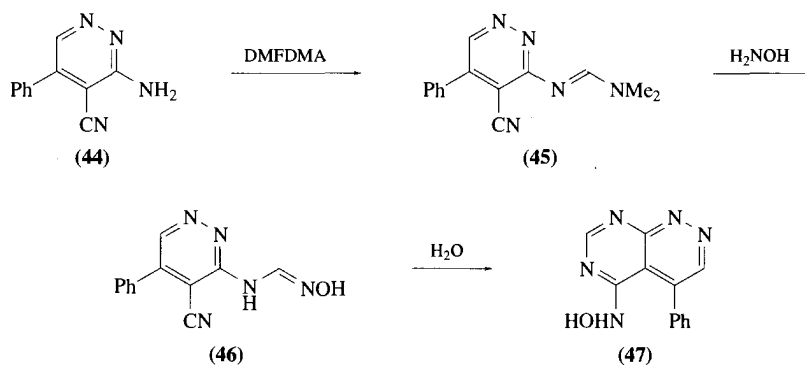
7.19.2.2.3 *Ring syntheses*(i) *Pyrimido[4,5-c]pyridazines (E)*

The most common synthetic approaches have been reported in the review by Wamhoff *et al.* <92AHC(55)129>. In addition, some new strategies have been developed in the last few years. A new



Scheme 7

alternative method of preparation of pyrimido[4,5-*c*]pyridazines starts with 3-amino-4-cyano-5-phenylpyridazine (44) which can be converted to the amidine (45) by treatment with *N,N*-dimethylformamide dimethyl acetal (DMFDMA). By treatment of this amidine (45) with hydroxylamine hydrochloride the formamidine group is converted into the corresponding formamide oxime (46). In boiling water cyclization takes place between the formamide oxime group and the adjacent cyano group and the pyrimido[4,5-*c*]pyridazine derivatives (47) are obtained (Scheme 8) <86S807>.

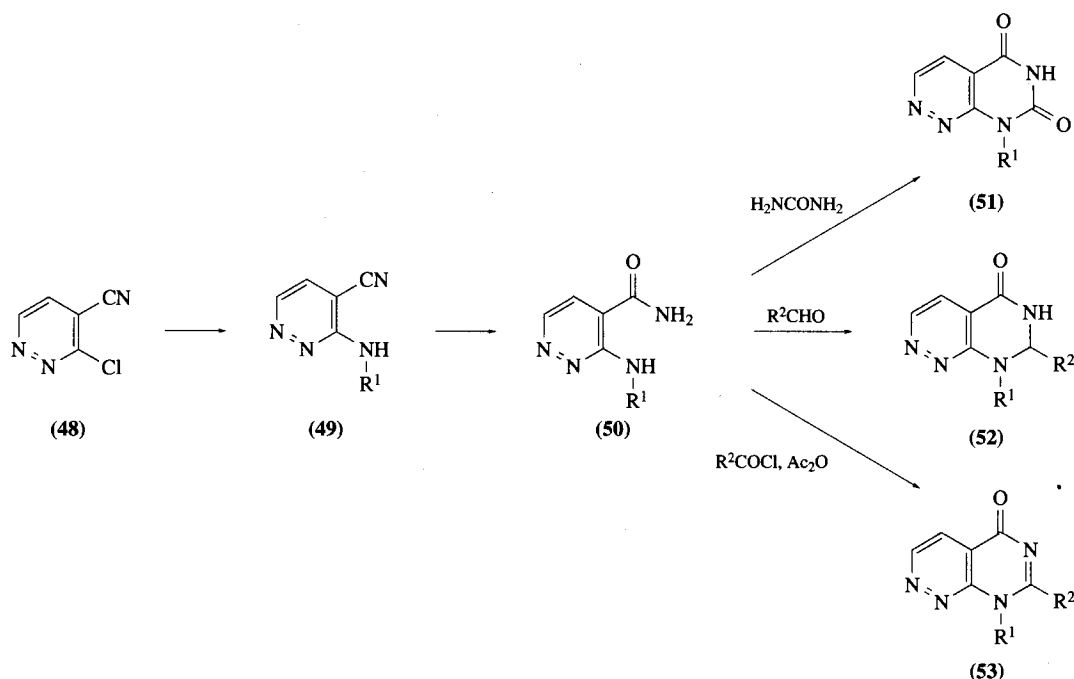


Scheme 8

Another facile synthesis of pyrimido[4,5-*c*]pyridazin-5,7(6*H*,8*H*)-diones (51), pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones (52), and dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones (53) starts from 3-chloro-4-pyridazinecarbonitrile (48) via aminocarbonitriles (49) and aminocarboxamides (50) (Scheme 9). Cyclization of the latter with urea at high temperatures affords the pyrimido[4,5-*c*]pyridazin-5,7(6*H*,8*H*)-diones (51). By heating of the carboxamides with aromatic aldehydes the dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones (52) are obtained <88JHC119>.

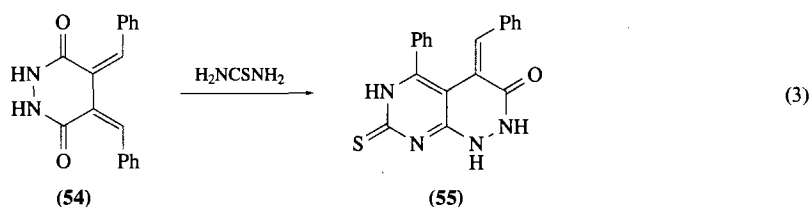
The pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones (53) are obtained by heating the carboxamides with acid chlorides in acetic anhydride. Oxidation of 7,8-diaryl-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones (52) employing potassium permanganate also yields the pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones (53) <88JHC119>.

Pyrimidopyridazinethione and -dithione are obtained by cyclocondensation of aminodiphenylpyridazinecarbonitrile with phenyl isocyanate and CS₂ <91ZN(B)835>. The cyclocondensation of 4,5-dibenzylidene-tetrahydropyridazine-3,6-dione (54) with thiourea in boiling ethanolic potassium



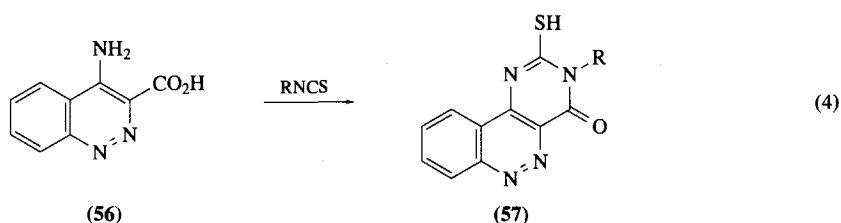
Scheme 9

hydroxide affords 4-benzyliden-1,2,4,4a,5,6-hexahydro-5-phenyl-7-thiopyrimido[4,5-*c*]pyridazine-3,7-dione (**55**) (Equation (3)) <86JPR932>.

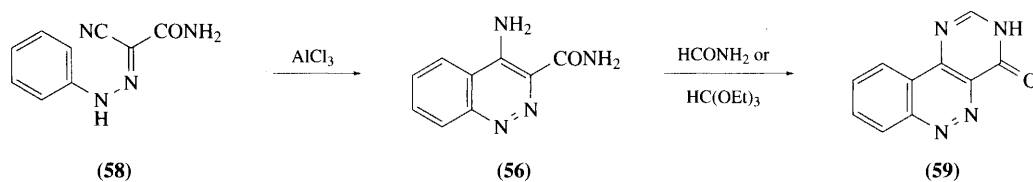


(ii) *Pyrimido[5,4-*c*]pyridazines (F)*

Some new synthetic approaches have been published in the 1990s. By refluxing 4-aminocinnoline-3-carboxylic acid (**56**) with aryl isothiocyanates substituted 2-thiol-3-(*N*-aryl)pyrimido[5,4-*c*]cinnolin-4(3*H*)-ones (**57**) are prepared (Equation (4)) <92AHC(55)129>.



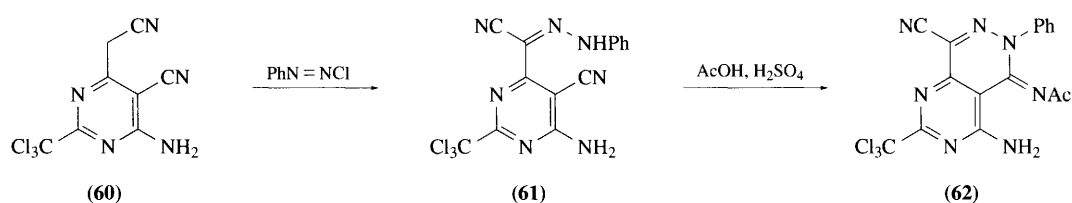
Another synthesis of pyrimido[5,4-*c*]cinnolin-4(3*H*)-ones (**59**) via 4-aminocinnolines (**56**) starts with arylhydrazono-cyanoacetic acid derivatives (**58**). Upon heating in the presence of AlCl_3 4-aminocinnolines (**56**) are formed. Cyclocondensation with formamide or triethyl *ortho*-formate affords the pyrimido[5,4-*c*]cinnolin-4(3*H*)-ones (**59**) (Scheme 10) <92JPS365>.



Scheme 10

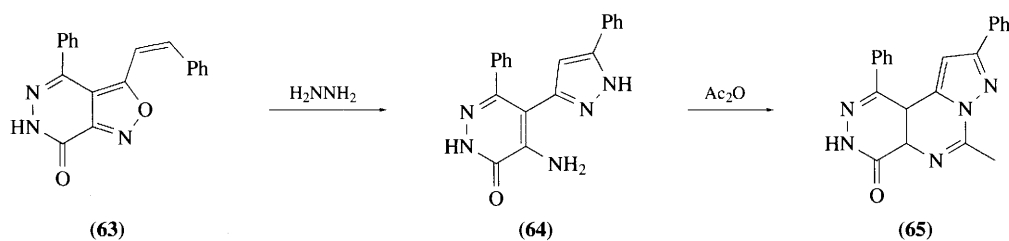
(iii) Pyrimido[4,5-d]pyridazines (G)

The most common synthetic approach by a Hofmann-type reaction of pyridazine-4,5-dicarboxamide or the cyclization of a β -enamino ester with guanidine or formamide have been reported in CHEC-I. Some new strategies have been developed. A novel and simple way to pyrimido[4,5-d]pyridazines is the coupling of a functionalized pyrimidine (e.g. (60)) with benzenediazonium chloride to the arylhydrazone derivative (e.g. (61)) which cyclizes to the pyrimidopyridazine (62) (Scheme 11) <82JCS(P1)2667>.



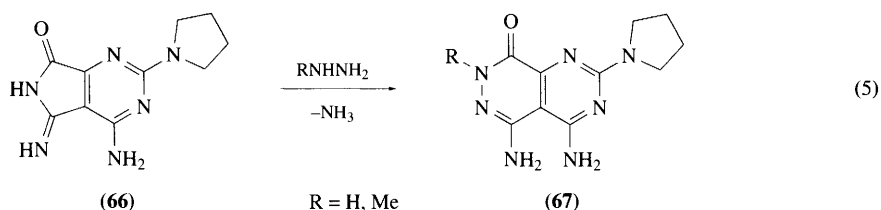
Scheme 11

Another strategy is the conversion of isoxazolo[3,4-d]pyridazin-7(6H)-ones (63) via pyrazole derivatives (64) into the new pyrazolo[1',5':1,6]pyrimido[4,5-d]pyridazin-7(8H)-ones (65) by final ring closure with acetic anhydride (Scheme 12) <86H(24)3143>.



Scheme 12

Pyrimido[4,5-d]pyridazines (67) are also obtained from pyrrolo[3,4-d]pyrimidines (66) and hydrazine or substituted hydrazines (Equation (5)) <88LA643>.



7.19.2.2.4 Important compounds and applications

It is reported that some of the new substituted 2-thiol-3-(N-aryl)pyrimido[5,4-c]cinnolin-4(3H)-ones show antimicrobial and antiinflammatory activities <92JPS(81)365>. Some pyrimido[4,5-c]py-

ridazine derivatives possess weak analgesic and bactericidal activities <84MI 719-01>. Some compounds have been screened for antitumor drug cross-resistance *in vivo* in a cisplatin-resistant murine P388 leukemia <91MI 719-01>.

7.19.2.3 Pyrazinopyridazines

7.19.2.3.1 Theoretical and experimental structural methods

(i) Pyrazino[2,3-*c*]pyridazines (*H*)

Some experimental and theoretical structural data concerning pyrazino[2,3-*c*]pyridazine derivatives, especially quinoxalino[2,3-*c*]cinnolines and pyridazino[3,4-*b*]quinoxalines, have been published <84MI 719-02, 85JHC1519, 86MRC777, 87JCS(P1)501, 87JCS(P1)507, 87JHC1219>. There are many NMR, mass, IR, and UV spectroscopic data available. In addition, an AM1 SCF-MO <88JOC3900> study and a MNDO calculation <87JCS(P1)507> have been published.

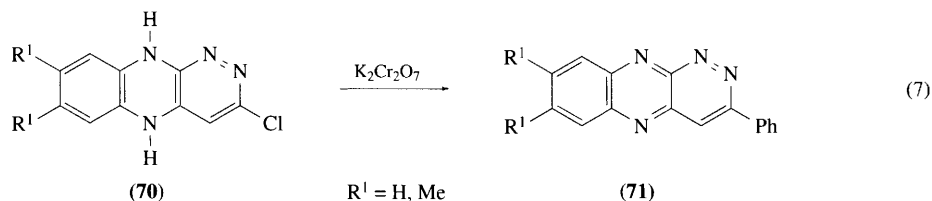
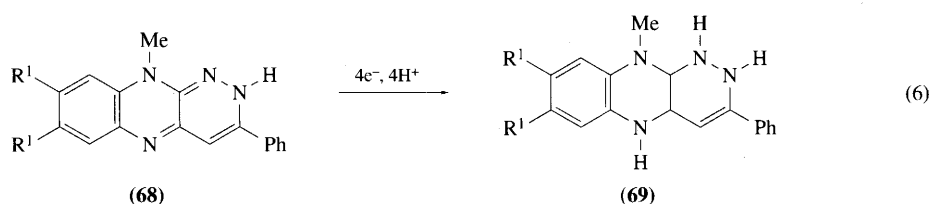
(ii) Pyrazino[2,3-*d*]pyridazines (*I*)

Only a few experimental and theoretical structural data were reported in CHEC-I. Subsequently, a range of pyrazino[2,3-*d*]pyridazine derivatives have been prepared and experimental data have been published <80FRP2487352, 81TL(22)4045, 84JHC1271, 88LA1197, 89MI 719-01, 90AP(323)89, 90MI 719-04, 90MI 719-03>. In addition semiempirical calculations using the AM1 SCF-MO <88JOC3900, 91MI 719-02> and MNDO-PM3 <91MI 719-02> methods have been reported.

7.19.2.3.2 Reactivity

(i) Pyrazino[2,3-*c*]pyridazines (*H*)

In ethanol-acetic acid the 2,10-dihydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxalines (**68**) cannot be reduced. By a preparative electrolysis at pH 1.60 the 1,2,4a,5,10,10a-hexahydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxalines (**69**) can be obtained (Equation (6)). However, 5,10-dihydropyridazino[3,4-*b*]quinoxalines (**70**) are easily oxidized by manganese oxide or potassium dichromate in hot acetic acid to give pyridazino[3,4-*b*]quinoxalines (**71**) (Equation (7)) <89JHC1511>.

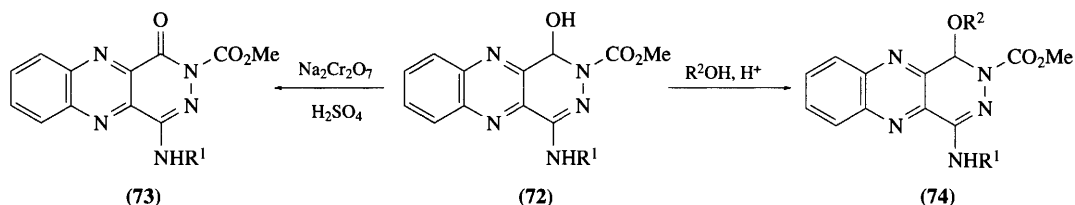


(ii) Pyrazino[2,3-*d*]pyridazines (*I*)

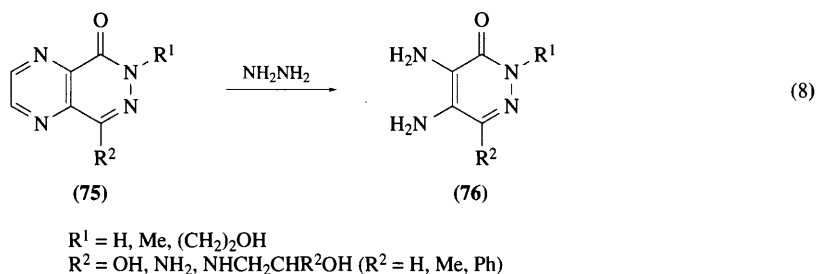
Pyrazino[2,3-*d*]pyridazines readily undergo nucleophilic displacements: their most common reactions were reported in CHEC-I. Some additional nucleophilic displacements of pyridazino[4,5-*b*]quinoxaline have been described <84JHC1271>. The oxidation of 4-*t*-butylamino-2-methoxy-

carbonyl-1-hydroxy-1,2-dihydropyridazino[4,5-*b*]quinoxaline (**72**; $R^1 = \text{Bu}^t$) with sodium dichromate in sulfuric acid yields the corresponding 1-oxo-1,2-dihydropyrazino[2,3-*d*]quinoxalines (**73**; $R^1 = \text{Bu}^t$) <80FRP2487352>. 4-*t*-Butylamino-2-methoxycarbonyl-1-hydroxy-1,2-dihydropyridazino[4,5-*b*]quinoxaline (**72**; $R^1 = \text{Bu}^t$) readily forms with methanol or isopropanol the respective acetals (**74**) (Scheme 13) <80FRP2487352>.

Ring cleavage of pyrazinopyridazines (**75**) with hydrazine hydrate leads to aminopyridazinones (**76**) (Equation (8)) <93MI 719-01>.



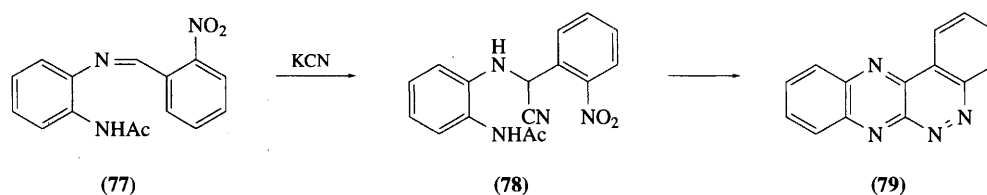
Scheme 13



7.19.2.3.3 Ring syntheses

(i) Pyrazino[2,3-*c*]pyridazines (**H**)

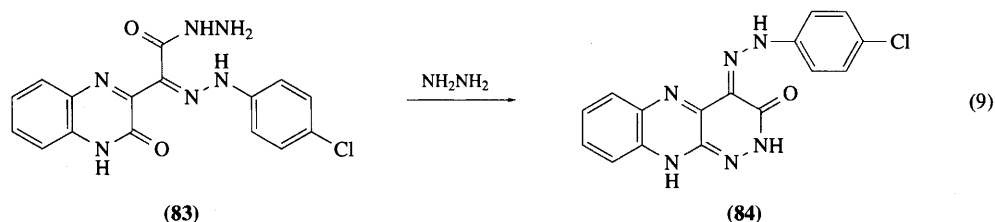
Some new syntheses have been published since 1982. The cyclization of 2-acetamido-*N*-(2-nitrobenzylidene)anilines (**77**) with potassium cyanide in methanol leads to quinoxalino[2,3-*c*]cinnolines (**79**) via the nitriles (**78**) (Scheme 14) <80JCR(S)208, 87JCS(P1)501, 87JCS(P1)507>.

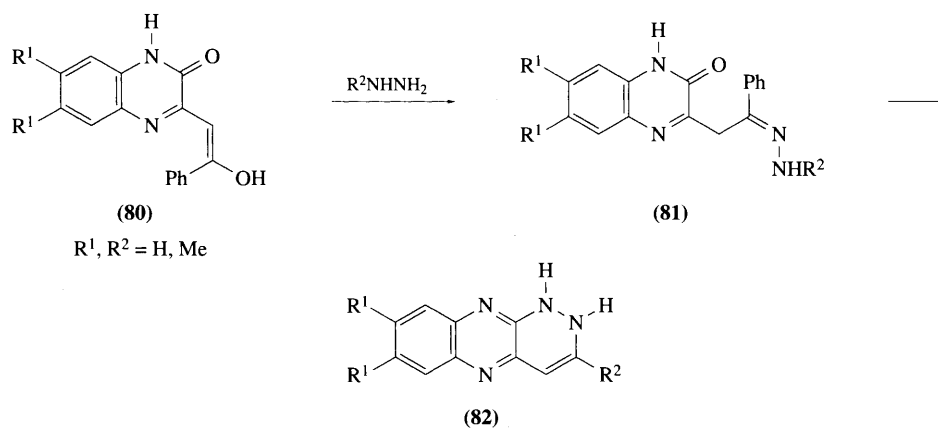


Scheme 14

Hydrazines react with the quinoxalines (**80**) in ethanolic-acetic acid to afford dihydropyrazino[3,4-*b*]quinoxalines (**82**). The postulated structures are in agreement with their NMR spectra (Scheme 15) <85JHC1519>.

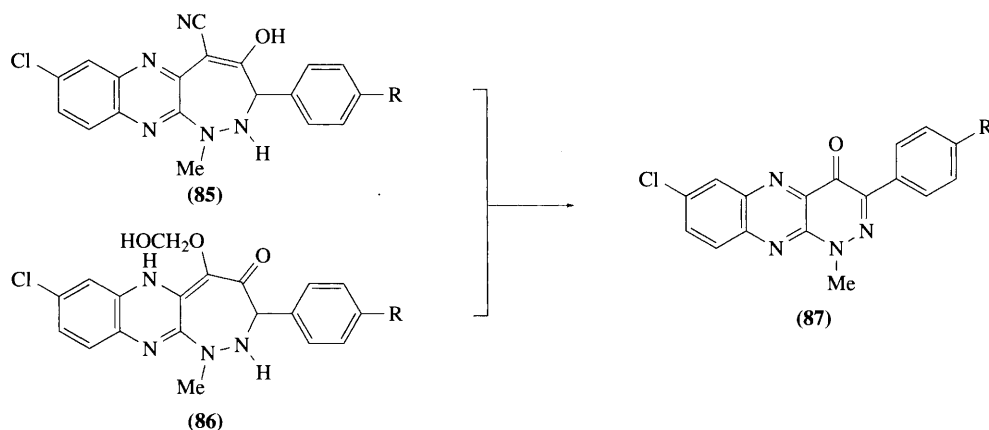
Cyclization of the quinoxaline α -hydrazonohydrazides (**83**) represents a novel approach to the synthesis of 4-chlorophenylhydrazono-3-oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]quinoxalines (**84**) (Equation (9)) <87JHC1219>.





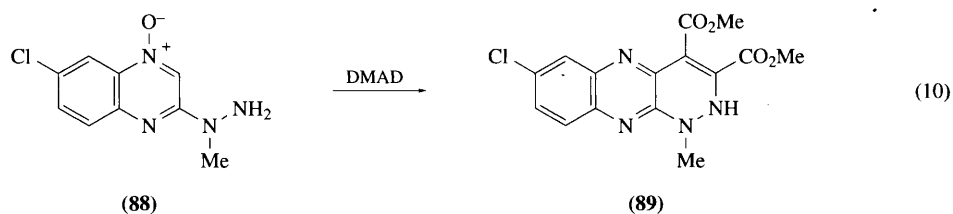
Scheme 15

The reaction of the diazepinoquinoxalines (85) and (86) with *N*-bromosuccinimide-water results in ring transformation to give the pyridazinoquinoxalines (87) (Scheme 16) <91JHC199>.



Scheme 16

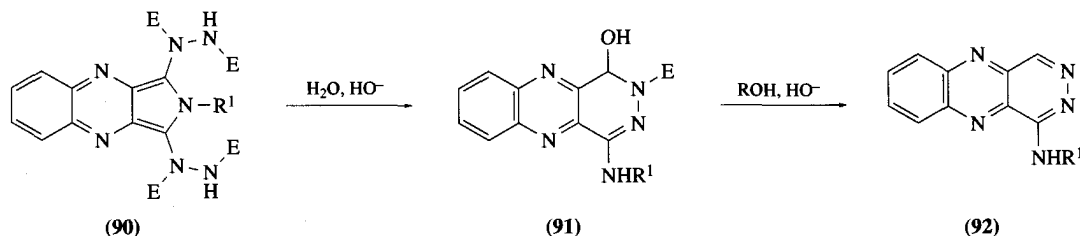
The pyridazino[3,4-*b*]quinoxaline (89) is synthesized by the 1,3-dipolar cycloaddition reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (88) with DMAD (Equation (10)) <91JHC199>.



(ii) *Pyrazino*[2,3-*d*]pyridazines (*I*)

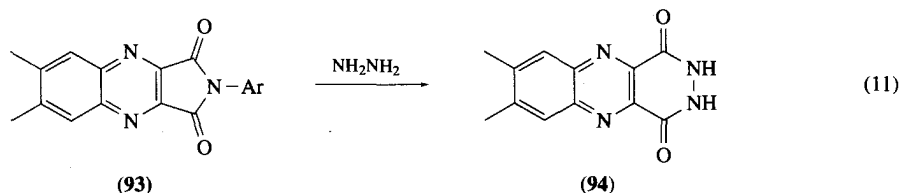
New syntheses of pyrazino[2,3-*d*]pyridazine derivatives have been described. Treatment of the substituted 1,3-bishydrazino-2-*t*-butylpyrrolo[3,4-*b*]quinoxalines (90; $R^1 = \text{Bu}^t$, $E = \text{CO}_2\text{Me}$) with

aqueous sodium hydroxide leads to the formation of the 1,2-dihydropyridazino[4,5-*b*]quinoxaline (**92**; $R^1 = \text{Bu}^t$). The first step, the solvolysis, is followed by ring opening and a final ring closure to the pyridazine ring (Scheme 17) <80FRP2487352>.



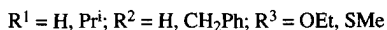
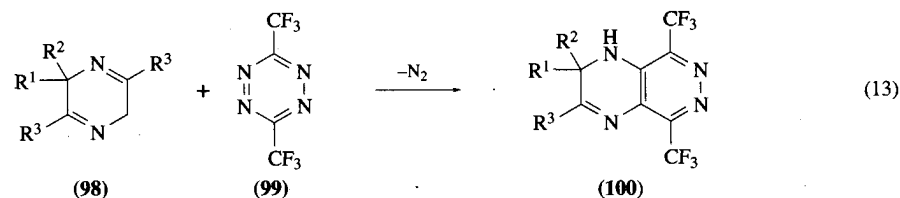
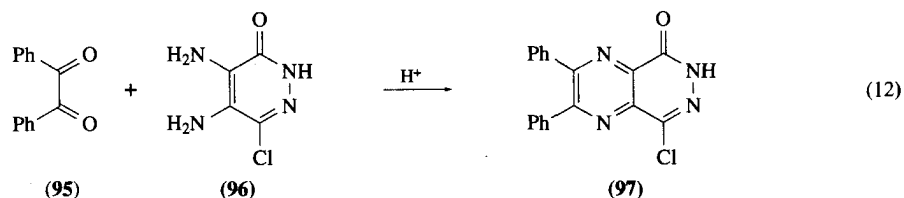
Scheme 17

Another example of the use of pyrrolo[3,4-*b*]quinoxalines is the cyclocondensation of the 6,7-dimethylquinoxaline-2,3-carboximides (**93**) with hydrazine giving dioxypyridazinoquinoxaline (**94**) (Equation (11)) <93MI 719-01>.



Pyrazino[2,3-*d*]pyridazine derivatives are also obtained by cyclocondensation of 4,5-diaminopyridazines with α -dioxo compounds. Thus, 4,5-diamino-3-chloro-1-methyl-6(1*H*)-pyridazinone (**96**) and benzil (**95**) at reflux temperature in acetic acid give a 97% yield of pyrazino[2,3-*d*]pyridazinone (**97**) (Equation (12)) <90MI 719-03>.

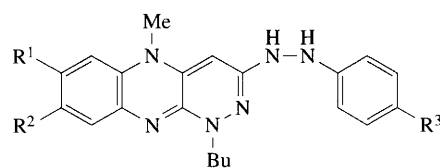
Pyrazinopyridazines (**100**) are also obtained by treating the pyrazines (**98**) with the tetrazine (**99**) (Equation (13)) <90AP(323)89>.



7.19.2.3.4 Important compounds and applications

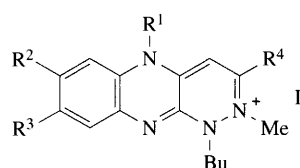
(i) Pyrazino[2,3-*c*]pyridazines (*H*)

Some pyridazino[3,4-*b*]quinoxaline derivatives (**101**) and (**102**) show activity against *Mycobacterium tuberculosis* <84MI 719-02, 89MI 719-02, 89MI 719-03>.



(101)

R¹ = H, Me
R² = H, Cl, Me
R³ = H, Me, NO₂

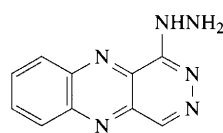


(102)

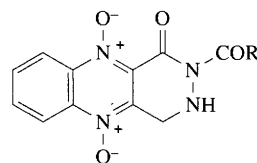
R¹ = Me, Bu
R² = H, Me
R³ = H, Me, Cl
R⁴ = subst. amines

(ii) *Pyrazino[2,3-d]pyridazines (I)*

Some pyrazino[2,3-*d*]pyridazine derivatives show a preventive effect against cucumber powdery mildew. Unfortunately, none show a curative effect <89MI 719-01>. 1-Hydrazinopyridazine[4,5-*b*]quinoxaline (103) shows an antihypertensive activity in spontaneously hypertensive rats and a hypotensive activity in normotensive anaesthetized rats <84JHC1271>. Some pyridazinoquinoxalines (104) are used as food additives and growth accelerators for pigs <80FRP2487352>.



(103)



(104)

R = alkyl, alkoxy, aryl
cycloalkyl, heterocyclic

7.19.2.4 Pyrimidopyrimidines

7.19.2.4.1 Introduction

A lot of information about the structure, reactivity, and the best synthetic approaches for pyrimidopyrimidines has been described in CHEC-I. Additionally, some new methods of preparation of pyrimidopyrimidines have been reported in reviews on the synthesis of fused pyrimidines by Delia and Warner <B-92MI 719-02> and on the use of uracils as versatile starting material in heterocyclic synthesis by Wamhoff, Dzenis, and Hirota <92AHC(55)129>. Pyrimidopyrimidines are especially interesting as structural analogues of natural compounds.

7.19.2.4.2 Theoretical and experimental structural methods

Proton NMR, IR, and UV spectral data for several substituted derivatives has been reported in CHEC-I. Also the pK_a values and the mass spectra for some derivatives have been reported, as well as Hückel MO calculations. For pyrimido[5,4-*d*]pyrimidine-2,4,6,8-tetrone tetrahydrate an x-ray crystal structure analysis of the disodium salt has been described. For both pyrimidopyrimidine ring systems molecular orbital calculations have been described using the semiempirical AM1 SCF-MO method <88JOC3900>. X-ray crystal structure studies <88JOC3900, 89AX(C)1194>, ¹H NMR data and the results of theoretical calculations are reported for some pyrimido[5,4-*d*]pyrimidine nucleosides <90JA3622>. Fluorescence spectral properties <90DP21>, polarographic <86MI 719-02, 86MI 719-03> and coulometric <86MI 719-04> studies are available for many pyrimido[5,4-*d*]pyrimidine derivatives.

7.19.2.4.3 Reactivity

(i) *Pyrimido[4,5-d]pyrimidines (J)*

The main reactions used on pyrimido[4,5-*d*]pyrimidines are nucleophilic displacements. The substitution by many types of nucleophilic agents of 4-chloropyrimido[4,5-*d*]pyrimidines, which are readily available by chlorination of pyrimido[4,5-*d*]pyrimidine-4-ones, has been described in CHEC-I and in a review by Wamhoff *et al.* (92AHC(55)129). Another type of reaction, covalent hydration, involves addition of water across a carbon–nitrogen double bond and has been thoroughly reviewed by Albert (76AHC(20)1). With unsubstituted pyrimido[4,5-*d*]pyrimidine covalent hydration occurs in humid air to give 4-hydroxy-1,2-dihydropyrimidino[4,5-*d*]pyrimidine. Ring cleavage of the unsubstituted ring of pyrimido[4,5-*d*]pyrimidines by water addition yields 6-amino-pyrimidine-5-carboxaldehydes (84JOC2065, 87H(25)343).

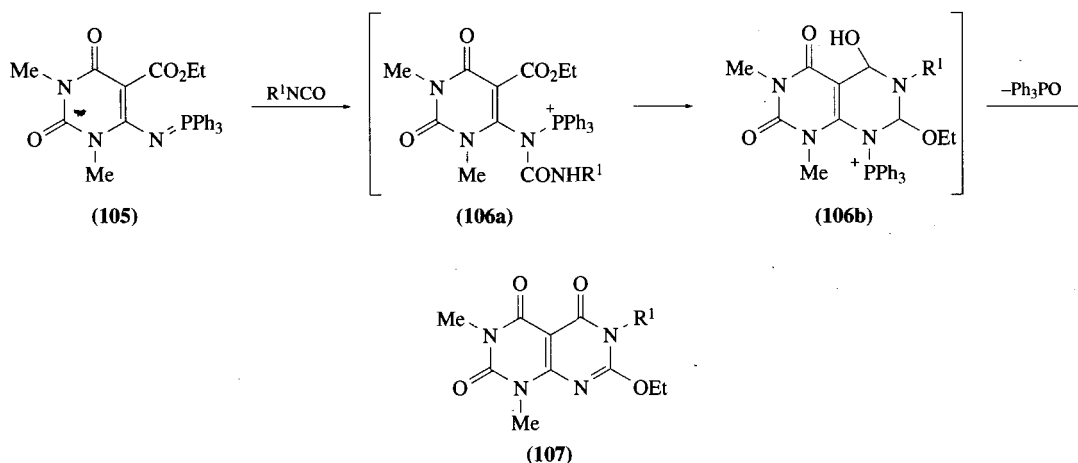
(ii) *Pyrimido[5,4-d]pyrimidines (K)*

Chlorination of hydroxypyrimido[5,4-*d*]pyrimidines leads to chloropyrimido[5,4-*d*]pyrimidines which are known to undergo a variety of nucleophilic substitutions. The reactions with amines, alkoxides, and many other compounds has been described in CHEC-I as well as in review articles by Delia (B-92MI 719-02) and Wamhoff *et al.* (92AHC(55)129).

7.19.2.4.4 Ring syntheses

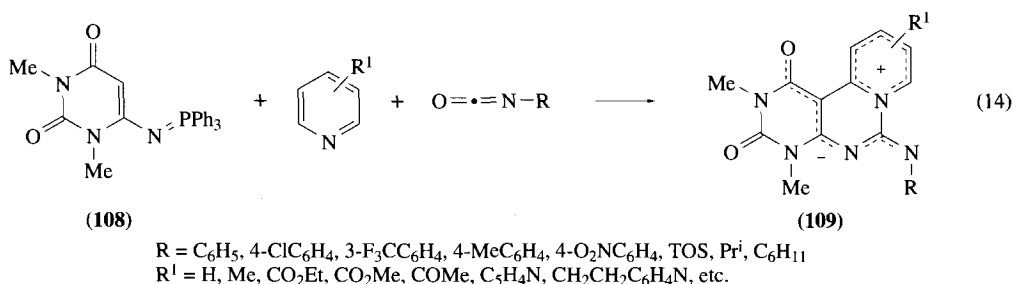
The most common synthetic approaches to both types of pyrimidopyrimidine have been described in CHEC-I and in review articles by Delia (B-92MI 719-02) and Wamhoff *et al.* (92AHC(55)129). In addition some new strategies in the preparation of pyrimido[4,5-*d*]pyrimidines have been developed in the last few years. A new approach is the aza-Wittig-type reaction of iminophosphoranes of 5-aminouracils with aromatic isocyanates which leads to functionalized pyrimido[4,5-*d*]pyrimidines. Ethyl 1,3-dimethyl-6-(triphenylphosphoranylideneamino)-uracil-5-carboxylate (**105**) reacts with isocyanates via adduct (**106a**) intermediates to afford 7-ethoxypyrimido[4,5-*d*]pyrimidines (**107**) (Scheme 18) (88S919).

This new approach is widely used as a facile one-pot reaction for different types of functionalized pyrimidines (90T7855).

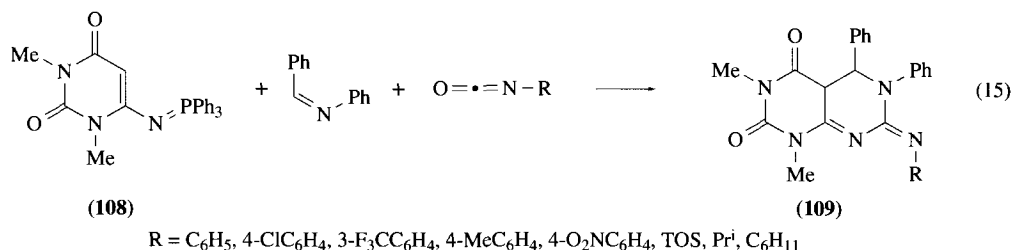


Scheme 18

A novel type of heteroannulation reaction has been reported by Wamhoff, Schmidt *et al.* (91TL4473, 93JOC6976). Uracil-iminophosphoranes (**108**) are converted into pyrimido[4,5-*d*]pyrimidine betaines (**109**) in a one-pot three-component reaction with isocyanates and heteroarenes (double bonds) (Equation (14)).

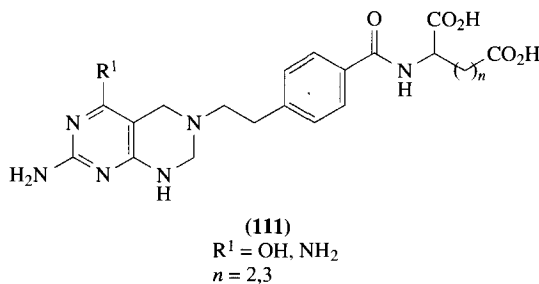


When the heteroarene was replaced by an acyclic imine partially saturated pyrimido[4,5-*d*]pyrimidines (**110**) were obtained (Equation (15)) <93H(35)1055>.



7.19.2.4.5 Important compounds and applications

Several dozen patents have been granted for work in the pyrimidopyrimidine series. Most of them have been reported in the review by Delia and Warner <B-92MI 719-02>. Some pyrimido[4,5-*d*]pyrimidine analogues of folic acid (**111**) have been prepared and screened for antitumor activity <93H(35)1397>.



Several patents have reported the preparation of pyrimidopyrimidine derivatives which are useful as bronchodilators <90EUP351058>, vasodilators <90EUP351058>, antiallergic agents <84EUP163599, 86JAP(K)61249988, 90EUP351058>, or antihypertensives <88GEP3601731>.

Pyrimido[5,4-*d*]pyrimidine nucleosides show a variety of biological effects. Several nucleosides have been prepared to prove their pharmacological <89MI 719-04, 93MI 719-02>, antitumor <89JMC629, 89MI 719-04, 89PNA(86)-8242, 91USP5041542, 93MI 719-02>, or antiviral <89JMC629, 91USP5041542, 93MI 719-02> properties. Other authors recognized an inhibition of phosphoribosylpyrophosphatase synthetase by some (ribofuranosylamino)pyrimido[5,4-*d*]pyrimidines <89MI 719-05>. It is known that some pyrimido[5,4-*d*]pyrimidines inhibit the primary and secondary drug resistance in antitumor chemotherapy <90GEP3833392>. Other patents describe antithrombotic and thrombocyte aggregation inhibiting activity <81GEP2926804, 86GEP3515874, 88EUP291873>.

7.19.2.5 Pyrazino[2,3-*b*]pyrazines

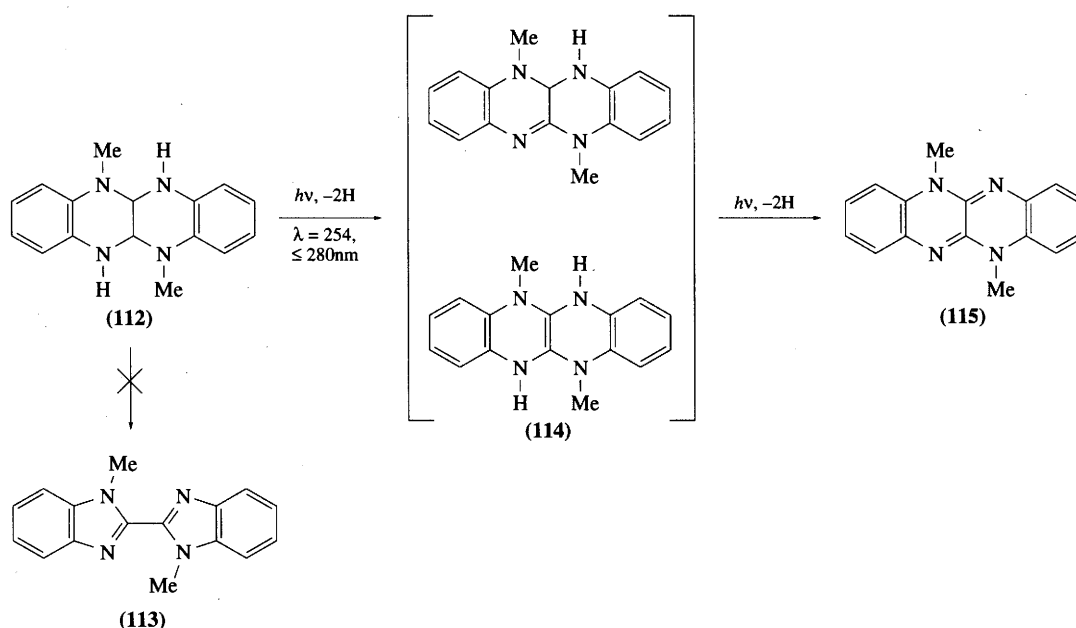
7.19.2.5.1 Theoretical and experimental structural methods

A lot of experimental data have been reported in CHEC-I. The x-ray crystal structure of pyrazino[2,3-*b*]pyrazine and some special spectroscopic investigations were reported. More experimental

data are now available <86MRC777>. With the AM1 SCF-MO method some pyrazino[2,3-*b*]pyrazine derivatives have been calculated <88JOC3900>. Some photoelectron spectroscopic data and model calculations on the through-bond effects in pyrazino[2,3-*b*]pyrazines have been reported <84JCS(P2)1517>.

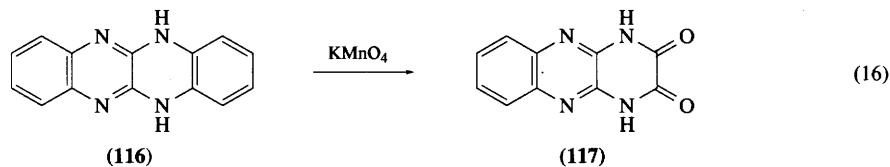
7.19.2.5.2 Reactivity

The dimer of 1,2,3,4,5,7a-hexahydroimidazo[1,2-*a*]pyrazine, formed by reaction of diethylene-tetramine with glyoxal or *N,N'*-dicyclohexylethyldiimine, undergoes catalytic hydrogenation giving *N*-(2-aminoethyl)pyrazine <93JHC839>. The photochemical dehydrogenation of dihydro-5,11-dimethylquinoxalino[2,3-*b*]quinoxaline (**112**), the condensation product of *N*-methyl-*o*-phenyl-endiamine and glyoxal, yields only one product, namely 5,11-dimethylquinoxalino[2,3-*b*]quinoxaline (**115**) (Scheme 19) <90CB2059>.



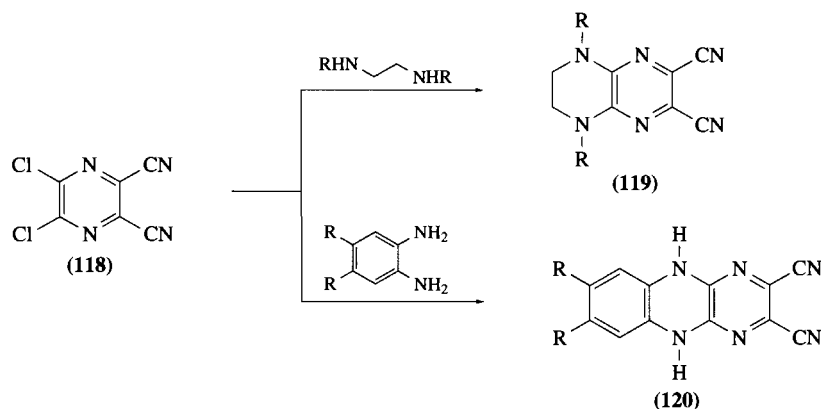
Scheme 19

Oxidation of dihydropyrazino[2,3-*b*]pyrazine (**116**) with KMnO_4 gives the corresponding dione (**117**) (Equation (16)) <89NKK2059>. The chemical <81CJC3237> and electrochemical reduction of pyrazino[2,3-*b*]pyrazines and the mechanisms have been described <82CJC2797, 84CJC1028, 88LA1197>.



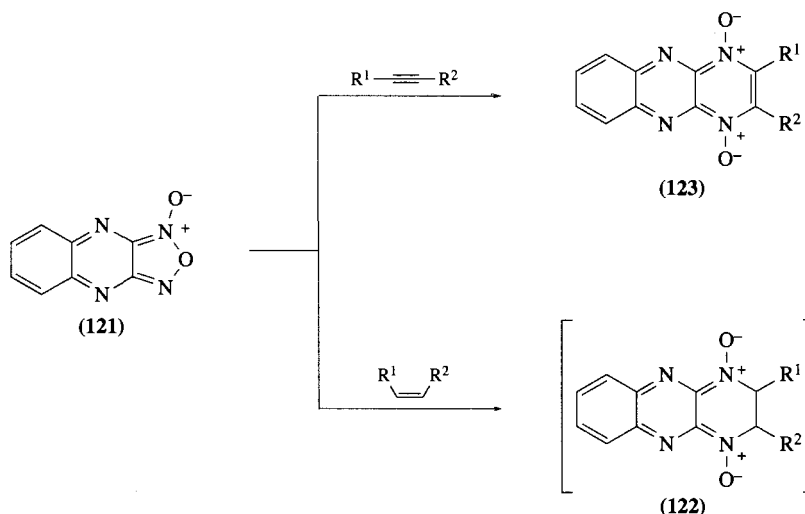
7.19.2.5.3 Ring Syntheses

A general synthetic approach consists of the reaction of 1,2-diaminopyrazines or *N,N'*-dimethyl-ethane-1,2-diamines with glyoxal. This method has already been described in CHEC-I. Additionally, some new approaches have been developed. Nucleophilic exchange of the chlorine atoms of 5,6-dichloropyrazine-2,3-dicarbonitrile (**118**) by 1,2-diamino compounds affords the pyrazino[2,3-*b*]pyrazines (**119**) and (**120**) (Scheme 20) <88LA1197>. Variation of the amines and treatment with hydrazine hydrate forms several polyaza derivatives <88LA1197>.



Scheme 20

Another report describes the synthesis of pyrazino[2,3-*b*]quinoxaline 1,4-dioxides (123) by condensation of furoxano[3,4-*b*]quinoxaline (121) with alkynes and alkenes. The pyrazino[2,3-*b*]quinoxaline 1,4-dioxides (123) are also isolated as the final products from the reaction with alkenes and oxidation of the initially formed dihydro derivatives (122) (Scheme 21) <88JHC813>.



Scheme 21

Cyclization of 1-methylquinoxalinium iodide by *o*- $\text{HXC}_6\text{H}_4\text{NH}_2$ ($\text{X} = \text{NH}, \text{O}$) in ethanolic dimethylamine at room temperature gives 53% and 70% yields of the corresponding quinoxalino[2,3-*b*]quinoxalines <84KGS706>.

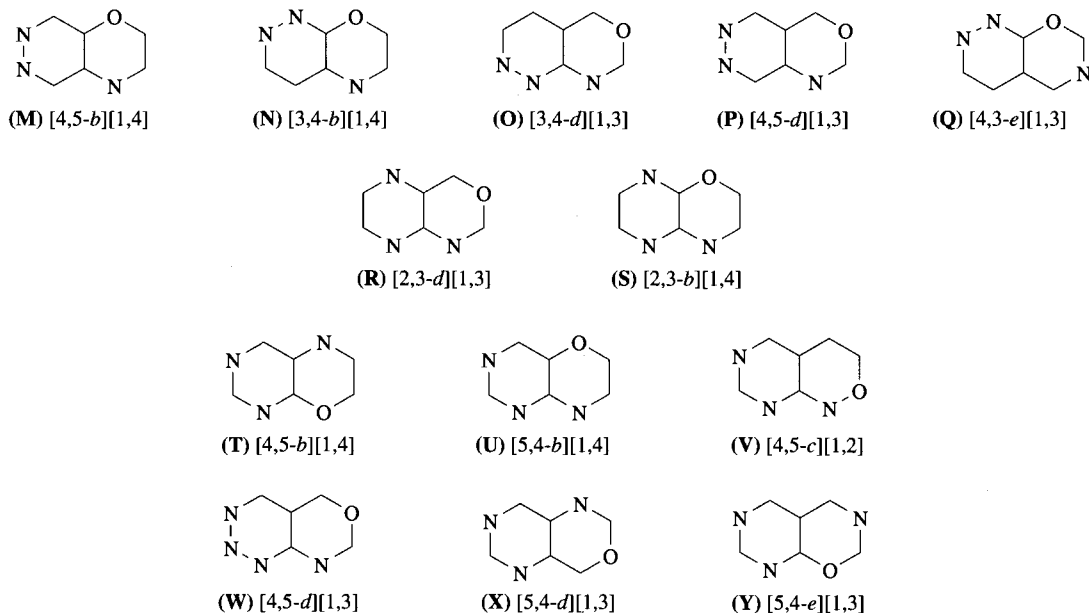
7.19.2.5.4 Important compounds and applications

The first application of pyrazino[2,3-*b*]pyrazines as vulcanization accelerators for rubber copolymerization has been reported in CHEC-I. Some new pyrazino[2,3-*b*]pyrazine derivatives are in use as electrophotographic developers <90JAP(K)2135365> and light-resistant fluorescent polymers <89JAP(K)01153750>. Some alkylsubstituted decahydropyrazino[2,3-*b*]pyrazines are suitable as delayed-action catalysts for the preparation of urethanes <83USP4528391>. Other pyrazinopyrazine derivatives are reported to have inhibitory effects on tomato spotted wilt virus <83MI 719-01>.

7.19.3 DIAZINOXAZINES

Diazinoxazines without bridgehead heteroatoms are divided into three groups: (i) pyridazinoxazines, of which five isomers (M)–(Q) are known; (ii) pyrazinoxazines, of which both

pyrazino[2,3-*d*][3,1]oxazines (**R**) and pyrazino[2,3-*b*][1,4]oxazines (**S**) have been reported; and (iii) pyrimidooxazines, the most studied group, of which derivatives of the isomers (**T**)–(**Y**) are known.



7.19.3.1 Pyridazinooxazines

7.19.3.1.1 Theoretical and experimental structural methods

(i) Pyridazino[4,5-*b*][1,4]oxazines (**M**)

¹H NMR and IR data are available in CHEC-I and no new structural information has been found. The spectroscopic data available in the literature are mentioned in the respective chapters.

(ii) Pyridazino[3,4-*b*][1,4]oxazines (**N**)

For pyridazino[3,4-*b*][1,4]oxazin-4-ones, x-ray analysis and theoretical calculations (AM1) have been reported. The results of both the theoretical and the x-ray method lie within the error limit. The AM1 method was reported as the best method for the calculations of nitrogen heterocycles <93UP 719-01>.

Only IR and ¹H NMR data for a 3-chloro-1,7-dimethylpyridazino[3,4-*b*][1,4]oxazine-4,5-dione are reported <81MI 719-01>.

(iii) Pyridazino[3,4-*d*][1,3]oxazines (**O**)

Only spectroscopic data are reported. No work dealing with structural methods has been published.

(iv) Pyridazino[4,5-*d*][1,3]oxazines (**P**)

Several pyridazino[4,5-*d*][1,3]oxazines have been reported but there is only limited data on their structures. For 2-phenylpyridazino[4,5-*d*][1,3]oxazin-4-one only IR and UV data are available <77JHC1099>. For 4-amino-2,3-dihydro-(7*H*)-pyridazino[4,5-*d*][1,3]oxazine a ¹H NMR spectrum is reported <77JHC1099>.

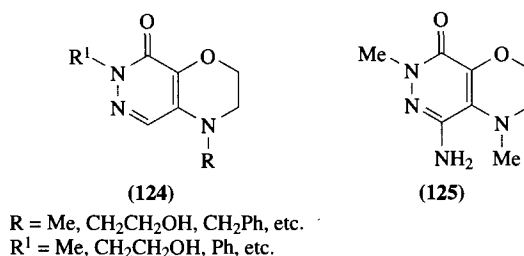
(v) Pyridazino[4,3-*e*][1,3]oxazines (**Q**)

No special structural methods were used on these compounds. Only spectroscopic data are available.

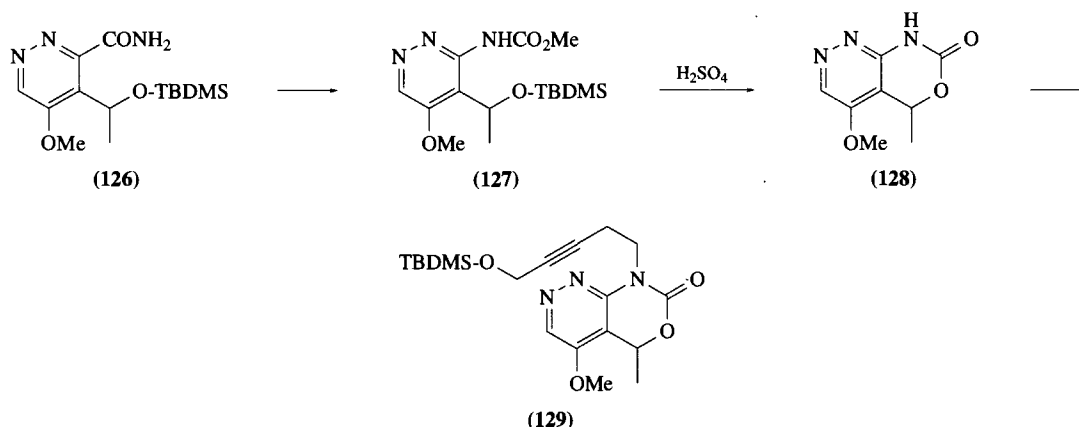
7.19.3.1.2 Reactivity

(i) Pyridazino[4,5-*b*][1,4]oxazines (**M**)

The cyclic secondary amine function at the 4 position of 3,4-dihydro-(2*H*)-pyridazino[4,5-*b*][1,4]-oxazin-8(7*H*)-one derivatives (**124**) and the primary amino group of 5-amino-3,4-dihydro-(2*H*)-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (**125**) show normal reactivities towards electrophilic attack <81MI 719-01>, though their quaternary salts were not formed because of the electron-drawing effect of the 8-CO group. Reactions of functional groups on the side chain were not influenced by the condensed ring.

(ii) Pyridazino[3,4-*d*][1,3]oxazines (**O**)

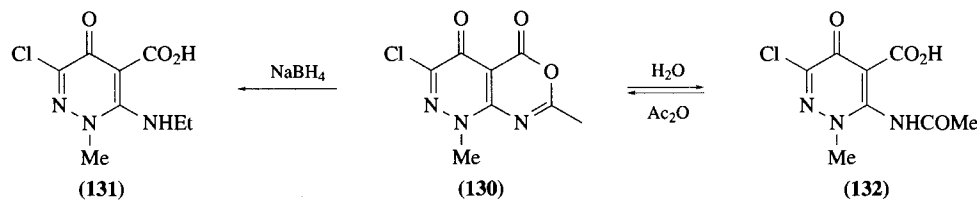
Boger used pyridazino[3,4-*d*][1,3]oxazines (**128**) and (**129**) in the total synthesis of PDE I, PDE II, and PDE I dimer methylester (functionalized 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indoles) <87JA2717>. In this route (Scheme 22) the 5-methoxy-4-(1-((*t*-butyldimethylsilyl)oxy)ethyl)-1,2-diazine-3-carboxamide (**126**) is transformed into the unstable *N*-carbomethoxy-amino-1,2-diazine (**127**) which is then cyclized using H_2SO_4 . In the next step a dienophile was fixed with a spacer group at the ring nitrogen employing *N*-alkylation conditions developed by Mitsunobu <72JA679>. This resulted in a system being ready for a Diels–Alder reaction.



Scheme 22

3-Chloro-1,7-dimethylpyridazino[3,4-*d*][1,3]oxazine-4,5-dione (**130**) is hydrolyzed in water at 100 °C to give 6-acetylamino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (**132**). This reaction is reversed in acetic anhydride.

With sodium borohydride at room temperature compound (130) could also be reduced to 3-chloro-6-ethylamino-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (131) (Scheme 23) <79JHC1213>.

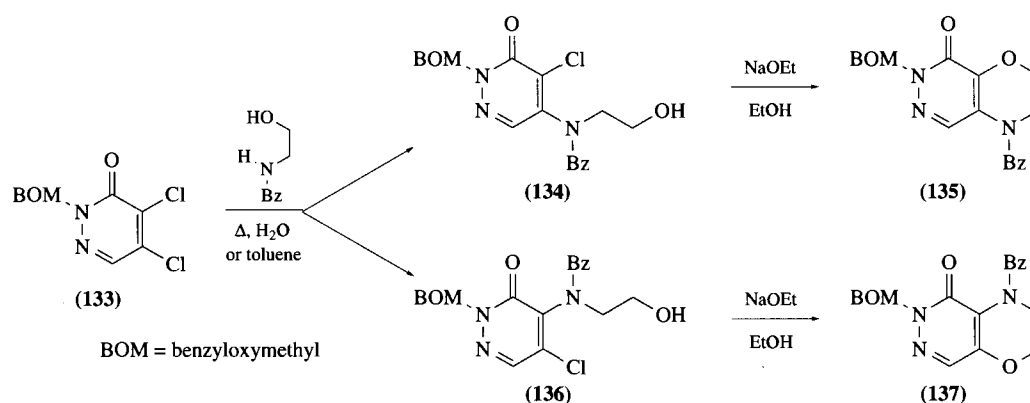


Scheme 23

7.19.3.1.3 Ring syntheses

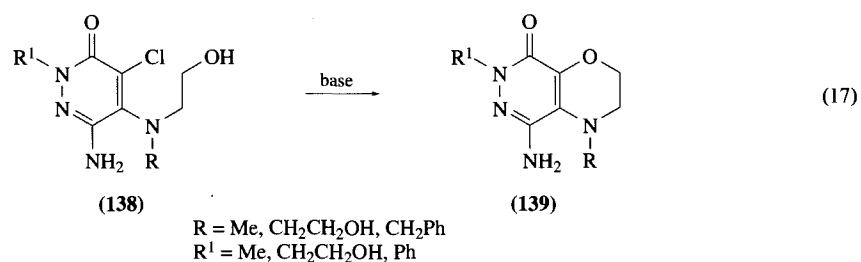
(i) Pyridazino[4,5-b][1,4]oxazines (M)

Several compounds have been synthesized starting from 2-benzyloxymethyl-4,5-dichloro-3(2*H*)-pyridazinone (133) (Scheme 24) <93H(36)519>. First, it was allowed to react with *N*-benzylaminoethanol in water or toluene. The ring closure of the precursors (134) and (136) to oxazinones (135) and (137) was achieved with sodium ethoxide in ethanol. The protection groups could be selectively removed as described in Section 7.19.3.1.2 <81MI 719-01>.



Scheme 24

A rather similar method was reported by Matsuo *et al.* <78JAP(K)53002497, 87JA2717>. 4-Chloro-5-(2-hydroxyethylamino)-3(2*H*)-pyridazin-3-ones (138) were converted upon treatment with base to the corresponding pyridazino[4,5-*b*][1,4]oxazinones (139). The ring closure fails for compound (138; R = H) (Equation (17)).

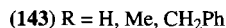


<78JAP(K)53002498>.



(ii) *Pyridazino[3,4-b][1,4]oxazines (N)*

(Equation (18)) $\langle 82\text{CPB}832 \rangle$.



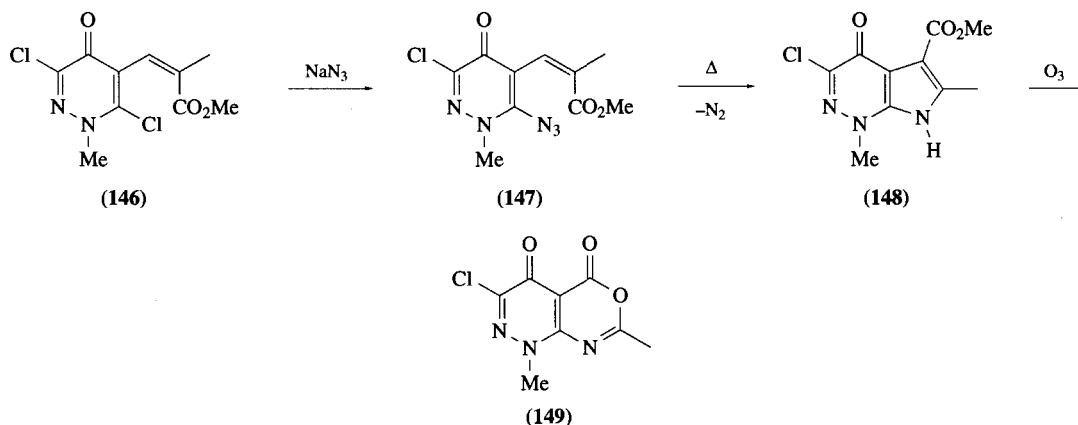
be converted into pharmaceutically interesting groups.



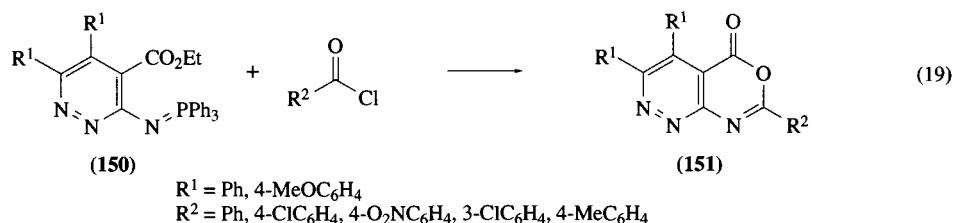
(iii) *Pyridazino[3,4-d][1,3]oxazines (O)*

d][1,3]oxazine-4,5-dione (**149**) (Scheme 26) $\langle 79\text{JHC1213} \rangle$.

<77JHC1099>.

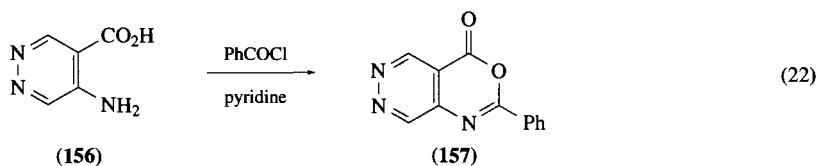
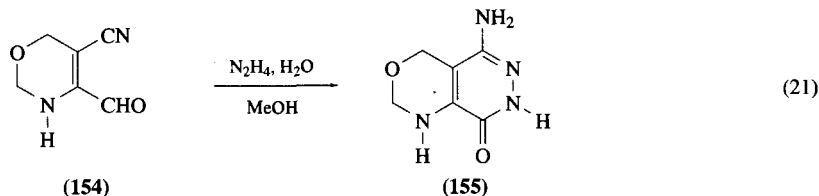
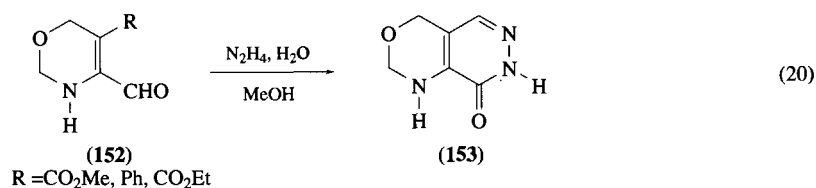


Scheme 26

*(iv) Pyridazino[4,5-d][1,3]oxazines (P)*

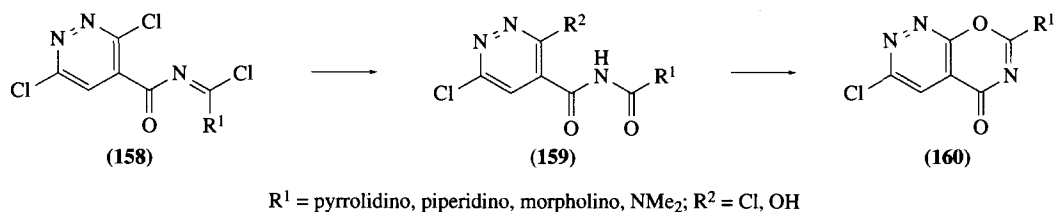
2,3-Dihydro-(8*H*)-5,6-pyridazino[4,5-*d*][1,3]oxazin-4-one (**153**) was prepared from the enamino aldehyde 4-methoxycarbonyl-5-formyl-2,3-dihydro(6*H*)-1,3-oxazine (**152**) with hydrazine hydrate in methanol (Equation (20)) <87CCC1773, 87CCC2953>. Using the nitrile (**154**) the resulting pyridazinoxazine (**155**) carries an amino group at position 7 (Equation (21)).

Another derivative was synthesized starting from 5-aminopyridazine-4-carboxylic acid (**156**). Its reaction with benzoyl chloride in pyridine gave 2-phenylpyridazino[4,5-*d*][1,3]oxazin-4-one (**157**) (Equation (22)).



(v) Pyridazino[4,3-*e*][1,3]oxazines (*Q*)

Starting from the pyridazinocarboximidoyl chlorides (**158**) the corresponding ureas (**159**) were prepared and subsequently cyclized into the pyridazino[4,3-*e*][1,3]oxazinones (**160**) (Scheme 27) <88AP(321)527>.

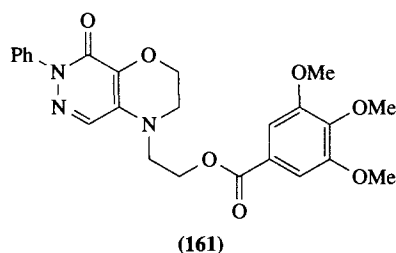


Scheme 27

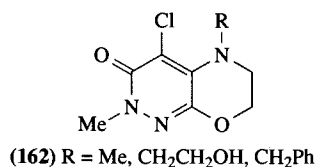
7.19.3.1.4 Important compounds and applications

(i) Pyridazino[4,5-*b*][1,4]oxazines (*M*)

Some members of this series are reported to have analgesic and antiinflammatory activities <82CPB832, 87JA2717>. The 3,4-dihydro-7-phenyl-4-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]-(2*H*)-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (**161**) was found to be one of the most potent derivatives.

(ii) Pyridazino[3,4-*b*][1,4]oxazines (*N*)

Some of the pyridazino[3,4-*b*][1,4]oxazines (**162**) are reported to have analgesic and significant antiinflammatory activities <93H(36)519>.



7.19.3.2 Pyrazinooxazines

7.19.3.2.1 Theoretical and experimental structural methods

(i) Pyrazino[2,3-*d*][1,3]oxazines (*R*)

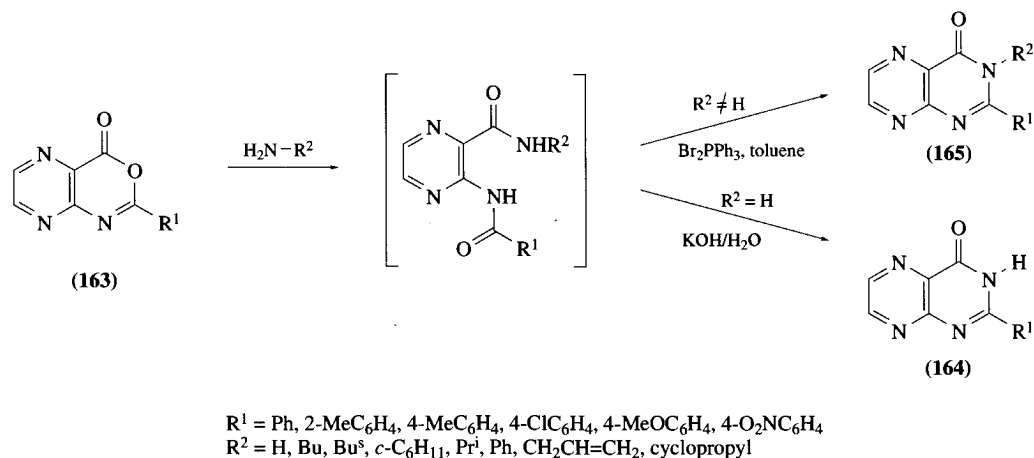
Only ^1H NMR, ^{13}C NMR, IR, and MS measurements have been reported for characterization of pyrazino[2,3-*d*][1,3]oxazines. The literature relating to their preparations contains these spectroscopical data. Neither x-ray analysis nor theoretical calculations have been reported.

(ii) *Pyrazino[2,3-b][1,4]oxazines (S)*

Nothing special has been reported; only routine spectroscopic data of derivatives is available in the literature cited.

7.19.3.2.2 *Reactivity*(i) *Pyrazino[2,3-d][1,3]oxazines (R)*

The 2-arylpyrazino[2,3-*d*][1,3]oxazin-4-ones (**163**) have been transformed into 2-aryl-(3*H*)-pteridin-4-ones (**164**) by aminolysis, and into 2-arylpteridin-4-ones (**165**) by recyclization using dibromotriphenylphosphorane (Scheme 28) <94S405>.

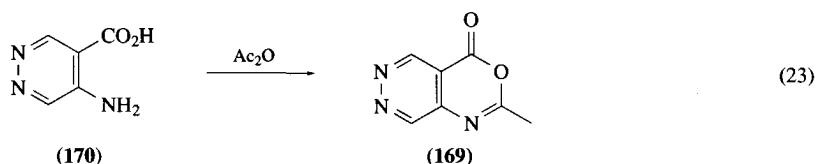


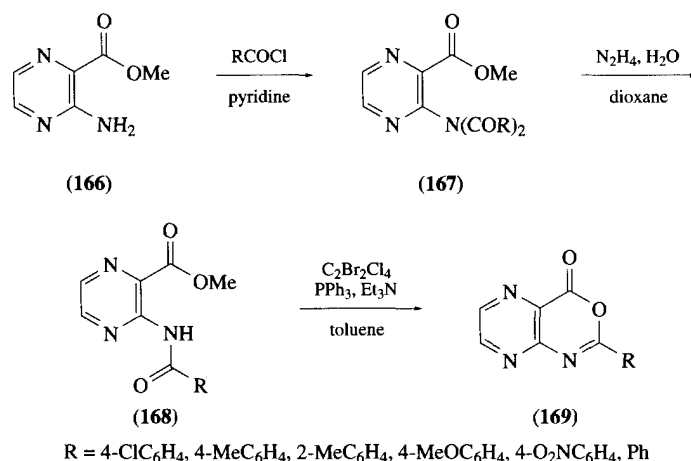
Scheme 28

7.19.3.2.3 *Ring syntheses*(i) *Pyrazino[2,3-d][1,3]oxazines (R)*

The synthesis of pyrazino[2,3-*d*][1,3]oxazin-4-ones (**169**) starts with a 2-aminopyrazine ester (**166**) which is treated with two equivalents of an aromatic acid chloride. With a partial hydrazinolysis the diacylamino group (**167**) is transformed into the monoacylamino group (**168**). Finally, cyclization with dibromotriphenylphosphorane affords the 2-arylpyrazino[2,3-*d*][1,3]oxazin-4-one (**169**) (Scheme 29) <78JAP(K)53002499>.

Another method for the preparation of these pyrazino[2,3-*d*][1,3]oxazines (**169**) is the alkylation-cyclization of an appropriate aminocarboxylic acid (**170**) and an acetanhydride <90JMC464, 93UP 719-01>. This one-step reaction is an extremely simple way to pyrazino[2,3-*d*][1,3]oxazines (Equation (23)).

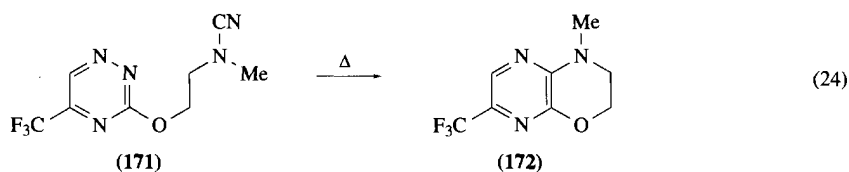




Scheme 29

(ii) *Pyrazino[2,3-b][1,4]oxazines (S)*

The triazine (171) <91AP(324)65> underwent intramolecular cycloaddition followed by elimination of nitrogen to give the 2,3-dihydro-4-methyl-7-trifluormethylpyrazino[2,3-*b*][1,4]oxazine (172) (Equation (24)). For a preparation of 6,7-dichloro derivatives see Section 7.19.3.2.4(ii).



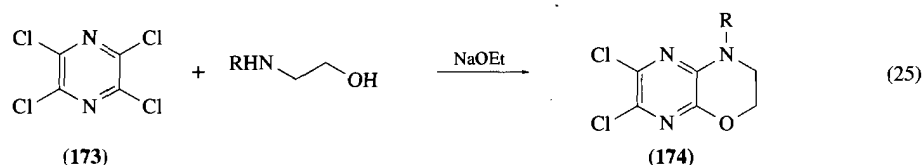
7.19.3.2.4 Important compounds and applications

(i) *Pyrazino[2,3-d][1,3]oxazines (R)*

2-Arylpyrazino[2,3-*d*][1,3]oxazin-4-ones are precursors for several pteridinones such as 2-aryl-(3*H*)-pteridin-4-ones and 2-arylpteridin-4-ones <78JAP(K)53002499>. This is a new synthetic approach for these interesting bicycles and proceeds in good yield.

(ii) *Pyrazino[2,3-b][1,4]oxazines (S)*

6,7-Dichloro-3,4-dihydro-(2*H*)-pyrazino[2,3-*b*][1,4]oxazines (174) and their *N*-alkyl derivatives possess insecticidal, fungicidal, and herbicidal activity. They can be easily prepared by the reaction of tetrachloropyrazine (173) with 2-aminoethanol or *N*-alkyl-2-aminoethanols and sodium ethoxide (Equation (25)) <77USP4029657>.



7.19.3.3 Pyrimidooxazines

In a review article Delia presents 88 references for the synthesis of pyrimidooxazines and pyrimidothiazines <B-92MI 719-02>. This chapter, therefore, is limited to results which were not reported there.

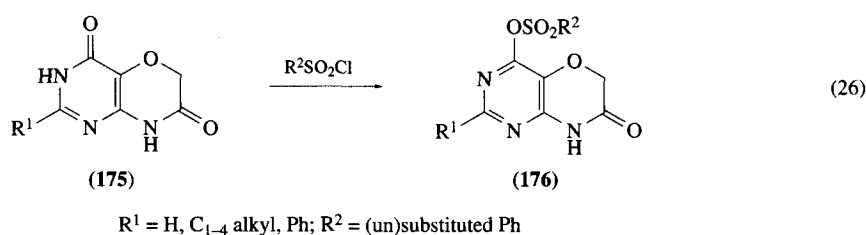
7.19.3.3.1 Theoretical and experimental structural methods

Although the pyrimidooxazine system is very important and often reported, experimental structural methods have only been used for routine characterization of compounds. The spectroscopic data mentioned in the literature relate to reactivity, synthesis, and important compounds and applications. No theoretical method has been used to gain more knowledge about this class.

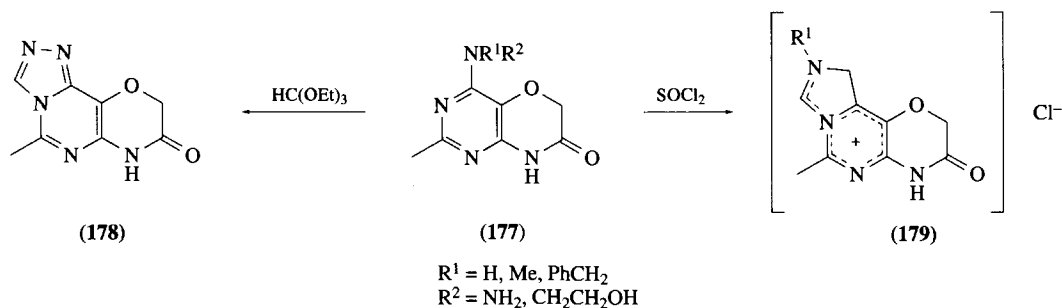
7.19.3.3.2 Reactivity

(i) Pyrimido[5,4-*b*][1,4]oxazines (*U*)

Pyrimido[5,4-*b*][1,4]oxazine-4,7-diones (**175**) can be transformed to 4-monosulfonic esters (**176**) by treatment with sulfonic acid chlorides (Equation (26)) <89MIP47293>.



N-substituted 4-aminopyrimido[5,4-*b*][1,4]oxazin-7-ones (**177**) can be converted into the triazolopyrimidooxazinones (**178**) or imidazopyrimidooxazinium salts (**179**). The triazolo fused compound (**178**) is accessible by treatment of the pyrimidooxazines (**177**) with $HC(OEt)_3$ whereas the imidazo-fused salts (**179**) were derived by reaction with $SOCl_2$ (Scheme 30) <89JHC739>.



Scheme 30

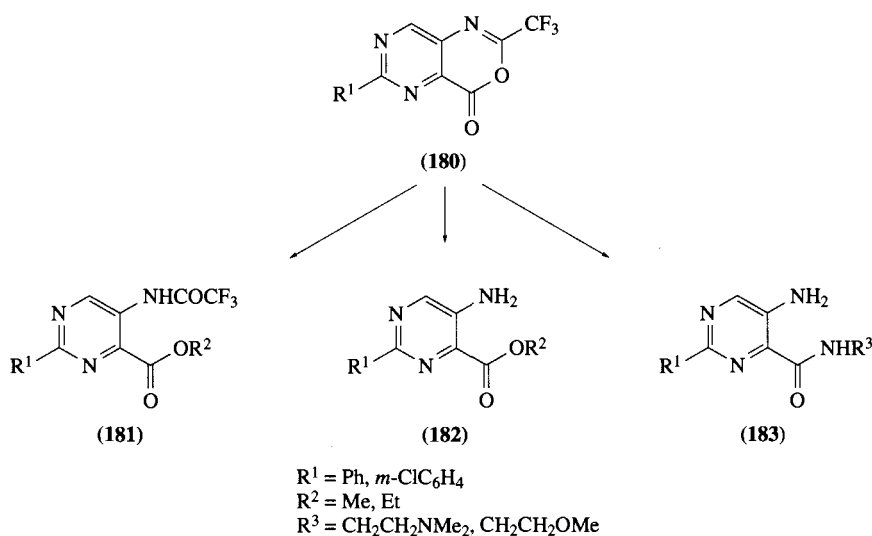
(ii) Pyrimido[5,4-*d*][1,3]oxazines (*X*)

6-Substituted 2-trifluoromethyl-(4*H*)-pyrimido[5,4-*d*][1,3]oxazin-4-ones (**180**) have been reported to be useful precursors for polysubstituted pyrimidines (**181**)–(**183**) (Scheme 31) <70JOC1680>.

7.19.3.3.3 Ring syntheses

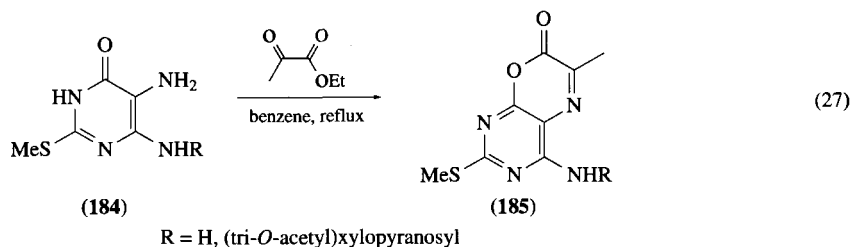
(i) Pyrimido[4,5-*b*][1,4]oxazines (*T*)

Two pyrimido[4,5-*b*][1,4]oxazin-7-one derivatives (**185**) have been prepared from 4,5-diaminopyrimidin-6(1*H*)-one derivatives (**184**) and ethyl pyruvate. One of these derivatives is a very unusual glycoside. It is remarkable that 5-amino-2-methylthio-4- β -D-[(tri-*O*-acetyl)xylopyranosylamino]-pyrimidin-6(1*H*)-one gives 32% of the expected pyrimido[4,5-*b*][1,4]oxazin-7-one, whereas the



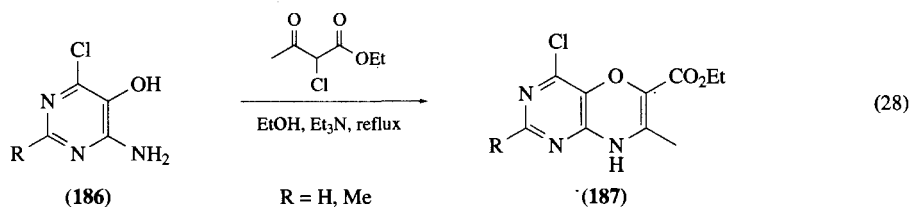
Scheme 31

4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one gives only 2.8% of the pyrimido[4,5-*b*][1,4]oxazin-7-one as a side product. The main product is a pteridinone (Equation (27)) <91H(32)1719>.



(ii) *Pyrimido[5,4-*b*][1,4]oxazines (U)*

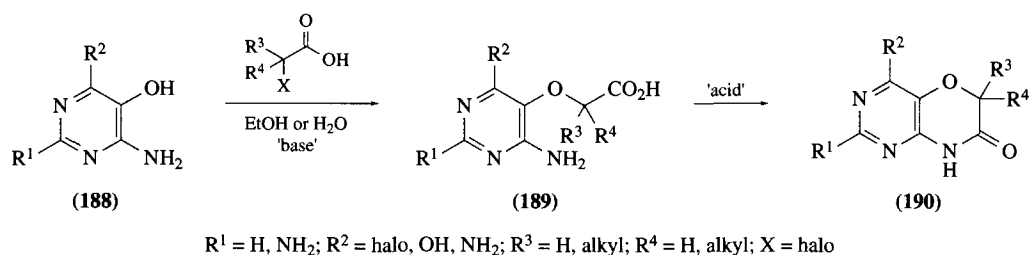
Ethyl (8*H*)-pyrimido[5,4-*b*][1,4]oxazine-6-carboxylate (**187**) could be obtained in about 82% yield by boiling 6-amino-4-chloro-5-hydroxypyrimidine (**186**) with ethyl 2-chloroacetoacetate in ethanol, i.e. triethylamine <73KGS1694>.



(8*H*)-Pyrimido[5,4-*b*][1,4]oxazin-7-ones (**190**) have been prepared by reaction of the corresponding pyrimidinole (**188**) with 2-halocarboxylic acids in aqueous or alcoholic solution in the presence of OH^- , CO_3^{2-} , or an alkali metal alcoholate to give the acid (**189**) which cyclizes in the presence of acid or a dehydrating agent (Scheme 32) <74MI 719-01>.

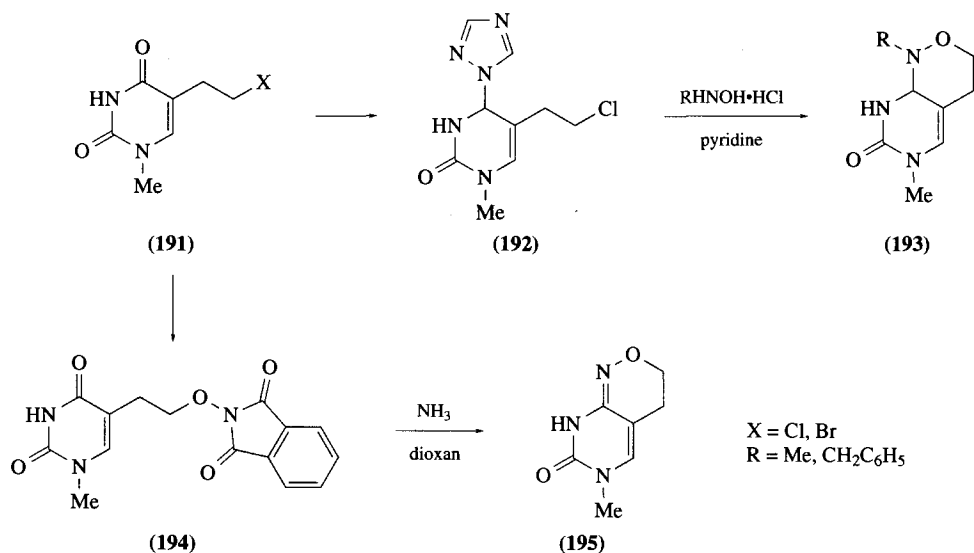
(iii) *Pyrimido[4,5-*c*][1,2]oxazines (V)*

An intramolecular ring closure is reported to give the pyrimido[4,5-*c*][1,2]oxazines (**193**) and (**195**) (Scheme 33). Starting from a 5-(2-chloroethyl)-1-methyluracil (**191**) which is converted into the



Scheme 32

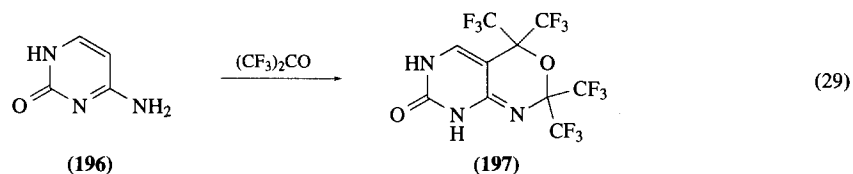
4-triazolopyrimidinone (192), cyclization occurs with *N*-methyl- or *N*-benzylhydroxylamine hydrochloride in anhydrous pyridine. This results in a 1-substituted-6-methyl-3,4-dihydro-(6*H*,8*H*)-pyrimido[4,5-*c*][1,2]oxazin-7-one (193). In the same way 1-methyl-5-(2-phthalimidooxyethyl)uracil (194) could be transformed into the 1-unsubstituted 3,4-dihydro-6-methyl-(6*H*,8*H*)-pyrimido[4,5-*c*][1,2]oxazin-7-one (195) using saturated dioxane-ammonia for cyclization (<88MI 719-01, 89H(29)1735>).



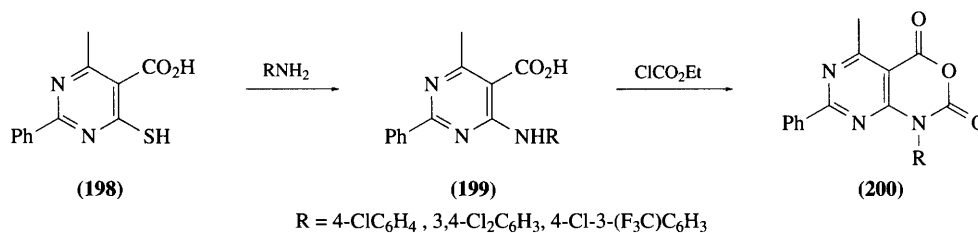
Scheme 33

(iv) *Pyrimido*[4,5-*d*][1,3]oxazines (*W*)

The reaction of 4-aminopyrimidines with hexafluoroacetone in DMF gives pyrimido[4,5-*d*][1,3]oxazines; *e.g.* treating cytosine (196) with hexafluoroacetone gave 5,7-di-(di-(trifluoromethyl))-1*H*,3*H*-pyrimido[4,5-*d*][1,3]oxazin-2-one (197) (Equation (29)) (<87IZV1433, 89IZV1656>).



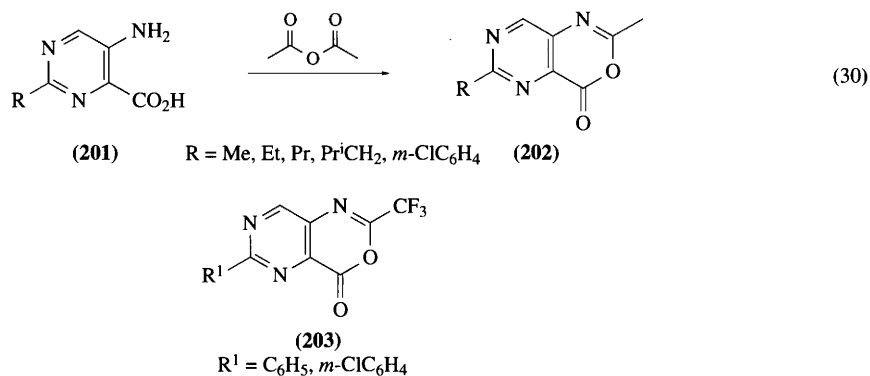
A new method for preparing pyrimido[4,5-*d*][1,3]oxazines (200) consists of heating 2-phenyl-4-thio-6-methylpyrimidine-5-carboxylic acid (198) with the corresponding anilines at 180–200°C to obtain aminopyrimidines (199) which can be cyclized using ethyl chloroformate (Scheme 34) (<86MIP130888>). These compounds inhibit the growth of *Staphylococcus aureus*, *Streptococci*, *corynebacteria*, and other pathogens.



Scheme 34

(v) *Pyrimido[5,4-d][1,3]oxazines (X)*

2,6-Disubstituted(4*H*)-pyrimido[5,4-*d*][1,3]oxazin-4-ones (202) were obtained by refluxing an appropriate 5-amino-4-pyrimidinecarboxylic acid (201) with an acid anhydride. Thus, condensation of mucobromic acid with *m*-chlorophenylhydrazine hydrochloride in alcohol and in the presence of sodium ethylate at 40°–50°C yielded 5-bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid. This and hydroxylamine reacted in an autoclave for 2.5 hours at 100°C in the presence of CuSO₄ · 5H₂O yielded after acidification and purification 5-amino-2-(3'-chlorophenyl)-4-pyrimidinecarboxylic acid (Equation (30)) <68USP3549627>. The trifluoromethyl compound (203) was synthesized in the same way using trifluoromethylacetic anhydride <70JOC1680>.

(vi) *Pyrimido[5,4-e][1,3]oxazines (Y)*

The cyclization reactions of chloro-substituted 2-azonioallene hexachloroantimonate salts with dimethylbarbituric acid (204) give highly substituted pyrimido[5,4-*e*][1,3]oxazinium hexachloroantimonate salts (205) and (207). Some of them could be converted into pyrimido[4,5-*d*]pyrimidines (206) (Scheme 35) <92S591>.

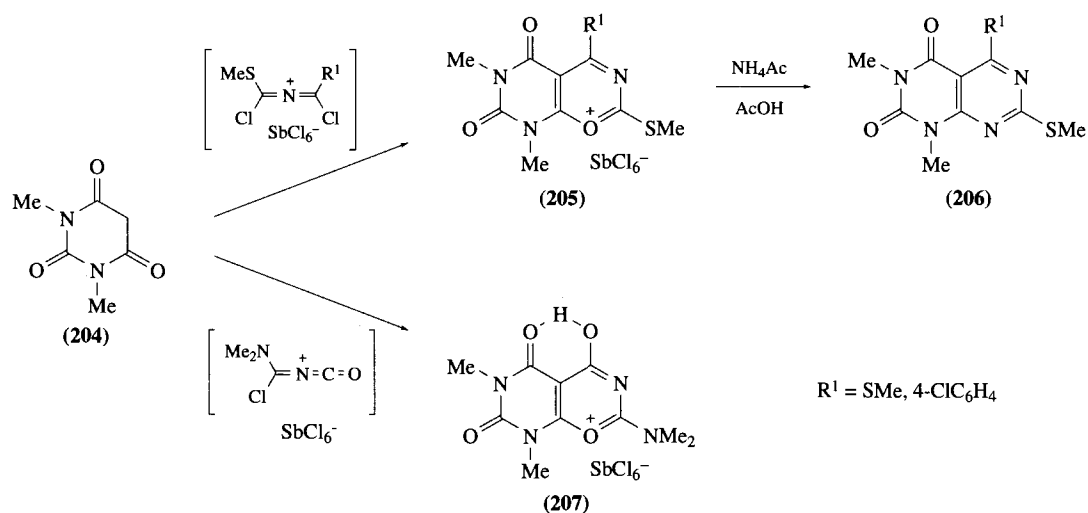
7.19.3.3.4 Important compounds and applications

(i) *Pyrimido[5,4-b][1,4]oxazines (U)*

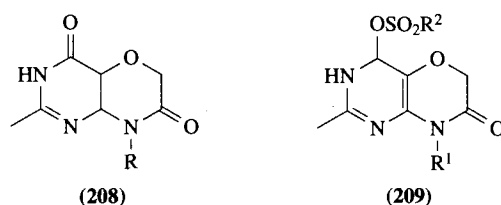
Mátyus *et al.* reported the synthesis and cardiotonic activity of pyrimido[5,4-*b*][1,4]oxazinones <90JHC151>. The synthesis started from 6-amino-2,3-dimethyl-4(3*H*)-pyrimidinone. Also 4-substituted pyrimido[5,4-*b*][1,4]oxazinones were transformed into pharmaceutically interesting products. Several compounds were prepared; some showed an ionotropic effect, for example (208) and (209).

The pyrimido[5,4-*b*][1,4]oxazin-4-ones (210) are of potential use as cardiotonics <87EUP228094>.

Some pyrimido[5,4-*b*][1,4]oxazin-4-ones (211) were tested for ionotropic activity and chosen for preclinical tests. The biochemical and pharmacological data show that the mechanism of action differs from that of other comparable substances <90EJM333>.



Scheme 35

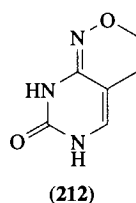


$\text{R}^1 = \text{alkyl}$
 $\text{R}^2 = \text{H}, \text{halo}, \text{N}_3, \text{N}_2\text{H}_3, \text{amino}$
 $\text{R}^3 = \text{H}, \text{alkyl}$
 $\text{R}^4 = \text{H}, \text{alkyl}$
 $\text{R}^5 = \text{H}, (\text{substituted}) \text{alkyl}$

$\text{R}^1 = \text{H}, \text{Me}, \text{Ph}$
 $\text{R}^2 = \text{Cl}, \text{tosyloxy}, \text{N}_3, \text{N}_2\text{H}_3, \text{amino}$
 $\text{N} = \text{PPh}_3, \text{morpholino}, \text{cyclopropylamino}$
 $(4\text{-benzyl-2-morpholinyl})\text{methylamino},$
 $2\text{-morpholinoethylamino}$
 $\text{R}^3 = \text{H}, \text{Me}, \text{Ph}$
 $\text{R}^4 = \text{H}, \text{Me}$
 $\text{R}^5 = \text{H}, \text{Me}, \text{CH}_2\text{Ph}, \text{CH}_2\text{CN}, \text{CH}_2\text{CO}_2\text{Et}$

(ii) *Pyrimido[4,5-c][1,2]oxazines (V)*

In the syntheses of oligonucleotides (6*H*), (8*H*)-3,4-dihydropyrimido[4,5-*c*][1,2]oxazin-7-one (212) was used as a base <92MI 719-01>. The resulting heptadecaoligodeoxyribonucleotides are effective primers in the polymerase chain reaction.

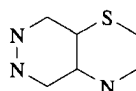


7.19.4 DIAZINOTHIAZINES

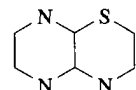
7.19.4.1 Introduction

Three general types of diazinothiazines are possible: pyridazinothiazines, pyrazinothiazines, and pyrimidothiazines.

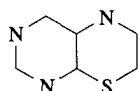
Although five pyridazinothiazine isomers are possible examples of only one, namely pyridazino[4,5-*b*][1,4]thiazine (**Z**) have been reported so far. Pyrazinothiazines could occur as two types but only the pyrazino[2,3-*b*][1,4]thiazines (**AA**) are known at present. Pyrimidothiazines are the best known diazinothiazines but derivatives of only three isomers (**AB**, **AC**, and **AD**) are currently known.



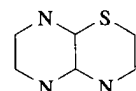
(**Z**) [4,5-*b*][1,4]



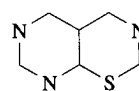
(**AA**) [2,3-*b*][1,4]



(**AB**) [4,5-*b*][1,4]



(**AC**) [5,4-*b*][1,4]



(**AD**) [5,4-*e*][1,3]

7.19.4.2 Pyridazinothiazines

7.19.4.2.1 Theoretical and experimental structural methods

(i) Pyridazino[4,5-*b*][1,4]thiazines (**Z**)

No theoretical calculations or x-ray analyses have been reported. Routine analytical data is reported in the literature cited in this chapter.

7.19.4.2.2 Reactivity

(i) Pyridazino[4,5-*b*][1,4]thiazines (**Z**)

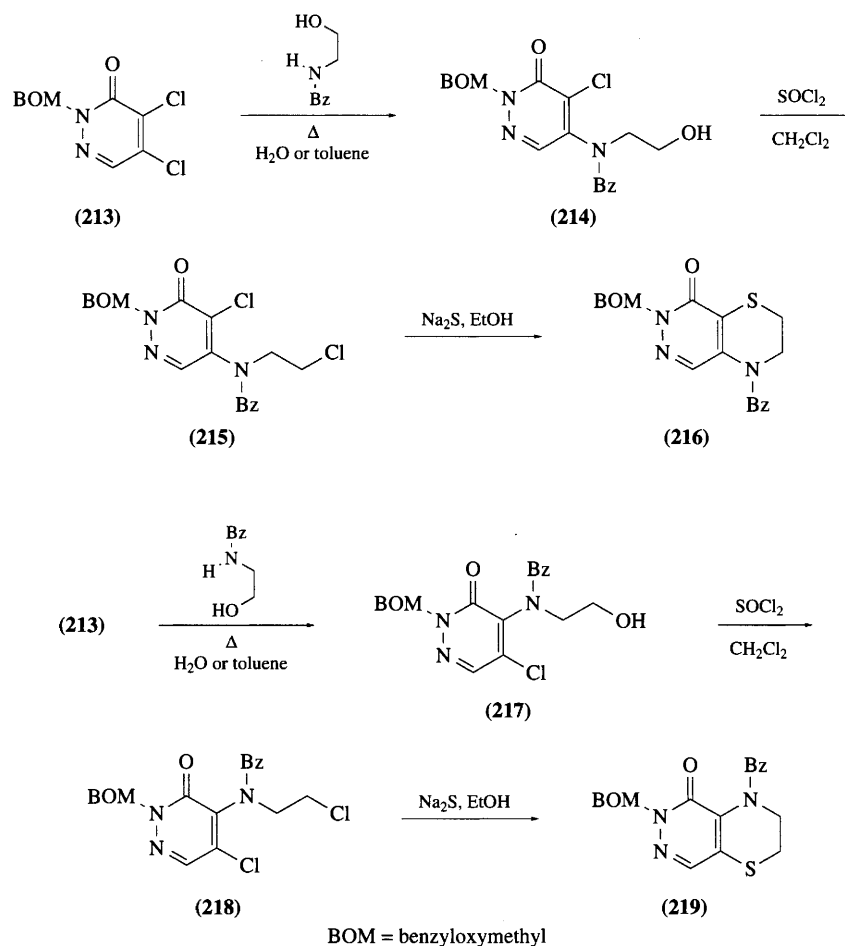
Some reactions depending on the removal of protecting groups have been reported <93H(36)519>. However, the pyridazino[4,5-*b*]thiazines are more notable as pharmaceuticals than as building blocks in organic synthesis.

7.19.4.2.3 Ring syntheses

(i) Pyridazino[4,5-*b*][1,4]thiazines (**Z**)

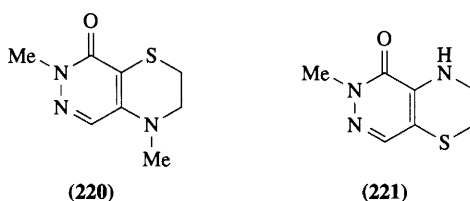
Several compounds have been synthesized starting from 2-benzoyloxymethyl-4,5-dichloro-3(2*H*)-pyridazinone (**213**) (Scheme 36) <93H(36)519>. First, reaction with *N*-benzylaminoethanol in water

or toluene gave amines (214) and (217) which with thionyl chloride gave the corresponding 2-chlorethylamino derivatives (215) and (218). Ring closure to thiazinones (215) $\rightarrow$ (216) and (218) $\rightarrow$ (219) was achieved with sodium sulfide in ethanol; the protection groups could be removed selectively <93H(36)519>.



Scheme 36

Similar products (220) and (221) were obtained by the intramolecular cyclization of 4-chloro-5-(2-chloroethylamino)-2-methyl-3(2*H*)-pyridazinone with sodium sulfide. The isomeric pyridazino[4,5-*b*][1,4]thiazinone has been prepared by cyclocondensation of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone with sodium 2-aminothioethylate <82CPB1030>. Although the reaction is similar to the one mentioned above, in this case the protecting groups could not be cleaved in the way reported by Zara-Kaczian and Mátyus <93H(36)519>.



7.19.4.2.4 Important compounds and applications

(i) Pyridazino[4,5-b][1,4]thiazines (**Z**)

The pyridazino[4,5-b][1,4]thiazinones (**216**) and (**219**)–(**221**) are pharmacologically interesting. They are reported to be depressants, carrageenin-induced edema reducing as well as having analgesic activity <78JAP(K)53002497>.

7.19.4.3 Pyrazinothiazines

7.19.4.3.1 Theoretical and experimental structural methods

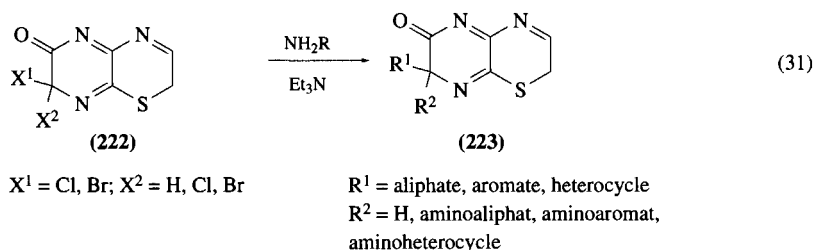
(i) Pyrazino[2,3-b][1,4]thiazines (**AA**)

Although there were many reports on pyrazino[2,3-b][1,4]thiazines in the 1970s nothing has been published since 1980. No theoretical calculations or x-ray analyses have been reported and routine analytical data are the only information available on the structure of these molecules.

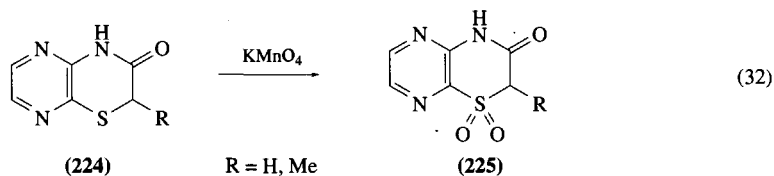
7.19.4.3.2 Reactivity

(i) Pyrazino[2,3-b][1,4]thiazines (**AA**)

7-Halo- or 7,7-dihalopyrazino[2,3-b][1,4]thiazin-6-ones (**222**) can be converted into the 7-amino or 7,7-diamino compounds (**223**) by treatment with aliphatic, aromatic, or heterocyclic amines in an organic solvent and in the presence of Et₃N <72MI 719-01>.



Pyrazino[2,3-b][1,4]thiazin-3-ones (**224**) have been converted into their 1,1 dioxides (**225**) using KMnO₄ as oxidative agent. All compounds were reported to be diuretics (Equation (32)) <71JAP32671>.



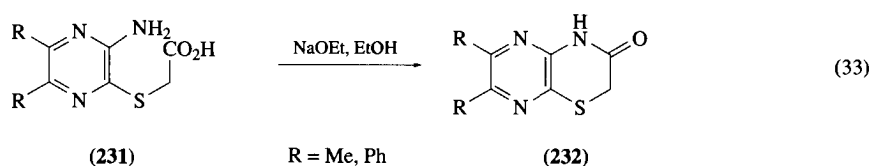
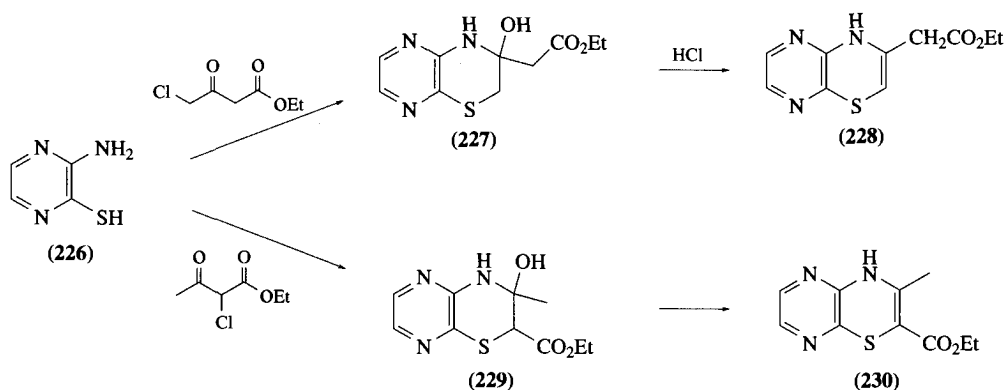
7.19.4.3.3 Ring syntheses

(i) Pyrazino[2,3-b][1,4]thiazines (**AA**)

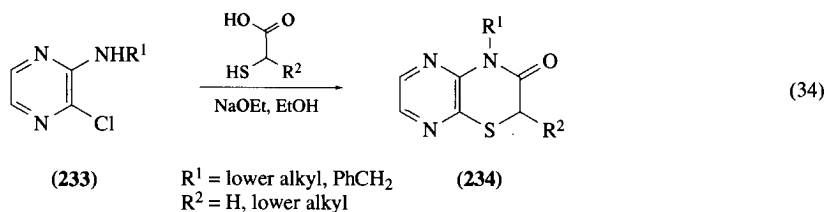
Pyrazino[2,3-b][1,4]thiazines (**228**) can easily be prepared by cyclization of the aminothiopyrazine (**226**) with ethyl 4-chloroacetoacetate. The resulting 2,3-dihydro product (**227**) was dehydrated with

ethanolic HCl <77KGS695>. Analogously, the pyrazino[2,3-*b*][1,4]thiazines (**230**) could be obtained from ethyl 2-chloroacetoacetate via an easily dehydrated hydroxy ester derivative (**229**) (Scheme 37).

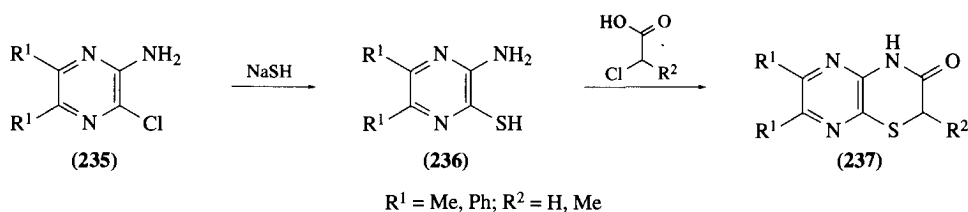
Pyrazino[2,3-*b*][1,4]thiazin-3-ones (**232**) have been obtained by cyclization of highly substituted aminopyrazines (**231**) using NaOEt—EtOH (Equation (33)) <75KGS66>.



The reaction of 2-chloro-3-(*N*-substituted amino)pyrazines (**233**) with thioglycolates gives 2,3-dihydro-4-substituted-(4*H*)-pyrazino[2,3-*b*][1,4]thiazin-3-ones (**234**) <71JAP32670, 74JAP(K)49041397> with analgesic properties (Equation (34)).



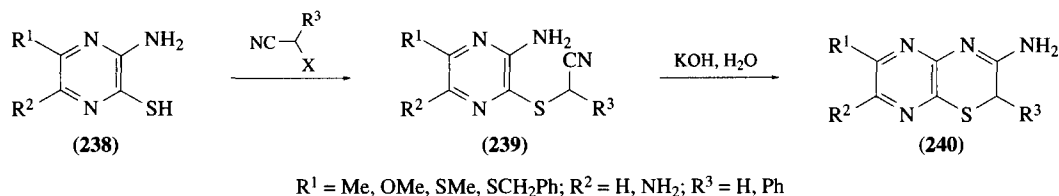
The 3-amino-2-chloropyrazines (**235**) can be transformed into the thiols (**236**) by NaSH and cyclization with 2-chloroacetic acid or 2-chloropropionic acid gives 2,3-dihydro-(4*H*)-pyrazino[2,3-*b*][1,4]thiazin-3-ones (**237**) <71KGS230>.



Scheme 38

6,7-Disubstituted 3-amino-2-hydropyrazino[2,3-*b*][1,4]thiazines (**240**) have been prepared from the *o*-aminothiols of 5,6-disubstituted pyrazines (**238**) by treatment with 2-haloacetonitrile or 2-

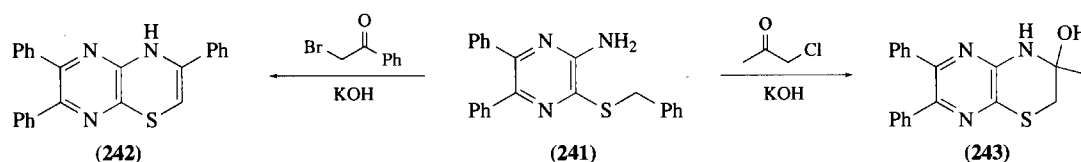
halo-2-phenylacetonitrile to give the methylthiopyrazines (239) which are cyclized by aqueous potassium hydroxide (Scheme 39) <72KGS944>.



Scheme 39

Treatment of 3-amino-2-benzylthiol-5,6-diphenylpyrazine (241) with phenacyl bromide and alcoholic KOH gave (4*H*)-3,6,7-triphenylpyrazino[2,3-*b*][1,4]thiazine (242). Cyclization of the same pyrazine (241) with chloroacetone gave a 2,3-dihydro-3-hydroxy-(4*H*)-6,7-diphenylpyrazino[2,3-*b*][1,4]thiazine (243) (Scheme 40) <70KGS1101>.

3-Amino-2-chloropyrazine upon treatment with sodium ethoxide in DMF saturated with H_2S gave 3-amino-2-thiopyrazine and cyclization to the pyrazino[2,3-*b*][1,4]thiazine was effected with phenacyl bromide in a similar way to that described above <70KGS1092>.

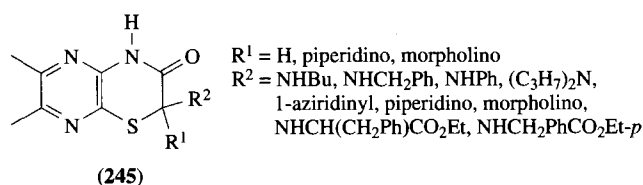
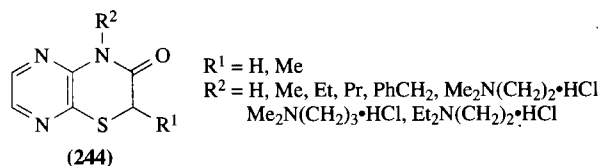


Scheme 40

7.19.4.3.4 Important compounds and applications

(i) Pyrazino[2,3-*b*][1,4]thiazines (AA)

Many 2,4-disubstituted pyrazino[2,3-*b*][1,4]thiazin-3-ones (244) show potent antipyretic, analgesic, and antiinflammatory activities <75MI 719-01>. Another interesting group of pyrazino[2,3-*b*][1,4]thiazin-3-ones (245) are the 2-disubstituted 6,7-dimethyl derivatives which are claimed to have oncostatic activity <71KGS1498>.



7.19.4.4 Pyrimidothiazines

A review article by Delia <B-92MI 719-02> discusses most work on pyrimidothiazines up to 1986. This chapter reviews the subsequent literature. Many pyrimidothiazines are well known because of their pharmaceutical importance.

7.19.4.4.1 Theoretical and experimental structural methods

(i) Pyrimido[4,5-*b*][1,4]thiazines (*AB*)

Proton and carbon-13 NMR studies of the protonation of biologically active derivatives of pyrimido[4,5-*b*][1,4]thiazines were reported in 1979 <B-79MI 719-02>.

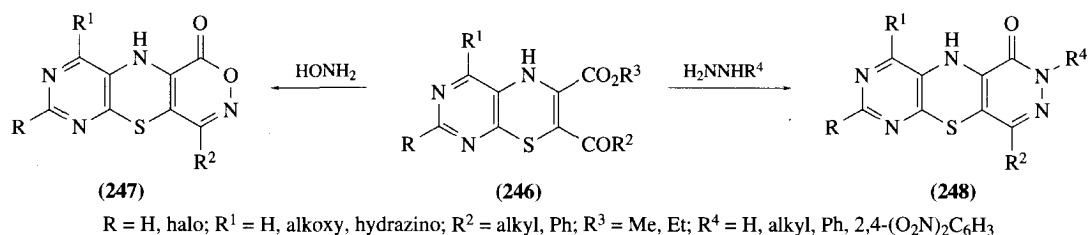
(ii) Pyrimido[5,4-*b*][1,4]thiazines (*AC*)

The structure of 3-methyl-2-oxo-6,7-dihydro-3*H*-pyrimido[5,4-*b*][1,4]thiazine-7-carboxylic acid has been characterized by x-ray analysis <89ACS(C)116>.

7.19.4.4.2 Reactivity

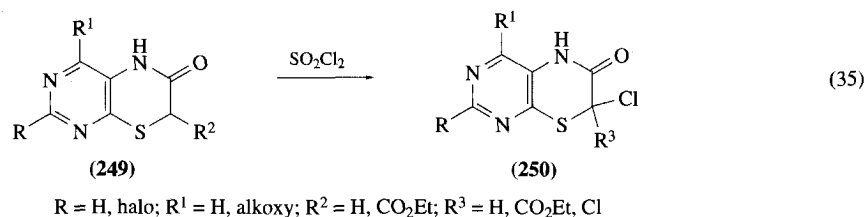
(i) Pyrimido[4,5-*b*][1,4]thiazines (*AB*)

The pyrimido[4,5-*b*][1,4]thiazines (**246**) can be used to build up pyrimido[4,5-*b*][1,4]thiazino[2,3-*d*][1,2]pyridazines (**248**) by reaction with several hydrazines <82MI 719-02>, or pyrimido[4,5-*b*][1,4]thiazino[2,3-*d*][1,2]oxazines (**147**) by reaction with hydroxylamine (Scheme 41) <82MI 719-02>.



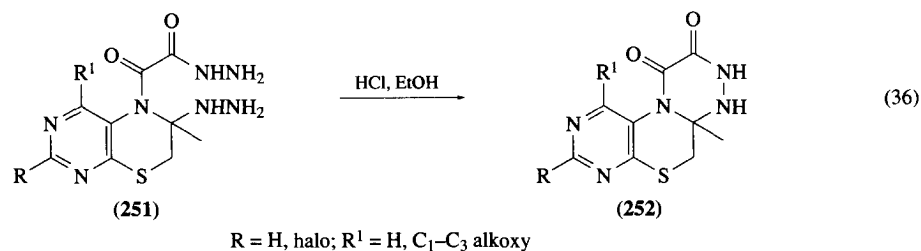
Scheme 41

Also described is the chlorination on of pyrimido[4,5-*b*][1,4]thiazines (**249**) → (**250**) with sulfuryl chloride in the presence of dibenzoyl peroxide as catalyst (Equation (35)) <82MI 719-03>.



Pyrimido[4,5-*b*][1,4]thiazines have been used to build up 1,2,4-triazino[4,3-*d*][1,4]thiazine deriva-

tives (**252**) <79MI 719-01> by cyclization of the dihydrazino compounds (**251**) in ethanol in the presence of HCl (Equation (36)).

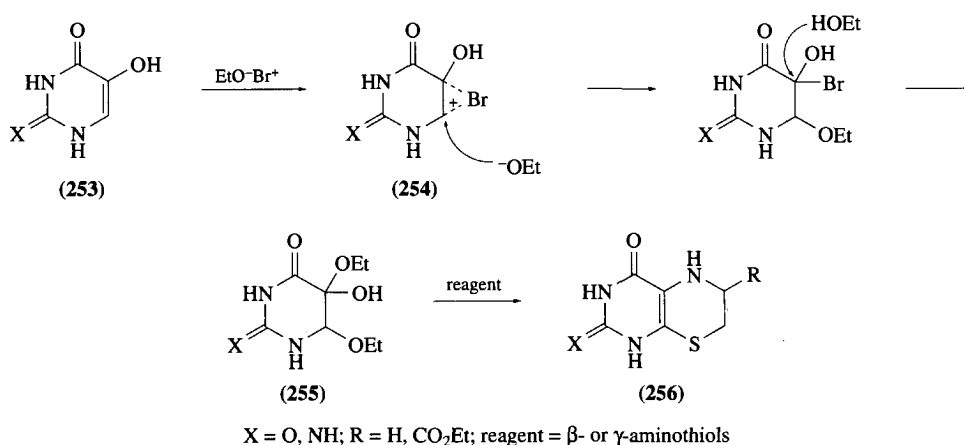


7.19.4.4.3 Ring syntheses

(i) Pyrimido[4,5-*b*][1,4]thiazines (**AB**)

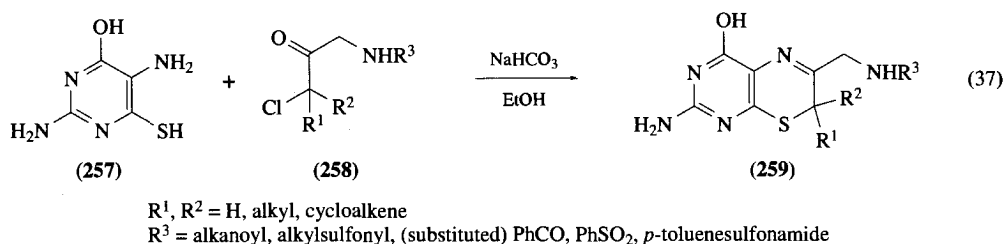
Pyrimido[4,5-*b*][1,4]thiazine can be obtained by a versatile and convenient method reported by Sako, Maki *et al.* <91JCS(P1)2675>: treatment of 5-hydroxyuracil (**253**; X = O) and 5-hydroxyisocytosin (**253**; X = NH) with *N*-bromosuccinimide in ethanol followed by the thermal condensation with β - and γ -aminothiols such as 2-aminothiophenol, cysteamine, L-cysteine, and D,L-homocysteine resulted in the formation of the pyrimido[4,5-*b*][1,4]thiazines (**256**). This new method for the construction of pyrimido[4,5-*b*][1,4]thiazine ring systems was shown to involve the condensation of 5,6-diethoxy-5-hydroxy-5,6-dihydropyrimidin-4(3*H*)-one intermediates (**255**) with β - and γ -aminothiols which is accelerated in the presence of an acid catalyst (Scheme 42).

This technique can also be used to build up benzo condensed pyrimido[4,5-*b*][1,4]thiazines and pyrimido[4,5-*b*][1,4]thiazepines.

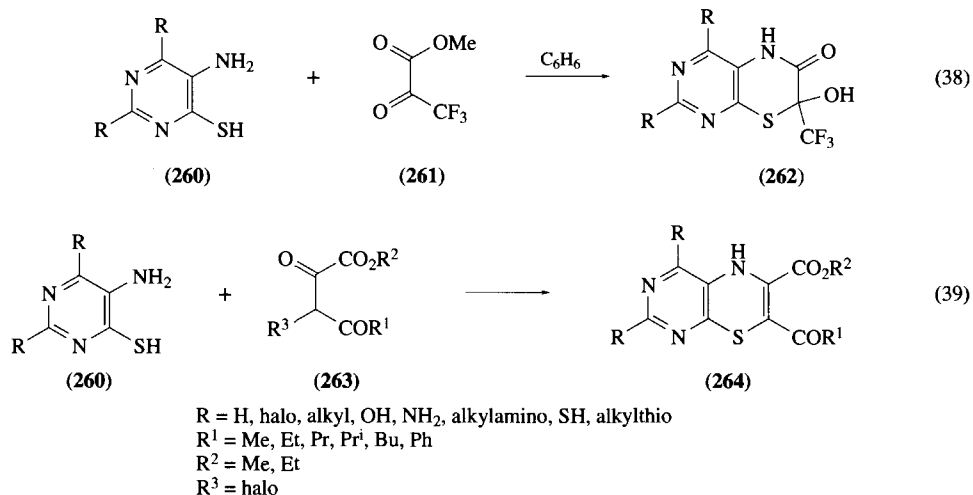


Scheme 42

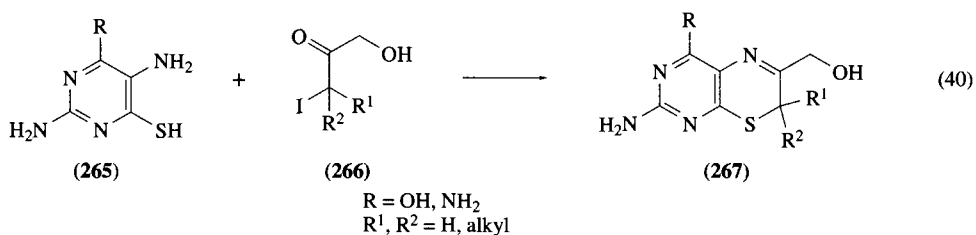
Another method for preparing pyrimido[4,5-*b*][1,4]thiazines is to reflux 2,5-diamino-4-hydroxy-6-thiopyrimidine (**257**) in ethanol with *N*-(3-chloro-2-oxopropyl)-*p*-toluenesulfonamide (**258**) and NaHCO₃ <90GEP3919214>. The resulting pyrimido[4,5-*b*][1,4]thiazines (**259**) are antimalarials (Equation (37)).



Pyrimido[4,5-*b*][1,4]thiazines (**262**) have been prepared by cyclocondensation of the aminothiols (**260**) with methyl trifluoropyruvate (**261**) in benzene <89KGS1492>, or with 4-substituted 3-halo-2,4-dioxobutyrates (**263**) at pH 2-5 in DMF to give 6-carbethoxy-7-acyl derivatives of 5*H*-pyrimido[4,5-*b*][1,4]thiazines (**264**) (Equations (38) and (39)).

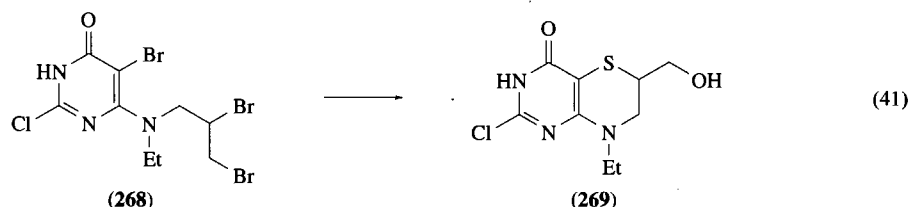


Another method for preparing substituted pyrimido[4,5-*b*][1,4]thiazines (**267**) is to cyclize 2,5-diaminopyrimidine-6-thiols (**265**) with 1-iodo-3-hydroxyacetones (**266**) (Equation (40)) <82EUP51852>. The resulting substituted pyrimido[4,5-*b*][1,4]thiazine is a synergist for sulfisoxazole and trimethoprim against *E. coli*.



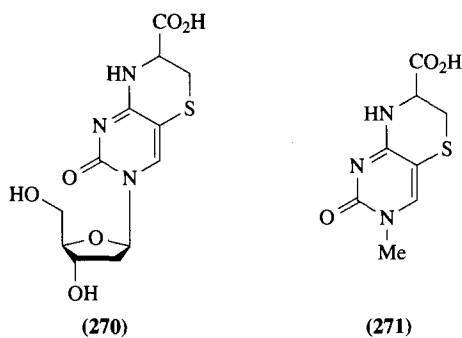
(ii) Pyrimido[5,4-*b*][1,4]thiazines (AC)

These compounds are also known as thiapteridines. Most syntheses of pyrimido[5,4-*b*][1,4]thiazines were developed for pteridines and then adapted for the thio analogues. Thus, the cyclization of polyfunctionalized pyrimidinones (e.g. (**268**) $\rightarrow$ (**269**)) is a well-known method (Equation (41)) <92H(34)729>.



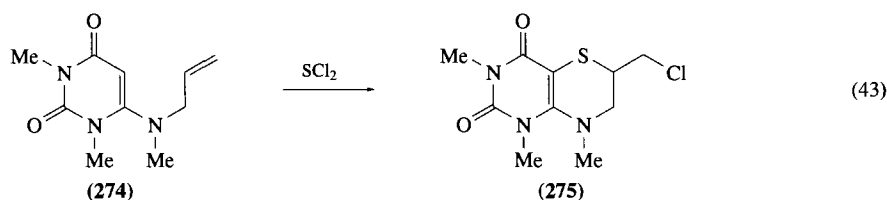
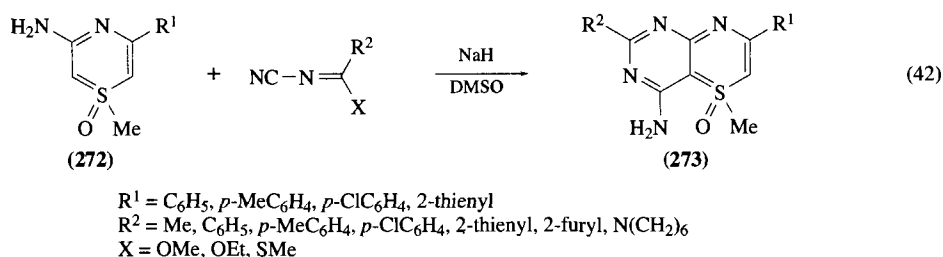
Pal *et al.* <88MI 719-02> have reported a synthesis of pyrimido[5,4-*b*][1,4]thiazine nucleosides: 5-bromo- or 5-iodo-deoxycytidine undergo 100% dehalogenation to 2'-deoxycytidine on heating with cysteine in 1 N aqueous potassium carbonate solution, whereas 1-methyl-5-chlorocytosine undergoes very little dehalogenation forming the cyclocondensation products (**270**) and (**271**) besides uncondensed products.

Several pyrimido[5,4-*b*][1,4]thiazin-*S*-oxides (**273**) have been prepared by Ried and Kuhnt

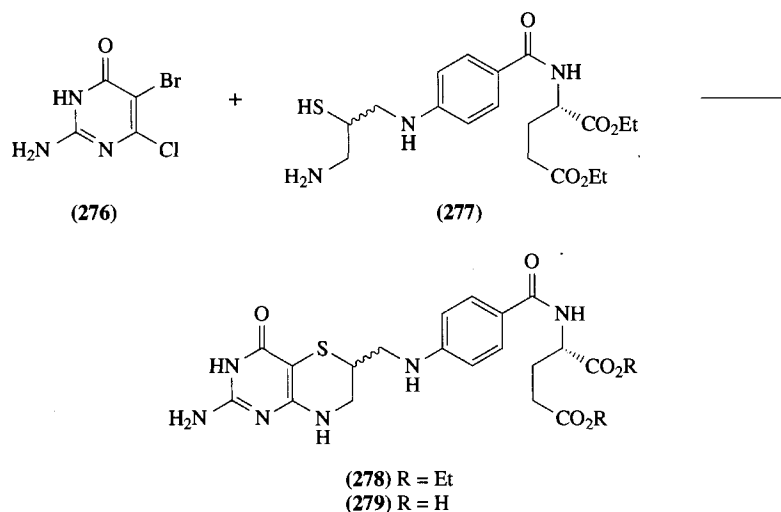


<87LA551> using 1-methyl-1,4-thiazin-1-oxides (**272**) and 1,3-biselectrophiles. Cyclocondensation gave the expected products in 35–96% yield (Equation (42)).

The cyclization of 1,3-dimethyluracil-6-(allylmethyl)amine (**274**) with sulfur dichloride also affords pyrimido[5,4-*b*][1,4]thiazines (**275**) (Equation (43)) <85IJC(B)1166>.



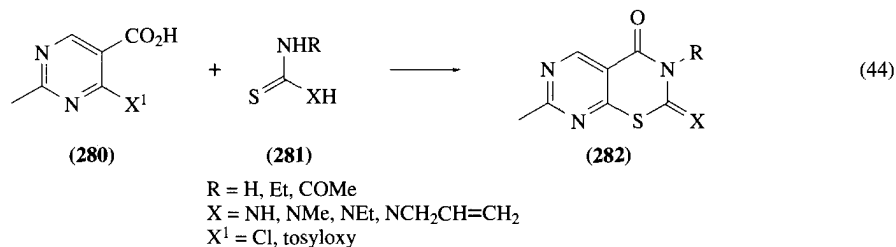
N-(*p*-{[(2-Amino-6,7-dihydro-4-oxo(3*H*),(8*H*)pyrimido[5,4-*b*][1,4]thiazine-6-yl)methyl]-amino}benzoyl)glutamic acid (**279**), a deaza-thia analogue of tetrahydrofolic acid, was first synthesized as a diastereoisomeric mixture by the thermal condensation of 5-bromo-6-chlorocytosine (**276**) with diethyl *N*-{*p*-[(3-amino-2-thiolopropyl)amino]benzoyl}glutamate (**277**) via an aliphatic *S*-*N* Smiles rearrangement in ethanolic pH 7 phosphate buffer solution followed by smooth alkaline hydrolysis of the ester protecting groups (Scheme 43) <94JCS(P1)833>.



Scheme 43

(iii) *Pyrimido[5,4-e][1,3]thiazines (AD)*

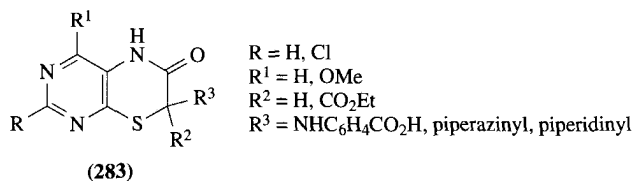
In the reactions of 4-chloro and 4-tosyloxy-2-methylpyrimidine-5-carboxylic acids (**280**) with thioureas (**281**) derivatives of 2,3-dihydro-1-methylpyrimido[5,4-e][1,3]thiazines (**282**) have been obtained (Equation (44)) <89MI 719-06>.

7.19.4.4 *Important compounds and applications*

The proceedings of a conference on the radio-labeling of antitumor pyrimidothiazines has been published <B-82MI 719-04>.

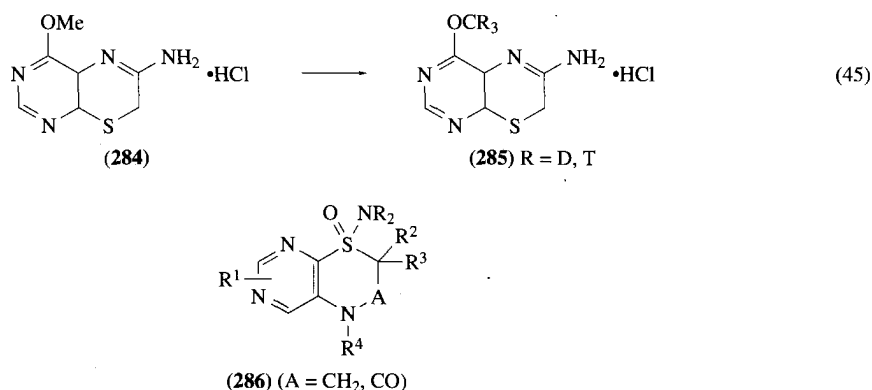
(i) *Pyrimido[4,5-b][1,4]thiazines (AB)*

Some 7-amino derivatives of 5*H*-pyrimido[4,5-*b*][1,4]thiazin-6-ones (**283**) have been reported to have antitumor activity <82MI 719-01>.



Tomizine (**284**) (4-methoxy-6-aminopyrimido[4,5-*b*][1,4]thiazine hydrochloride) is a neoplasmodic inhibitor. For pharmacokinetic studies tomizine was labeled with deuterium and tritium in the 4-methoxy group (**285**) (Equation (45)) <89MI 719-07>.

Pyrimido[4,5-*b*][1,4]thiazines (**286**) have been shown to be muscle relaxants <91JAP(K)3118380>.

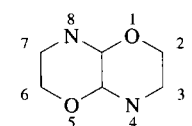
(ii) *Pyrimido[5,4-b][1,4]thiazines (AC)*

Some compounds like [((aminooxypyrimido[5,4-*b*][1,4]thiazin-6-yl)alkyl)benzoyl]amino]pentandioates (**279**) have been disclosed as inhibitors of the enzyme glycine ribonucleotide formyl transferase (GARFT) <93USP10861>.

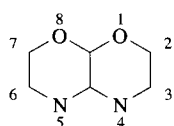
7.19.5 OXAZINOXAZINES

7.19.5.1 Introduction

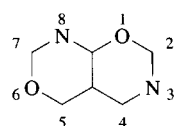
Examples of the following four oxazinoxazines are known in the literature: 1,4-oxazino[3,2-*b*][1,4]oxazine (**AE**), 1,4-oxazino[2,3-*b*][1,4]oxazine (**AF**), 1,3-oxazino[5,4-*e*][1,3]oxazine (**AG**), 1,3-oxazino[5,4-*d*][1,3]oxazine (**AH**).



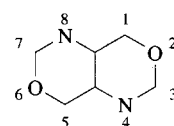
(**AE**) 1,4-[3,2-*b*][1,4]



(**AF**) 1,4-[2,3-*b*][1,4]



(**AG**) 1,3-[5,4-*e*][1,3]



(**AH**) 1,3-[5,4-*d*][1,3]

7.19.5.2 Theoretical and Experimental Structural Methods

(i) 1,4-Oxazino[3,2-*b*][1,4]oxazines (**AE**)

X-ray crystal structure determinations <80JCR(S)349, 85TL1853, 86CB887, 91BSF952, 92CJC2764> are available and so are ^{13}C NMR spectra <92CJC(70)2764>, ^1H NMR spectra <77MI 719-01>, and 2d-CH experiments <92CJC(70)2764>. A three-step mechanism for ring-chain tautomerism has been proposed <92JOC2446> and is based on the collected NMR data. These are also used to describe the stereoelectronic effects in the conformational behavior of 1,4-oxazino[3,2-*b*][1,4]oxazines <92T(48)2715>.

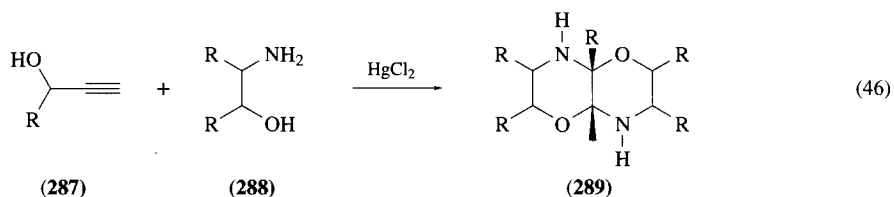
7.19.5.3 Reactivity

Although there is information on the structure and physical data of oxazinoxazines there is nothing reported about their reactivities. No syntheses starting with these systems have been described.

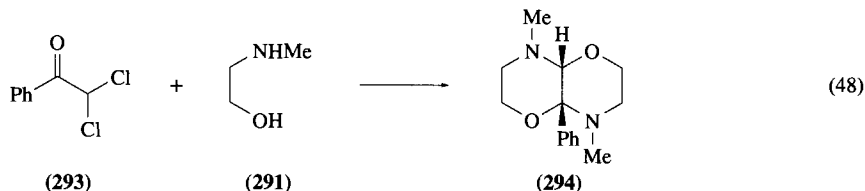
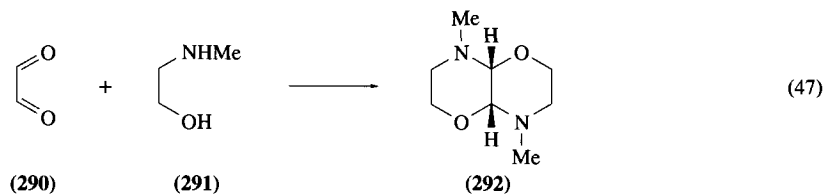
7.19.5.4 Ring Syntheses

(i) 1,4-Oxazino[3,2-*b*][1,4]oxazines (**AE**)

Several syntheses for the preparation of 1,4-oxazino[3,2-*b*][1,4]oxazine derivatives are known. The reaction of 2-propyn-1-ols (**287**) with 2-aminoalcohols (**288**) and mercury(II) chloride gives *cis*-1,4-oxazino[3,2-*b*][1,4]oxazine derivatives (**289**) (Equation (46)) <86CB887>.

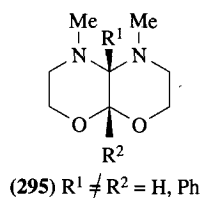


Another strategy is the reaction of 2-methylaminoethanol (**291**) with glyoxal (**290**) <85TL(26)1853> or 2,2-dichloroacetophenone (**293**) <80JCR(S)349> to give the products (**292**) and (**294**), respectively (Equations (47) and (48)).



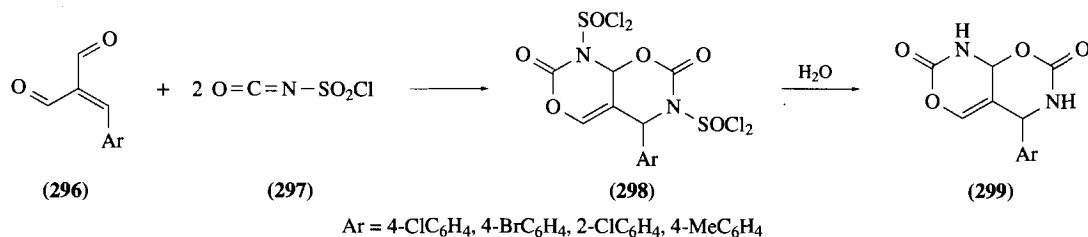
(ii) 1,4-Oxazino[2,3-b][1,4]oxazines (**AF**)

The 1,4-oxazino[2,3-b][1,4]oxazines (**295**) are prepared in the same way as the isomers (**294**) <80JCR(S)349> and appear as side products in the reaction ((**293**) + (**291**) → (**294**)). The isomers can be separated by fractional crystallization.



(iii) 1,3-Oxazino[5,4-e][1,3]oxazines (**AG**)

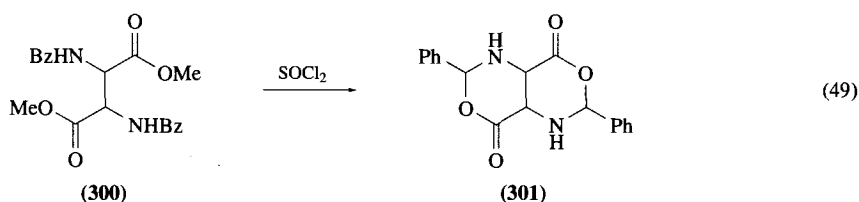
The cycloaddition of two equivalents of chlorosulfonyl isocyanate (**297**) with (arylmethylene)malonaldehydes (**296**) affords the fused 1,3-oxazin-2-one derivatives (**298**) which can be hydrolysed to the derivatives (**299**) (Scheme 44) <92T(48)4551>.



Scheme 44

(iv) 1,3-Oxazino[5,4-d][1,3]oxazines (**AH**)

The cyclocondensation of *meso*-[MeO₂CCH(NHBz)]₂ (**300**) with SOCl₂ gives the 1,3-oxazino[5,4-d][1,3]oxazine-1,5-dione (**301**) (Equation (49)) <79AP(312)968>.



7.19.5.5 Important Compounds and Applications

No applications of oxazinooxazines have been described. Only one patent on 1,4-oxazino[3,2-*b*][1,4]oxazines has been reported <75IZV1365>, and the oxazinooxazines seem to be compounds of lesser interest.

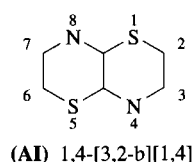
7.19.6 OXAZINOTHIAZINES

No examples of these heterocyclic ring systems have been reported.

7.19.7 THIAZINOTHIAZINES

7.19.7.1 Introduction

Only the symmetric 1,4-thiazino[3,2-*b*][1,4]thiazine system (**AI**) has been reported <87JA4308>.

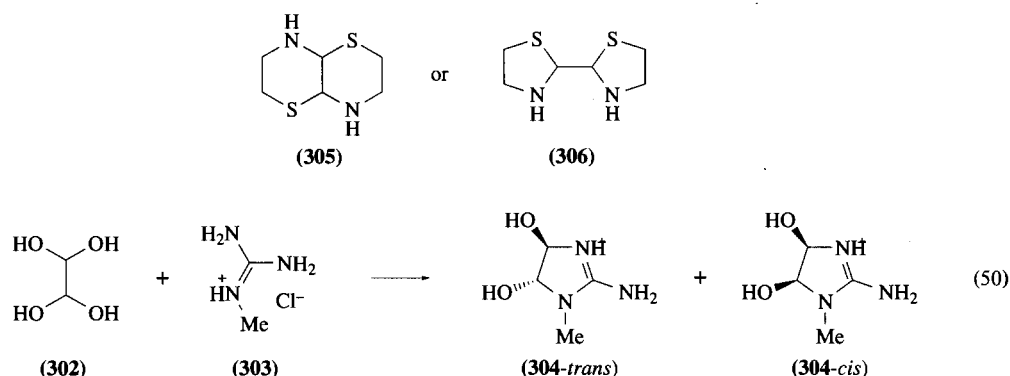


7.19.7.2 Theoretical and Experimental Structural Methods

Proton NMR data is available <87JA4308> for compound (**305**) but the structure (**306**) cannot be eliminated. Other experimental data have not been reported yet.

7.19.7.3 Ring Syntheses

The described synthesis of 1,4-thiazino[3,2-*b*][1,4]thiazine (**305**) <87JA4308> starts with the reaction of aqueous glyoxal (**302**) with *N*-methylguanidinium chloride (**303**) in water (pH 8). The resulting 2-amino-4,5-dihydro-4,5-dihydroxy-1-methylimidazolium chloride (**304**) is treated with 2-aminoethane thiol in H₂O (pH 8–9) to give either (**305**) or (**306**). The NMR spectrum of the product supports both of the structures (**305**) and (**306**): there is only one diastereomer <87JA4308>.



7.20

Bicyclic 6-6 Systems: Five or More Heteroatoms

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7.20.1 INTRODUCTION

The material covered in this chapter deals with ring systems comprising two fused six-membered heterocyclic rings having five or more heteroatoms at positions other than the ring fusion positions. There are 44 different ring systems of this type known, of which 26 are diazino ring systems. There are none having five heteroatoms distributed 1:4 between the two rings, none having seven heteroatoms, and only one having eight heteroatoms. Pyrimido[5,4-*e*]-1,2,4-triazines (**8**) dominate the chapter. These are 7-azapteridines, and there are more references in the literature to them than to all of the other ring systems put together.

Structures (**1**)–(**44**) show all the ring systems known which contain two fused six-membered heterocyclic rings having five or more heteroatoms at positions other than the ring fusion positions including diazinotriazines, diazinothiadiazines, diazinooxadiazines and diazinodioxazines, dioxino-, oxazino-, and thiazino-ring systems, triazino ring systems, and other known systems. The material in the rest of the chapter is then organized following the standard arrangement of material in all chapters of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). It is not arranged according to ring system.

7.20.2 THEORETICAL METHODS

In the mid-1960s, energy levels, wave functions, and charge densities were calculated for 74 azanaphthalenes, including many of the ring systems dealt with in this chapter <66JSP(19)25>. Since then, further work has been carried out on two of the possible isomeric pyrimidotriazine ring systems, and π -electron densities and frontier electron densities have been calculated for toxoflavin (**45**) and fervenulin (**46**), as well as for the 6-azalumazine (**47**), using Hückel LCAO–MO methods <76JCS(P1)713, 78CPB367>. Also calculated have been the spin densities for a radical anion observed by ESR during a demethylation reaction of toxoflavin (**45**) <73JA5735>, as well as for a radical anion derived from the 4-*N*-oxide of toxoflavin <75CPB2001>. In the mid-1980s, CNDO/2 calculations have been used to show that the charge density on N-4 in the tetrahydropyrazino-[2,3-*e*]-1,2,4-triazine (**48**) is higher than on either N-1 or N-2, a result in agreement with the hydrogen bonding pattern seen in the crystal structure of this compound <86JHC33>. Apart from these few examples, little theoretical work has been reported on the heterocyclic systems covered in the present chapter.

7.20.3 EXPERIMENTAL STRUCTURAL METHODS

7.20.3.1 Introduction

Spectroscopic data accompany most of the work on the ring systems discussed here. The extreme diversity of systems, however, makes it impossible in the space available to summarize or collate all the data in any useful way, and in any event the information is for the most part routine. Accordingly, the discussion focuses largely on specialized and out-of-the-ordinary spectroscopic applications, devoted to solving particular problems. Attention is drawn, nevertheless, to original source material which carries useful compilations of routine data.

7.20.3.2 NMR Spectroscopy

A commonly observed phenomenon in proton NMR is the nonequivalence due to restricted rotation of the two methyl groups of an NMe₂ substituent. 5-Dimethylamino-3-methylpyrimido[5,4-*e*]-1,2,4-triazine (**49**), a 7-azapteridine, displays this property and exhibits two methyl singlets in TFA and also in DMSO solution (δ 4.30, δ 3.88, and δ 3.7, δ 3.3, respectively). The corresponding

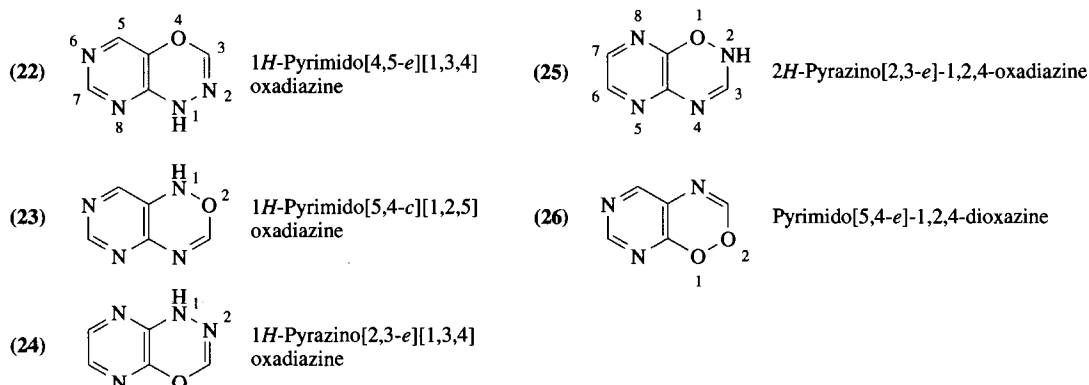
Diazinotriazines

(1)	Pyridazino[3,4- <i>e</i>]-1,2,4-triazine	(5)	Pyrimido[4,5- <i>d</i>]-1,2,3-triazine
(2)	Pyridazino[4,3- <i>e</i>]-1,2,4-triazine	(6)	Pyrimido[4,5- <i>e</i>]-1,2,4-triazine
(3)	Pyridazino[4,5- <i>d</i>]-1,2,3-triazine	(7)	Pyrimido[5,4- <i>d</i>]-1,2,3-triazine
(4)	Pyridazino[4,5- <i>e</i>]-1,2,4-triazine	(8)	Pyrimido[5,4- <i>e</i>]-1,2,4-triazine
		(9)	Pyrazino[2,3- <i>e</i>]-1,2,4-triazine

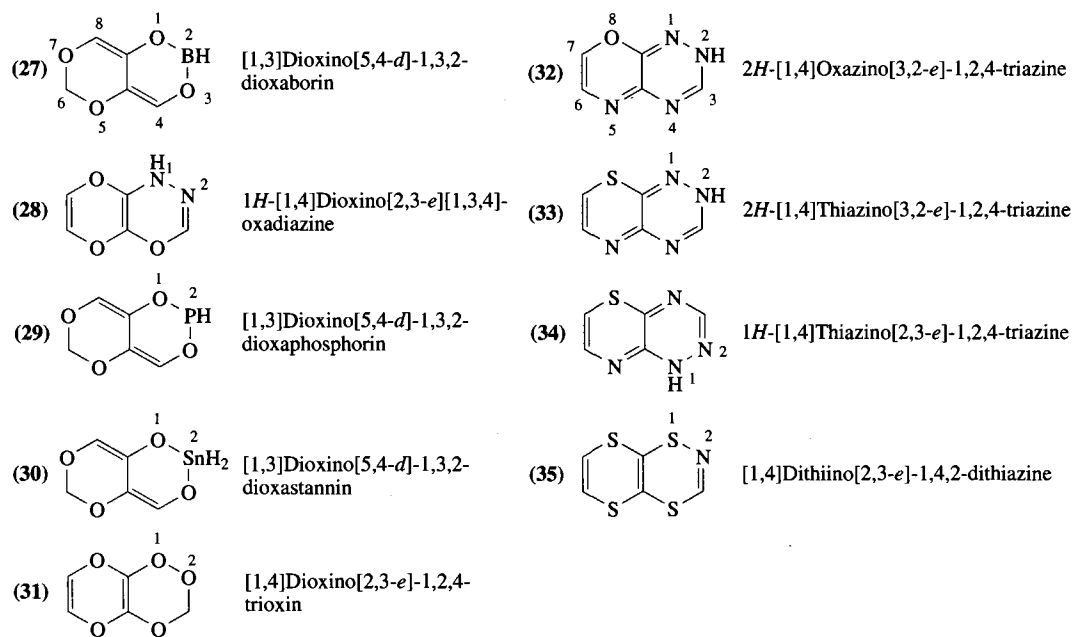
Diazinothiadiazines

(10)	1 <i>H</i> -Pyridazino[3,4- <i>e</i>][1,3,4]-thiadiazine	(15)	1 <i>H</i> -Pyrimido[4,5- <i>c</i>][1,2,6]thiadiazine
(11)	1 <i>H</i> -Pyridazino[4,3- <i>e</i>][1,3,4]-thiadiazine	(16)	1 <i>H</i> -Pyrimido[4,5- <i>e</i>][1,3,4]thiadiazine
(12)	1 <i>H</i> -Pyridazino[4,5- <i>e</i>][1,3,4]-thiadiazine	(17)	1 <i>H</i> -Pyrimido[5,4- <i>e</i>][1,3,4]thiadiazine
(13)	2 <i>H</i> -Pyridazino[4,5- <i>e</i>]-1,2,4-thiadiazine	(18)	2 <i>H</i> -Pyrimido[4,5- <i>e</i>]-1,2,4-thiadiazine
(14)	2 <i>H</i> -Pyridazino[3,4- <i>e</i>]-1,2,3-thiadiazine	(19)	1 <i>H</i> -Pyrazino[2,3- <i>c</i>][1,2,6]thiadiazine
		(20)	1 <i>H</i> -Pyrazino[2,3- <i>e</i>][1,3,4]thiadiazine
		(21)	2 <i>H</i> -Pyrazino[2,3- <i>e</i>]-1,2,4-thiadiazine

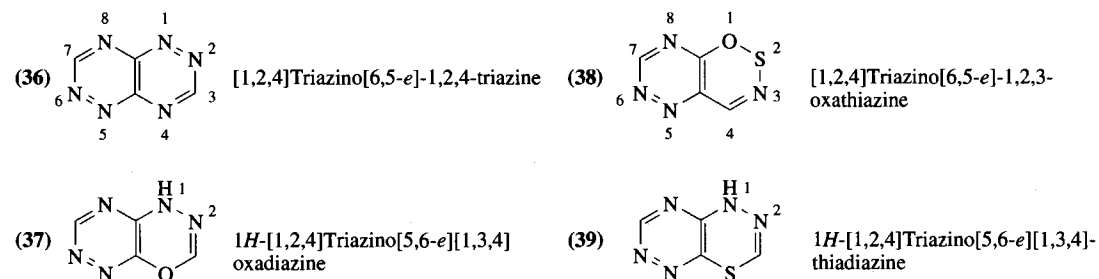
Diazinooxadiazines and diazinodioxazines



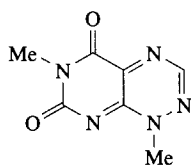
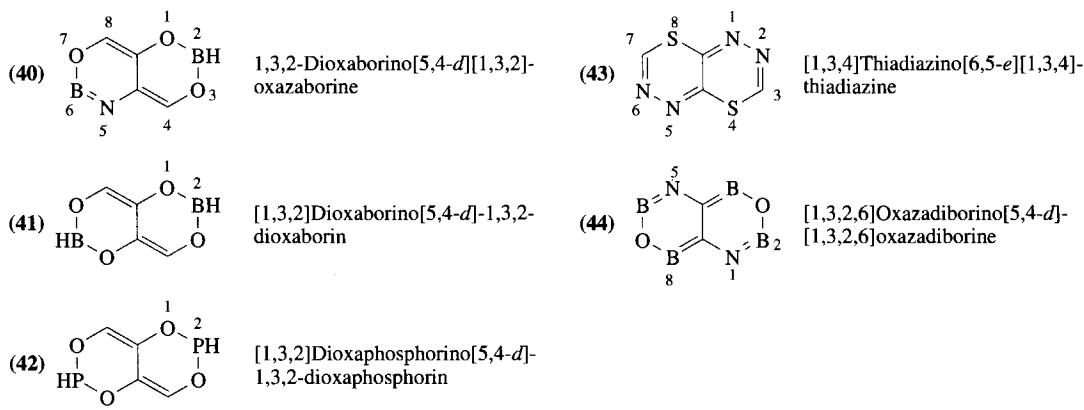
Dioxino-, Oxazino-, and Thiazino- ring systems



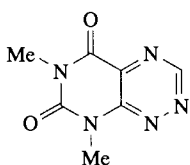
Triazino ring systems



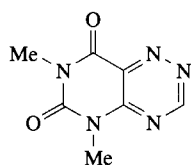
Other systems



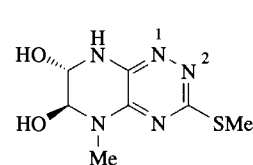
(45) toxoflavin



(46) fervenulin

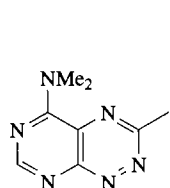


(47)

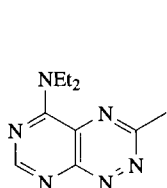


(48)

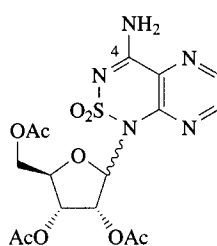
diethyl compound (50) in TFA exhibits two 2-proton quartets (δ 4.67, δ 4.32) and two 3-proton triplets (δ 1.63, δ 1.51) $\langle$ 71AJC633 $\rangle$. In a 4-aminopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide the two amino protons may sometimes have the same chemical shift. In each of the two nucleosides (51) and (52), however, the protons of the 4-amino groups are magnetically nonequivalent, again due to restricted rotation, and in the NMR spectra each amino group appears as a pair of doublets, revealing geminal coupling through the nitrogen atom. The glucoside (52) has a β -anomeric configuration, as shown by the coupling constant value, $J_{1,2} = 9$ Hz. In this glucoside (52) there is also restricted rotation about the glycosidic bond, which manifests itself in discrete rotamers observable by NMR (see Section 7.20.4) $\langle$ 86LA1872, 87LA961 $\rangle$.



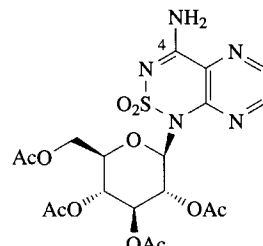
(49)



(50)



(51)

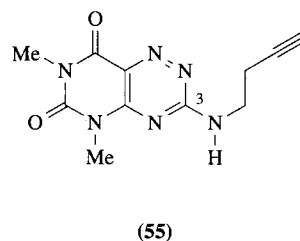
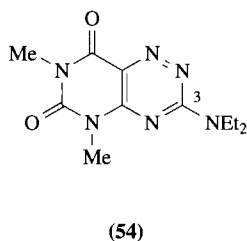
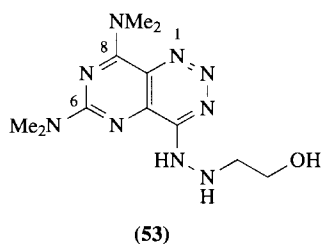


(52)

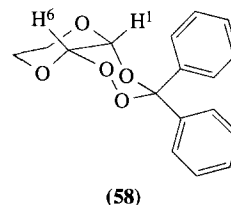
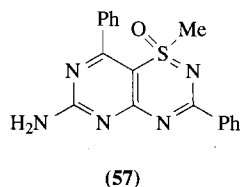
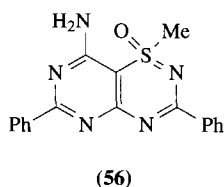
A study on restricted rotation has been carried out on the pyrimido[5,4-*d*]-1,2,3-triazine (53) which contains two NMe₂ groups at positions 6 and 8. At 20°C these give rise to two six-proton singlets at δ 3.14 and δ 3.55. At -40°C, however, each of these singlets splits into a pair of peaks, at δ 3.08 and δ 3.18, and at δ 3.24 and δ 3.79, respectively. The latter pair, with the greatest chemical shift difference (45.0 Hz), is assigned to the 8-NMe₂ group, since one of the methyl groups in this would be affected much more than the other by the lone pair on N-1, thus accentuating the difference in their chemical shifts. The 6-NMe₂ group can more readily adopt a coplanar conformation than can the 8-NMe₂, and it therefore has the higher energy barrier to rotation: 13.93 kcal mol⁻¹ (58.31 kJ mol⁻¹) vs 13.44 kcal mol⁻¹ (56.26 kJ mol⁻¹) $\langle$ 84JCS(P1)1475 $\rangle$.

Two examples of restricted C—N bond rotation at position 3 of pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) are to be found in compounds (54) and (55). The NMR spectrum of (54) shows

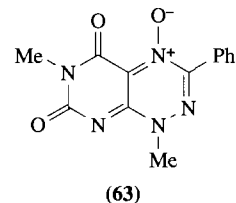
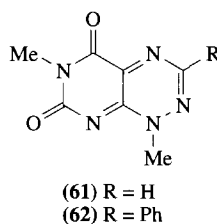
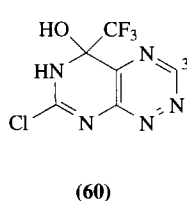
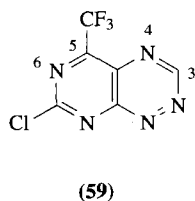
two nonequivalent ethyl groups, while the spectrum of compound (**55**) reveals two NH signals which coalesce at 90°C <88JOC800>.



The pyrimido[4,5-*e*]-1,2,4-thiadiazine derivative (**56**) furnishes an example of a nuclear Overhauser effect (NOE) measurement. Irradiation of the NH₂ group in compound (**56**) gives a 7% NOE for the adjacent methyl group on sulfur, and serves to distinguish this structure from its isomer (**57**) <87S940>. Another example comes from the [1,4]dioxino[2,3-*e*]-1,2,4-trioxin compound (**58**), for which the observed large vicinal NOE enhancements of H-1 (17.4%) and H-6 (15.3%) require a *cis* ring fusion <86TL2953>.



Proton NMR may also be used to determine the site of covalent solvation. For example, in the pyrimido[5,4-*e*]-1,2,4-triazine (**59**) water adds to the 5,6 position, giving hydrate (**60**). Hydration at the 3,4 position is precluded, since H-3 in the hydrate (**60**) still resonates at very low field (δ 9.9) <71JCS(C)2475, 74JCS(P1)1565>. Also of interest is the observation that addition of adenosine to a solution of toxoflavin (**61**) causes an upfield shift of protons in the latter, and a downfield shift of protons in the purine, up to a certain concentration. At higher concentrations this trend is reversed. These results have been interpreted in terms of molecular stacking of the triazine molecules, both with themselves and with the purine molecules <73IZV480>. And finally, the two methyl groups of 3-phenyltoxoflavin (**62**) are found to resonate at δ 3.64 and δ 4.63 in TFA solution. In the 4-*N*-oxide derivative (**63**), however, these two resonances move to higher field, at δ 3.48 and δ 4.40, respectively <75CPB2001>.

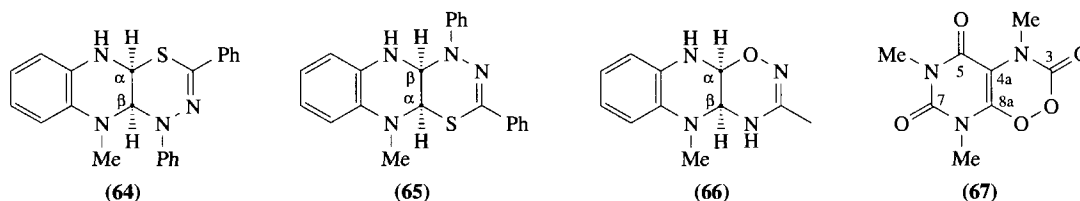


Comprehensive tables of routine proton NMR data on pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) (**8**) may be found in <70JCS(C)139, 70JCS(C)2661, 73AJC1689, 74AJC1781, 74JOC2866, 75JOC2205, 87JHC1657>, and routine data on the 2,2-dioxides of pyrazino[2,3-*c*][1,2,6]thiadiazines (**19**) in <84JHC861, 88JHC891, 91LA301>. Routine proton NMR data for some less common ring systems may be found as follows: pyrazino[2,3-*e*]-1,2,4-triazines (**9**) <86JHC33>, pyridazino[4,5-*e*][1,3,4]thiadiazines (**12**) <90S1020, 92JHC825>, pyrimido[4,5-*c*][1,2,6]thiadiazines (**15**) <77HCA521>, pyrimido[4,5-*e*][1,3,4]thiadiazines (**16**) <81JHC799, 85JHC381>, pyrazino[2,3-*e*][1,3,4]thiadiazines (**20**) <81JHC799, 86MRC777>, pyrazino[2,3-*e*]-1,2,4-oxadiazines (**25**) <86MRC777>, [1,2,4]triazino[6,5-*e*]-1,2,4-triazines (**36**) <88S877>, and [1,2,4]triazino[5,6-*e*][1,3,4]thiadiazines (**39**) <88S778>.

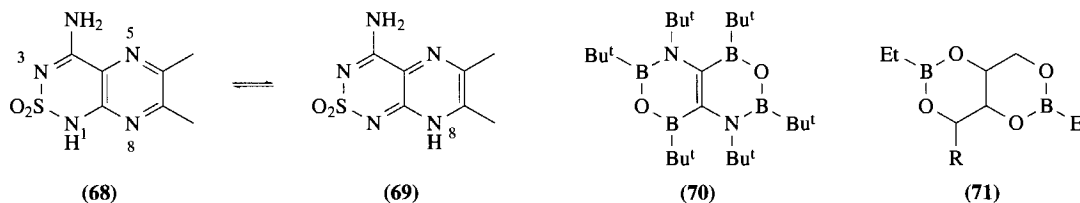
Carbon-13 NMR assignments have been made for some of the ring systems under review. Comprehensive data are available for the 2,2-dioxides of pyrazino[2,3-*c*][1,2,6]thiadiazines (**19**)

<88H(27)2201, 88JHC891, 88JST423, 88LA121, 90JHC785, 92JMC3977>, and routine data are also available for pyrazino[2,3-*e*]-1,2,4-triazines (**9**) <86JHC33>.

Carbon-proton coupling may be used to effect in the assignment of structure. The carbon atoms marked α in compounds (**64**)–(**66**) are attached to either sulfur or oxygen atoms, both being more electronegative than nitrogen, and the coupling between these carbons and their attached hydrogens is greater than the corresponding coupling for the carbons marked β , by about 10 Hz. This allows a differentiation between regioisomers (**64**) and (**65**) <86MRC777>. Coupling of carbon atoms with *N*-methyl groups may also be useful. In the pyrimido[5,4-*e*]-1,2,4-dioxazine (**67**), carbons 3, 4a, 5, and 8a all appear as quartets on account of coupling with the adjacent *N*-methyl groups. Carbon 7 appears as a heptet, being coupled to two adjacent *N*-methyl groups. All coupling constants are 7 Hz <90JHC667>.



The tautomeric equilibrium between structures (**68**) and (**69**) can be demonstrated by natural abundance ^{15}N NMR. Although the 1-*H* tautomer (**68**) predominates, establishment of the equilibrium is sufficiently slow to cause broadening of the signals for N-1 and N-8. The N-3 and N-5 signals are sharp. In DMSO solution, and relative to CH_3NO_2 , the observed chemical shifts are: N-1, δ 251.5 (broad); N-3, δ 178.9; N-5, δ 59.8; N-8, δ 86.1 (broad); NH_2 , δ 284.0 <88H(27)2201>. The ^{11}B nuclei in the [1,3,2,6]oxazadiborino[5,4-*d'*][1,3,2,6]oxazadiborine (**70**) resonate in CHCl_3 solution as two singlets at δ 37.0 and δ 46.3 <90AG(E)900>, and in [1,3,2]dioxaborino[5,4-*d'*]-1,3,2-dioxaborins of type (**71**) the ^{11}B nuclei resonate in the region δ 31–35 <80AG(E)548, 80LA1176>.

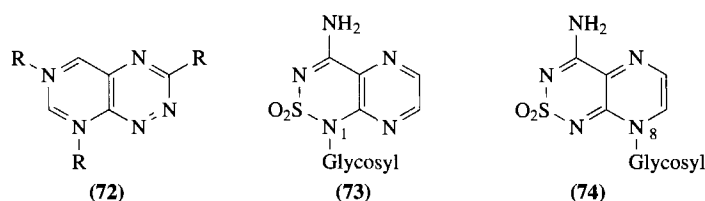


7.20.3.3 UV Spectroscopy

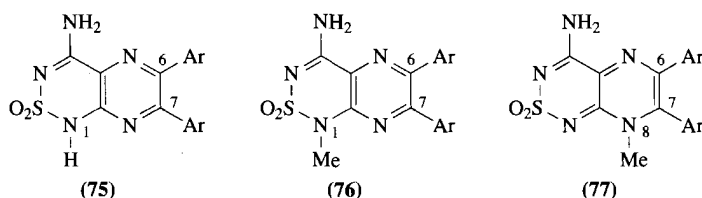
UV spectra of compounds based on the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) ring system (**72**) have been thoroughly documented. These typically show their most intense absorption peak below 220 nm, with another shouldered peak in the 300–325 nm region. There is also a low intensity $n \rightarrow \pi^*$ absorption at about 500 nm which accounts for the characteristic orange to red color of these compounds <70JCS(C)139>. Extensive tables of UV data for this ring system may be found in <70JCS(C)2661, 71AJC633, 73AJC1689, 74AJC1781, 74JOC2866, 75JOC2205>.

The 2,2-dioxides of pyrazino[2,3-*c*][1,2,6]thiadiazines (**19**) have also received substantial attention for their UV spectra <84JHC861, 88LA121>, and the position of attachment of the sugar in N-1 and N-8 glycosides (**73**) and (**74**) can be assigned by comparing their UV spectra with the corresponding spectra of *N*-methyl model compounds <86LA1872, 87LA961, 90JHC785>.

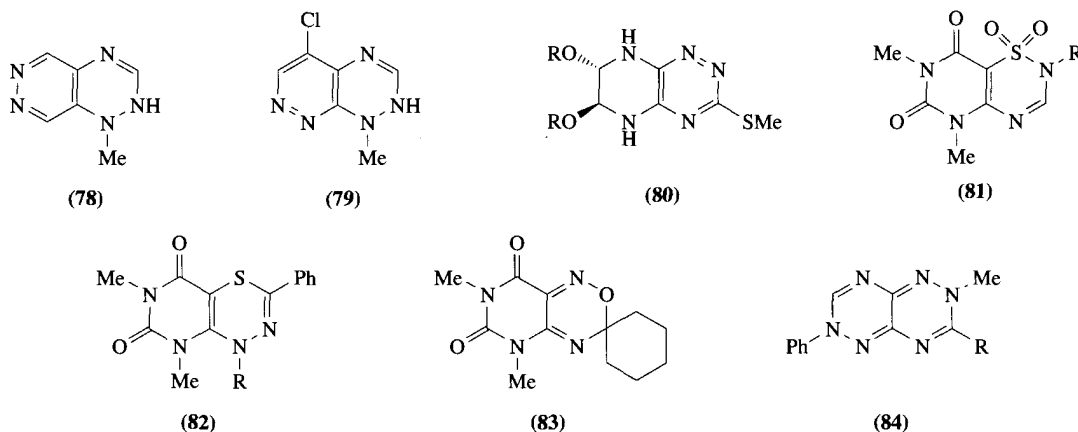
A detailed study has been made of the spectroscopic properties and photostability of other



derivatives, (75)–(77), of the same ring system <90MI 720-01>. Compounds of type (75) and (76) have very low quantum yields of photolysis, with the exact value depending upon the 6- and 7-substituents, whereas photolysis is observed for the 8-methyl compounds (77). Compounds (75) and (76) show a strong absorption maximum in the region 360–410 nm. In contrast, the 8-methyl compounds (77) absorb at higher wavelengths (440–470 nm) with markedly reduced extinction coefficients. The 1-methyl compounds (76) exhibit much higher fluorescence quantum yields than the 8-methyl derivatives, and also emit at shorter wavelengths. No phosphorescence is observed from any of these molecules.

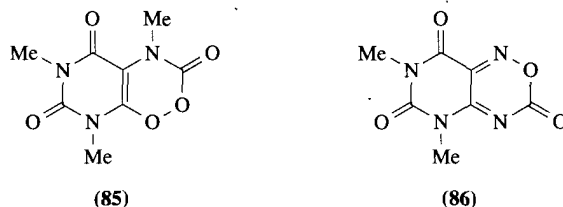


Various other ring systems for which routine UV data are available are exemplified by structures (78) <74JHC167>, (79) <74JHC167>, (80) <86JHC33>, (81) <63JOC1994>, (82) <85JHC381>, (83) <66LA(692)134>, and (84) <88S877>.



7.20.3.4 IR Spectroscopy

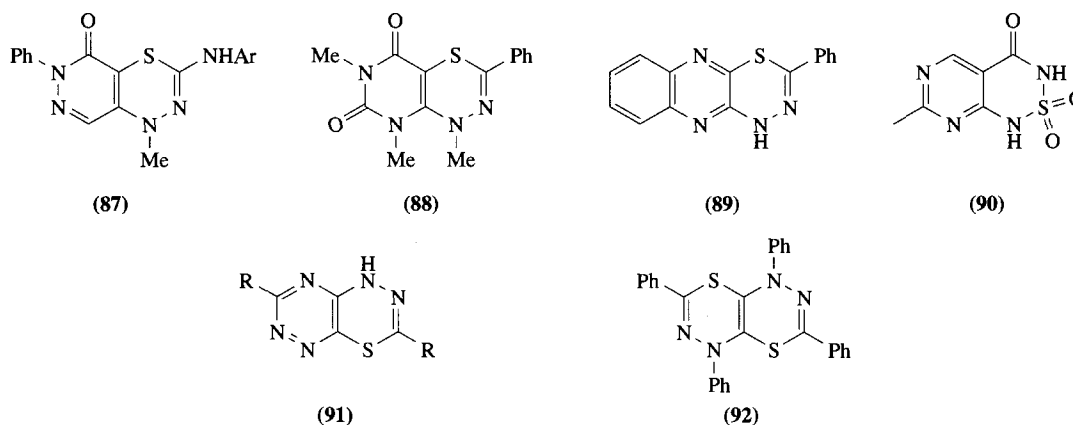
Infrared spectroscopy has not been an important tool in the study of the heterocyclic systems under review. Collections of data are available for pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) (8) <74JOC2866, 75JOC2205>. Of interest are the high frequencies of some of the carbonyl stretching bands in compound (85) (1840, 1795, and 1735 cm^{-1}) <90JHC667>, and compound (86) (1780 and 1740 cm^{-1}) <86JHC1661>.



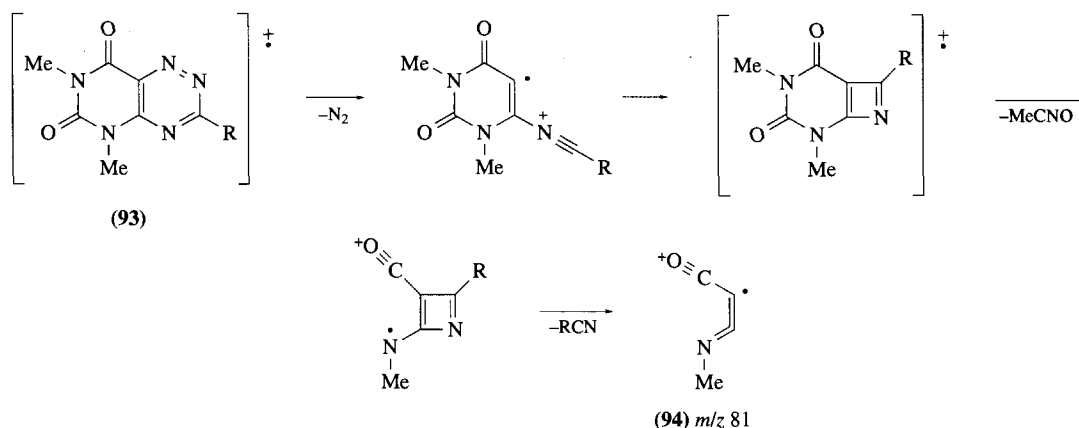
7.20.3.5 Mass Spectrometry

A feature in the mass spectra of many five- or six-heteroatom bicyclic systems is the stability of the parent ion. As a rule, this is either the most intense peak in the spectrum, or is a prominent

peak, as in the five-heteroatom systems (87)–(90) <77HCA521, 81JHC799, 85JHC381, 90S1020>, or the six-heteroatom systems (91) and (92) <71TL4985, 88S778>.

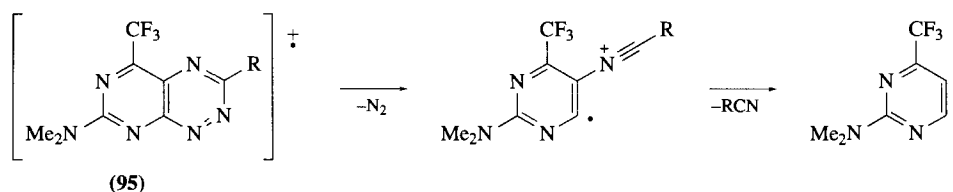


A few systems have been studied in more detail. Pyrimido[4,5-*e*]-1,2,4-triazines of type (93) (1,3-dimethyl-6-azalumazines) give a strong molecular ion, but the most intense peak in these compounds occurs typically at m/z 81, due to species (94) formed from (93) by successive loss of N_2 , MeCNO, and RCN (Scheme 1) <78CPB367>.

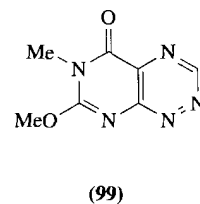
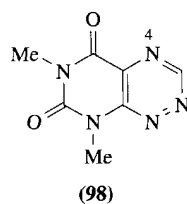
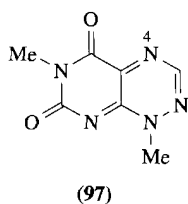
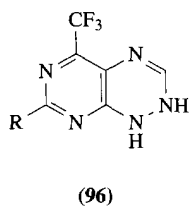


Scheme 1

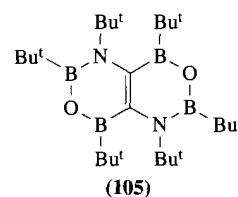
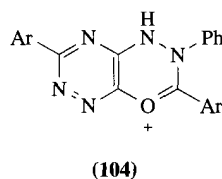
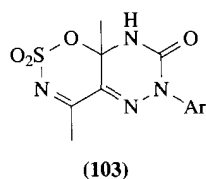
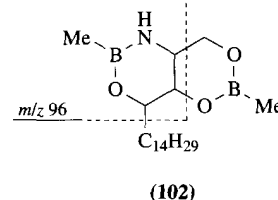
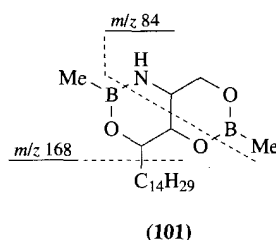
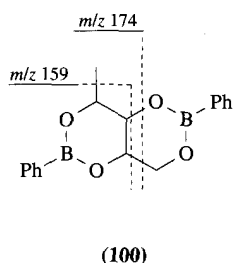
The isomeric pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) (95) characteristically lose N_2 from the triazine ring, followed by loss of HCN or nitrile (Scheme 2) <72OMS(6)467, 74JCS(P1)1565>. Fragmentation patterns have also been worked out for alkoxy derivatives of this ring system <74AJC1781>. The 1,2-dihydro derivatives (96) of the same series exhibit various fragmentation patterns which can be elucidated but there is no simple consistent pattern such as is found for the fully aromatic compounds <73OMS(7)225>. Toxoflavin (97), fervenulin (98), and their *O*-methyl isomer (99) all show a primary fragmentation leading to an $[M^+ - 28]$ species. Deuterium labeling, however, shows that while this corresponds to loss of N_2 in compounds (98) and (99), it corresponds to loss of CO in the isomer (97) <79KGS1270>. The 4-*N*-oxides of toxoflavin (97) derivatives, and also of fervenulin (98) derivatives, show very characteristic $[M^+ - 16]$ peaks, as well as strong parent ions <71TL851, 75CPB2001, 76JCS(P1)713, 77JHC175, 82JHC1309>.



Scheme 2



Mass spectra of phenylboronates derived from 1,3-diols, as in sugars, reveal characteristic fragmentations, for example as shown in compound (100) <72CC1051, 78AMS(7B)1578, 79CAR(72)35>, and the related cyclic boronate obtained from 4D-hydroxysphinganine shows prominent ions at m/z 84 (base peak), 96, and 168, arising from the fragmentations shown in Structures (101) and (102) <77OMS(12)651>. Finally, three other uncommon ring systems may be mentioned. In a series of compounds of type (103), which are derivatives of [1,2,4]triazino[6,5-*e*]-1,2,3-oxathiazine, all examples showed peaks at $[M^+ - \text{CONH}]$, $[M^+ - \text{SO}_2]$ and $[M^+ - \text{MeCNSO}_2]$ <91SC1695>. [1,2,4]Triazino[5,6-*e*][1,3,4]-oxadiazines of type (104) show a base peak of $[M^+ - \text{ArCO}]$ <87SI28>. And, in the mass spectrum of compound (105) the molecular ion M^+ is the strongest peak <90AG(E)900>.

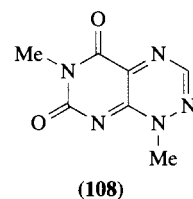
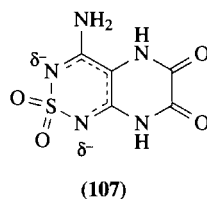
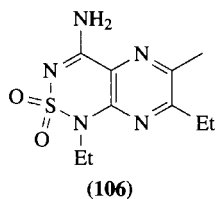


7.20.3.6 X-ray Crystallography

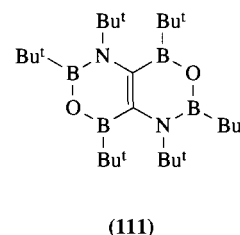
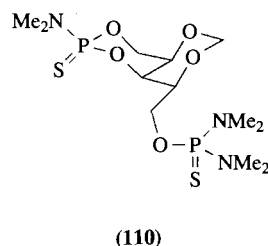
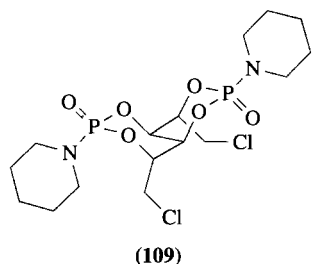
A few of the ring systems under review have been the subject of detailed x-ray structural investigation. Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides adopt an envelope conformation, with the sulfur atom at the flap. In compound (106), for example, the sulfur atom is 0.629 Å out of plane <88H(27)2201, 92JMC3977>. Compound (107), which contains the same ring system, crystallizes from aqueous media as an anion, with the crystals consisting of a three-dimensional network of hydrogen bonds involving all the oxygen and nitrogen atoms. The negative charge is counterbalanced by a H_3O^+ ion. The $\text{S}=\text{O}$ and $\text{C}=\text{O}$ bonds are elongated somewhat, and the thiadiazine presents an envelope conformation, puckered at the sulfur atom. Bond length measurements suggest a non-aromatic de-localized structure as in structure (107), and not an aromatic flat structure with the negative charge delocalized on to the $\text{S}=\text{O}$ groups <88JST(172)423>.

Another ring system which has received attention is the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) system. The structure of toxoflavin (108) was originally established by x-ray diffraction <61RTC307>, and x-ray measurements of several other related derivatives of this ring system have been published <86MI 720-01, 88KGS1654, 88MI 720-01, 91KPS110, 92JAN1961>.

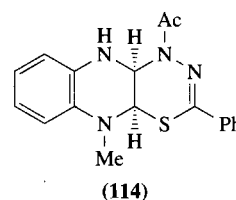
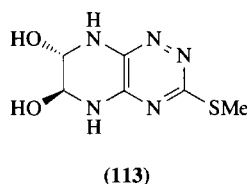
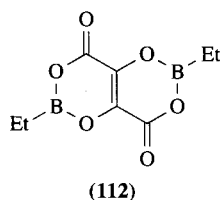
The structure of several [1,3,2]dioxaphosphorino[5,4-*d*]-1,3,2-dioxaphosphorin derivatives, for example compound (109), have been confirmed by x-ray crystal analysis <85IZV1550, 87IZV1193, 89IZV426>, as have structures of some [1,3]dioxino[5,4-*d*]-1,3,2-dioxaphosphorins, e.g. (110) <83IZV329, 88ZOB2743>. In the crystal of the unusual hexa-*t*-butyl[1,3,2,6]oxazadiborino[5,4-*d*][1,3,2,6]oxazadiborine (111) the two carbon atoms, the two boron atoms attached to them, and the two nitrogen atoms are all in the same plane. The two oxygen atoms, however, and the two



remaining boron atoms are not in this plane, nor are the *t*-butyl groups. Despite the nonplanarity of the system, there nevertheless appears to be a naphthalene-like cyclic delocalization of the π -electron system, since the bond distances lie between single and double bond values $\langle 90\text{AG(E)900} \rangle$.



The diethyl[1,3,2]dioxaborino[5,4-*d*]-1,3,2-dioxaborin compound (**112**) is particularly interesting, since it is thermochromic. It is colorless at room temperature, but changes reversibly to bright yellow if cooled below -5°C . Crystals of both the “hot” and the “cold” form were obtained and studied by x-ray diffraction. In both forms the two fused rings lie in a plane. On cooling the “hot” form, the ethyl groups change conformation, chelation occurs between boron atoms of one molecule and carbonyl oxygens of another, and the crystal of the “cold” form consists of stacked polymer layers $\langle 83\text{CB}3338, 85\text{JA}1684 \rangle$. Two other ring systems which have been studied by x-ray techniques are the pyrazino[2,3-*e*]-1,2,4-triazine (**113**) $\langle 86\text{JHC}33 \rangle$, and the benzo fused pyrazino[2,3-*e*][1,3,4]thiadiazine (**114**) $\langle 87\text{KGS}701 \rangle$.

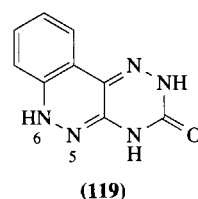
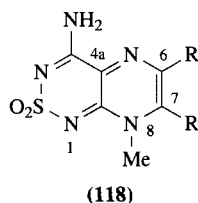
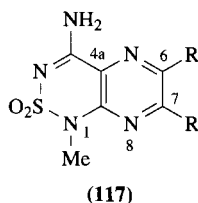
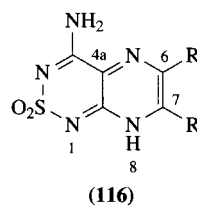
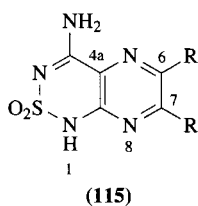


7.20.4 THERMODYNAMIC ASPECTS

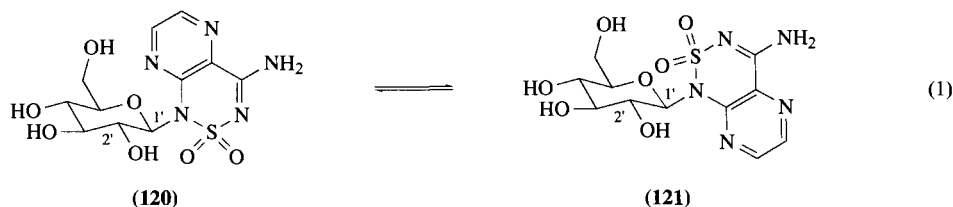
While different tautomeric forms are possible for many of the systems described in this chapter, few of them have been investigated in detail. It is known, however, that 4-amino-6,7-disubstituted pyrazino[2,3-*c*][1,2,6]thiadiazines exist predominantly as the 1-H tautomer (**115**) in organic solvents and in the solid state. On the other hand, the 8-H tautomer (**116**) is preferred in water, although this depends to some extent on the 6- and 7-substituents. These conclusions were arrived at by comparing the UV and ^{13}C NMR spectra of the 1-Me and 8-Me derivatives, (**117**) and (**118**), respectively, with the spectra of the corresponding N—H compounds. The 4a carbon atoms of 8-Me compounds (**118**) resonate at about 6 ppm lower field than the 4a carbon atoms of the 1-Me compounds (**117**), and the 6- and 7-carbon atoms of (**118**) resonate at about 20 ppm higher field than those of (**117**) $\langle 84\text{JHC}861, 88\text{H}(27)2201, 89\text{MI} 720-01 \rangle$.

NMR was used to establish structure (**119**) as the predominant tautomer of a benzo fused pyridazino[3,4-*e*]-1,2,4-triazine derivative. In the proton NMR spectrum of compound (**119**), H-6 appears as a singlet at δ 13.62. This is replaced by a doublet, however, when (**119**) is isotopically labeled at position-5 with a ^{15}N atom. The small coupling constant of this doublet ($J = 8$ Hz)

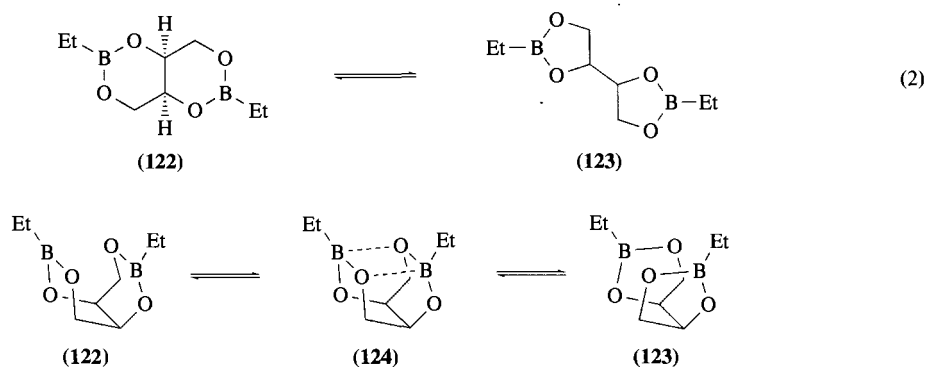
requires coupling through two bonds, and precludes the possibility of the NH proton being attached directly to N-5 <79CCC2438>.



The glucoside of 4-aminopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide has been shown to exist as an unusual pair of rotamers, **(120)** and **(121)** (Equation (1)). In the NMR spectrum of this compound at room temperature, H-1' appears as a pair of doublets centered at δ 5.15 and δ 6.02. These signals coalesce at higher temperatures. Likewise H-2' at room temperature appears as a pair of triplets at δ 4.28 and δ 4.16, also coalescing at higher temperatures. The lower field H-1' signal at δ 6.02 is assigned to conformer **(120)** in which H-1' should be strongly deshielded by the adjacent SO₂ group. In contrast, the lower-field H-2' signal at δ 4.28 is assigned to conformer **(121)** in which it is the H-2' proton which is deshielded by the SO₂ group. The energy barrier of rotation is 15.8 kcal mol⁻¹ (66.1 kJ mol⁻¹) <87LA961>.

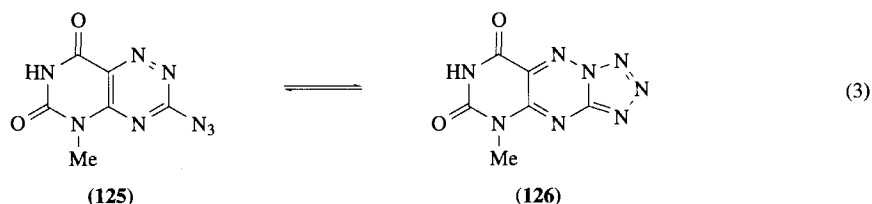


A very interesting tautomeric system is presented by the *cis*-fused tetrahydro[1,3,2]dioxaborino [5,4-*d*]-1,3,2-dioxaborin **(122)**. This is prepared from a threitol type precursor and is obtained as a mixture with isomer **(123)** in a ratio of 3:1 (Equation (2)). The particular stereochemistry of **(122)** permits the molecule to adopt a conformation in which the two boron atoms and two of the oxygen atoms assume a four-centered transition state **(124)**, thus allowing establishment of a dynamic equilibrium with the isomeric structure **(123)** (Scheme 3). The *trans*-fused analogue of **(122)**, prepared from an erythritol type precursor, is unable to enter into this tautomeric equilibrium <80LA1176>.



Scheme 3

The 3-azido compound (**125**) exists in equilibrium with its cyclized isomer (**126**) and the position of equilibrium varies with both temperature and solvent (Equation (3)). The azido isomer (**125**) predominates in aqueous solution, and is also favored by higher temperatures. Addition of sodium azide shifts the equilibrium towards the tricyclic isomer (**126**) <86KGS114>.



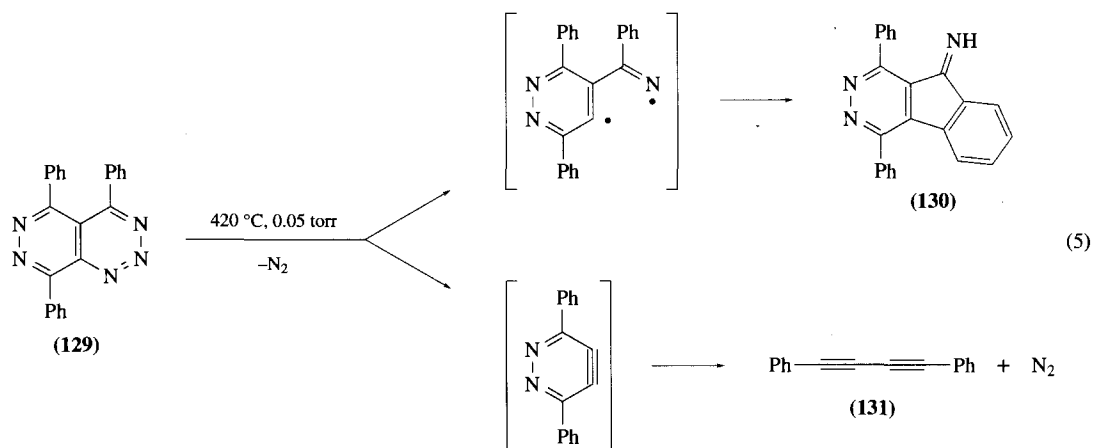
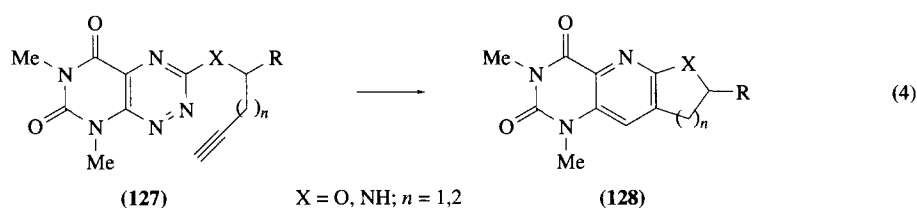
7.20.5 REACTIVITY OF FULLY CONJUGATED RINGS

7.20.5.1 Introduction

For purposes of this chapter, fully conjugated rings are defined as those which contain no sp^3 hybridized carbon or nitrogen atoms. This definition includes all ring systems which would normally be termed "heteroaromatic". While several of the bicyclic systems dealt with in the present section may contain one ring which is not fully conjugated, all the reactions described involve the other, fully conjugated ring.

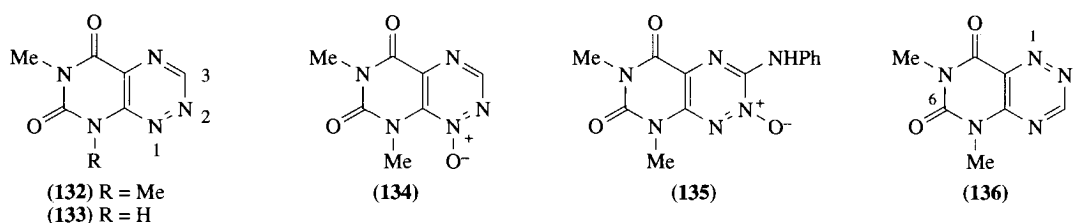
7.20.5.2 Thermal and Photochemical Reactions that are Unimolecular

Two reactions come under this heading. The first is a useful intramolecular Diels–Alder reaction leading to an easy preparation of 6,7-annulated deazapteridines. For example, the alkyne group of a pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) of type (**127**) undergoes cycloaddition to the azadiene system in the triazine ring, and, after elimination of nitrogen, a product of type (**128**) is obtained (Equation (4)). The reaction also goes with a terminal cyano group in place of the alkyne. It also proceeds, although not so readily, with the isomeric pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) (**6**) <88JOC800, 88JOC3568>. The second reaction to be mentioned involves the vapor phase pyrolysis of the pyridazino[4,5-*d*]-1,2,3-triazine (**129**) giving two products (**130**) and (**131**) via the mechanisms suggested below (Equation (5)) <75JCS(P1)1747>.



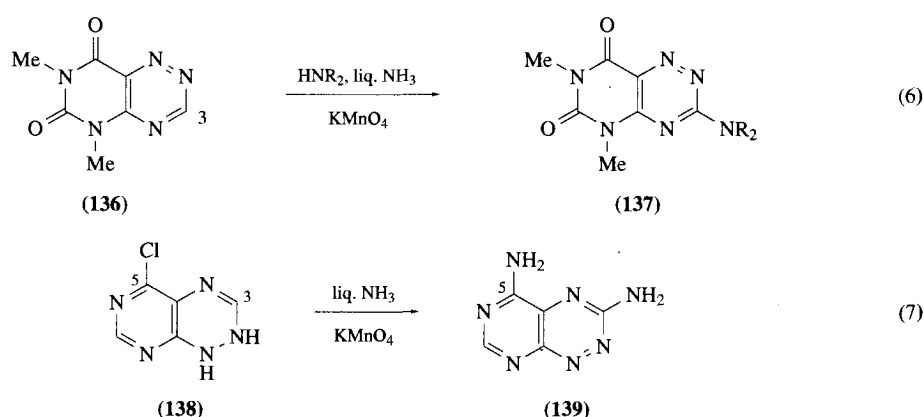
7.20.5.3 Electrophilic Attack

The electron deficiency arising from the presence of five or more heteroatoms means that electrophilic attack on fully aromatic rings is not an important reaction in any of the systems being dealt with here. In the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) series, however, peracid oxidation can lead to *N*-oxide formation. For fervenulin (132), Hückel calculations suggest that the most reactive site should be N-1 <76JCS(P1)713>, and indeed fervenulin (132) as well as its 3-methyl and 3-(2-pyridyl) derivatives afford the 1-*N*-oxide, for example (134), on treatment with H₂O₂ in trifluoroacetic acid <72CB3334>. On the other hand, 3-anilinofervenulin gives a product said to be the 2-*N*-oxide (135) on the basis of steric hindrance by the *peri*-8-methyl group <82JHC1309>. Protonation of fervenulin (132) and reumycin (133) occurs at N-2. Protonation of isofervenulin (136) occurs at N-1, N-2, and also at O-6 <88KGS1532>.

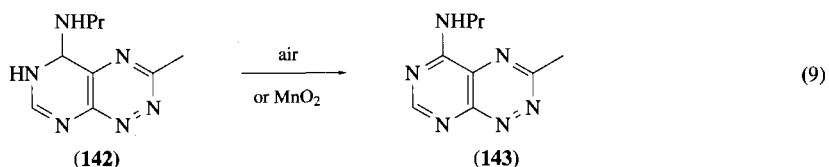
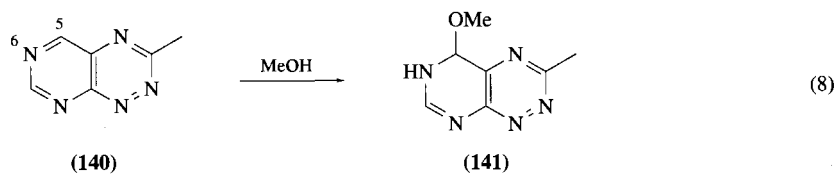


7.20.5.4 Nucleophilic Attack and Reduction

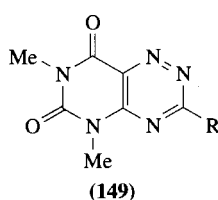
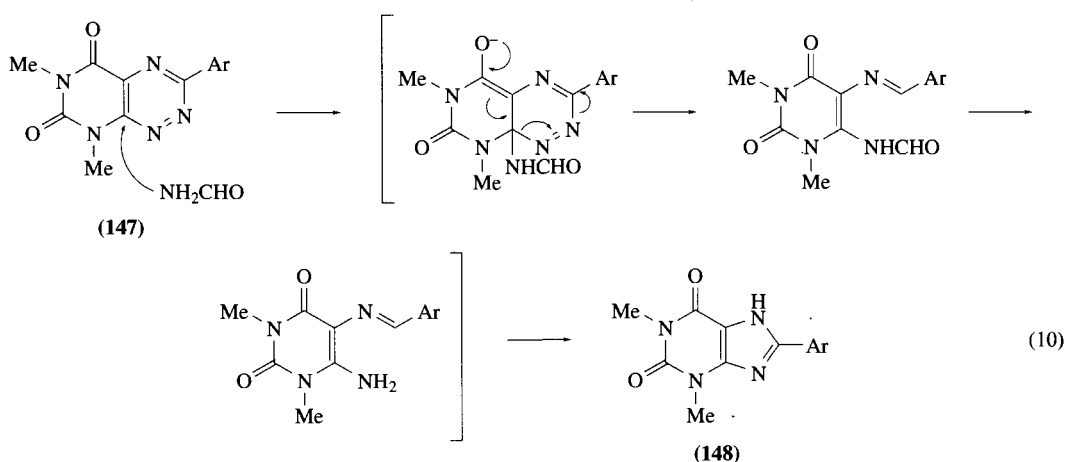
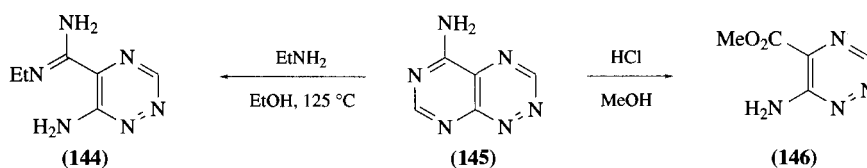
Nucleophilic attack on fully conjugated rings in the present series of compounds may result in substitution, addition, or ring cleavage. Nucleophilic substitution of good leaving groups such as halogen is important, and is dealt with in Section 7.20.7. Nucleophilic substitution of hydrogen is unusual, although isofervenulin (136) may undergo Chichibabin amination at position 3 on treatment with an amine in liquid ammonia containing potassium permanganate, giving (137) (Equation (6)) <88KGS1696>. In a similar reaction, the 1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazine (138) gives (139) (Equation (7)). Here the 5-chlorine atom is simultaneously substituted <87JHC1657>.

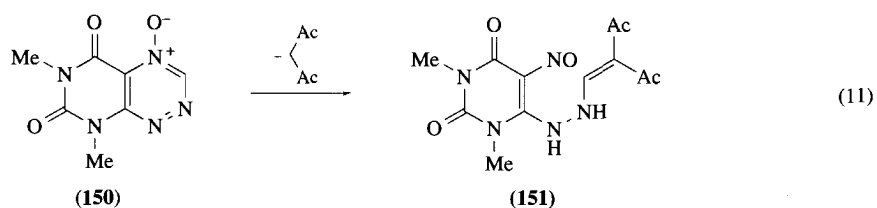


Nucleophilic addition takes place readily to the 5,6-carbon-nitrogen double bond in a pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine), giving covalent adducts <73AJC1689>. These adducts are often stable. Thus addition of methanol to compound (140) gives adduct (141) which can be isolated (Equation (8)) <70JCS(C)139>. The analogous nitrogen adduct (142) is similarly formed and is readily oxidized to the fully aromatic system (143) (Equation (9)) <72JCS(P1)237>. Although a 5-methyl group will block this covalent addition, an electron-attracting 5-trifluoromethyl or 5-ethoxycarbonyl group will promote it <71JCS(C)2475, 74JCS(P1)1565>.

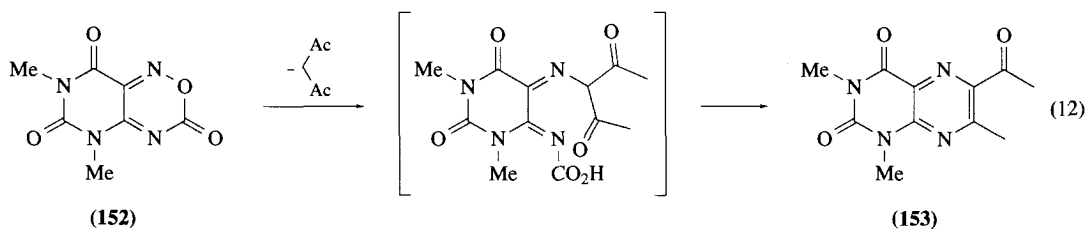


Nucleophilic attack on a fully aromatic pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) can sometimes cleave the pyrimidine ring. Thus compound (145) yields triazine (144) in hot ethanolic ethylamine <69JOC2102>, and triazine (146) in methanolic HCl (Scheme 4) <71JOC2974>. The triazine ring in fervenulin (147) contracts to the imidazole ring in (148) on treatment of (147) with formamide. Although the intermediates have not been characterized, this reaction presumably goes via nucleophilic addition to the triazine ring, followed by ring cleavage with loss of nitrogen, hydrolysis, recyclization, and oxidation (Equation (10)) <76H(4)749>. A similar triazine to imidazole ring contraction occurs on treatment of 6-azapteridines (149) with sodium dithionite in formic acid <78CPB367, 73CPB926>. The triazine ring in fervenulin 4-*N*-oxide (150) is cleaved by a variety of carbon and nitrogen nucleophiles, as in the conversion of (150) to (151) (Equation (11)) <87KFZ1446, 91MI 720-01>.

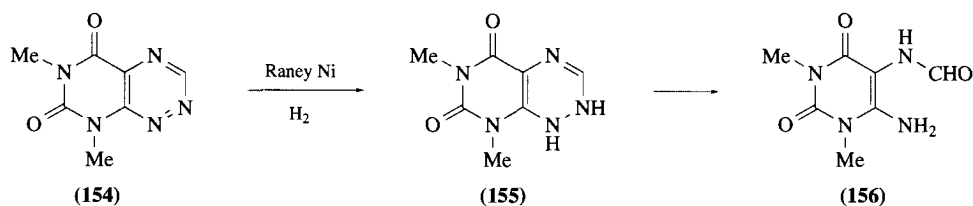




An unusual reaction occurs when the pyrimido[5,4-*c*][1,2,5]oxadiazine (**152**) is allowed to react with a variety of carbon nucleophiles. Nucleophilic attack at a ring nitrogen atom is followed by ring cleavage, and then decarboxylation and recyclization onto the nucleophile residue. The result is a 6,7-disubstituted pteridine (Equation (12)) (**153**). Appropriate choice of nucleophile may lead to many different types of substituent on the pteridine <86JHC1661, 91H(32)79>.



It is difficult to obtain products from the catalytic reduction of the triazine ring in compound (**154**). Very mild conditions allow isolation of the unstable intermediate (**155**), but normally ring-opened products such as the formamide (**156**) are obtained (Scheme 5) <72CB3334, 81KPS85>.



Scheme 5

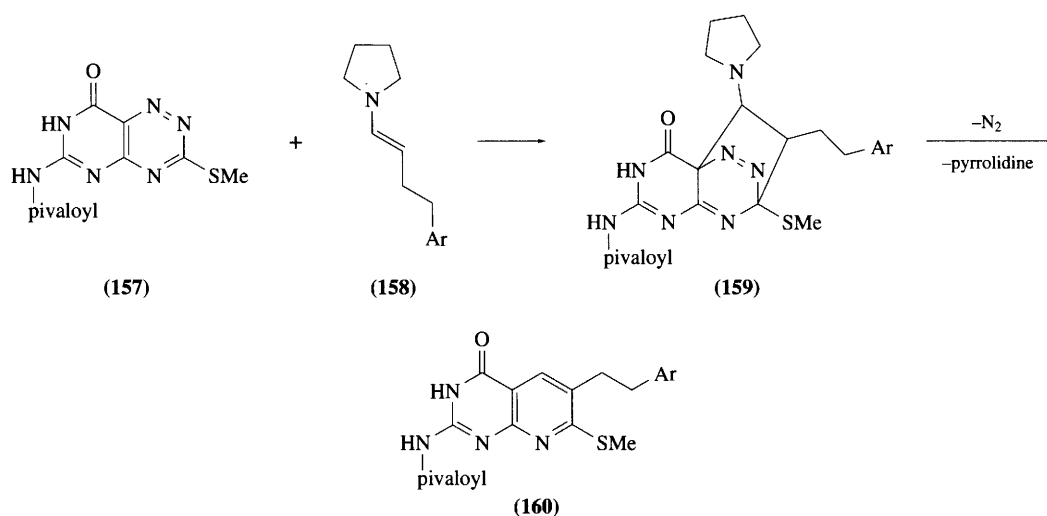
7.20.5.5 Cyclic Transition States with a Second Molecule

The triazine ring of pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) offers a formal diene system capable of undergoing cycloaddition with electron-rich dienophiles, and this concept has been developed into a useful synthesis for 5-deazapteridines <88H(27)1925>. Thus, reaction of the derivative (**157**) with (**158**) leads to cycloadduct (**159**), which with loss of nitrogen and pyrrolidine affords the 5-deazapteridine (**160**) (Scheme 6). The pivaloyl group is used to increase solubility. 6-Azapteridines can also participate in azadiene reactions with ketones and with vinyl ethers, again giving 5-deazapteridines <90KGS224>.

7.20.6 REACTIVITY OF NONCONJUGATED RINGS

7.20.6.1 Introduction

Three points of clarification may be made concerning the organization of material in this section. Firstly, several of the bicyclic systems dealt with may contain one ring which is fully conjugated or heteroaromatic. All the reactions to be described, however, involve the other, nonconjugated ring. Secondly, for purposes of this section, lactams and similar ring systems are considered to be nonconjugated, since as normally depicted the lactam nitrogen atom is formally *sp*³ hybridized.



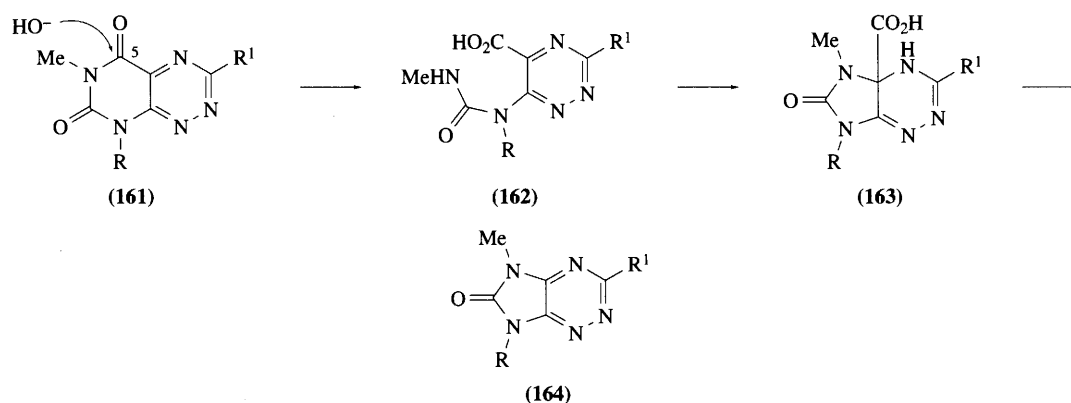
Scheme 6

Thirdly, some of the nonconjugated rings dealt with are isomeric with aromatic rings. For example, a lactam is isomeric with a hydroxyheteroaromatic ring. Chemical reactions of nonconjugated ring systems of this type are treated separately below (see Section 7.20.6.2).

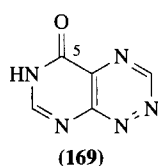
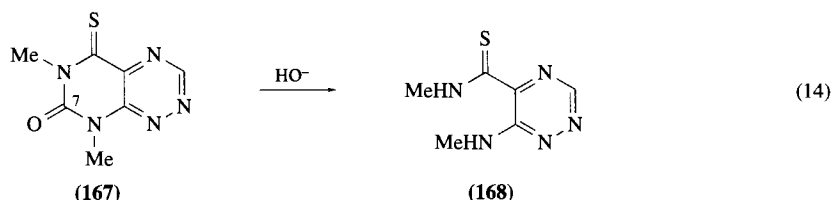
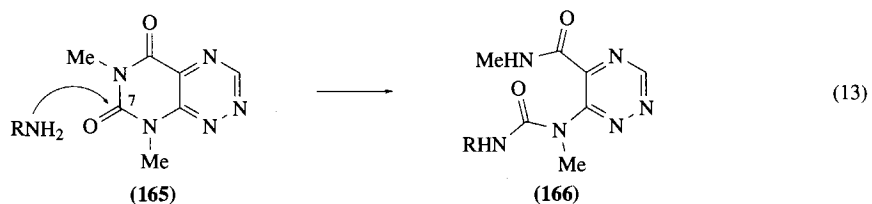
7.20.6.2 Isomers of Aromatic Compounds

7.20.6.2.1 Pyrimidotriazines (azapteridines) (6) and (8)

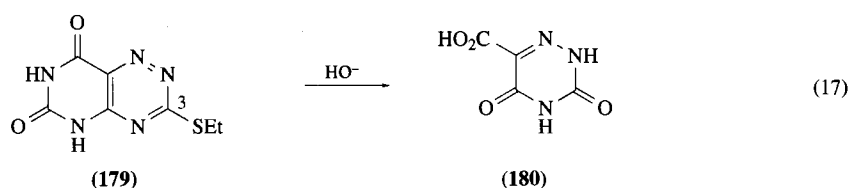
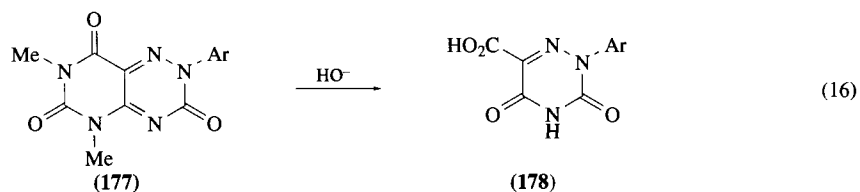
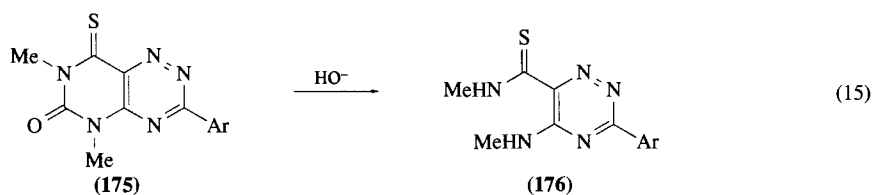
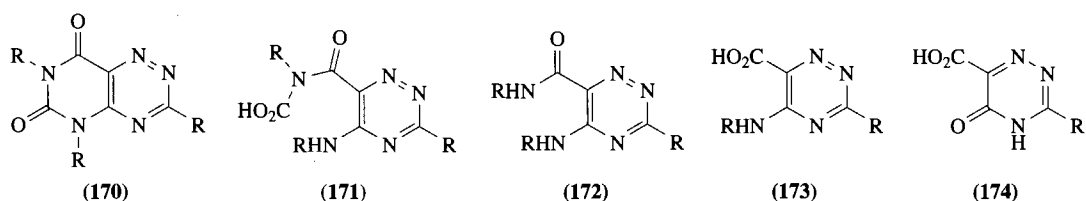
Fervenuin and reumycin derivatives of type (161) suffer attack at position-5 by hydroxide ion. This results in cleavage of the pyrimidine ring, giving (162) which can recyclize to (163) <87KGS1252, 87MI 720-01, 88MI 720-02>. Intermediate (163) may also be formed directly from (161) via a benzilic acid type rearrangement. Decarboxylation of (163) followed by oxidation leads to a 6-azapurine (164) <78CPB3154, 80JHC869, 88KGS1696>. These reactions are shown in Scheme 7. Amines, on the other hand, attack fervenuin (165) at position 7, giving ring-opened products (166) (Equation (13)) <74JCS(P1)1818>, and the thione analogue (167) is similarly attacked at position 7 by hydroxide, giving (168) (Equation (14)) <73CPB926>. The pyrimidine ring of (169) is cleaved by nitrogen nucleophiles, which attack at position 5 <72JCS(P1)247>.



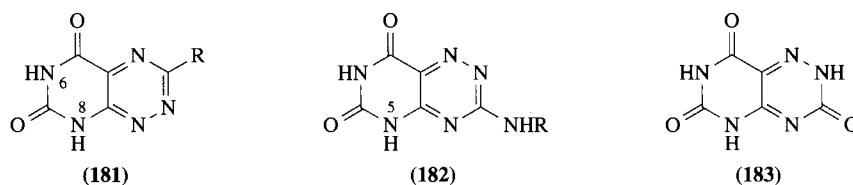
Scheme 7



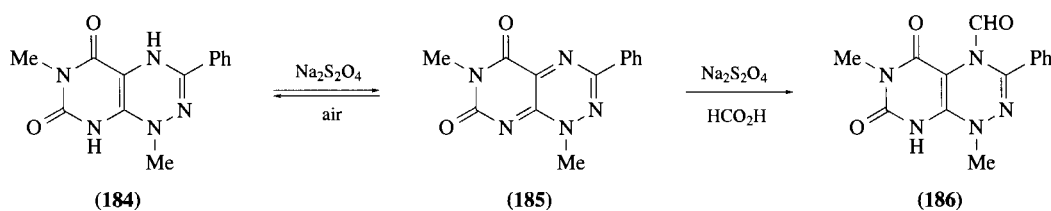
The isomeric pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) (170) are also susceptible to ring cleavage on treatment with alkali. Different products (171)–(174) are obtained from derivatives (170) depending upon the reaction conditions, but it is always the pyrimidine ring that is cleaved [87JPR290, 87KGS1555]. The thione analogue (175) reacts similarly to give (176) (Equation (15)) [73CPB926], and hydrolysis of isoferenulones (177) offers a route to 6-azauracils (178) (Equation (16)) [80JHC1365]. Prolonged reaction times in these reactions may simultaneously hydrolyze a 3-amino or a 3-ethylthio group, as in the conversion of (179) to (180) (Equation (17)) [64CB5, 69JPR438].



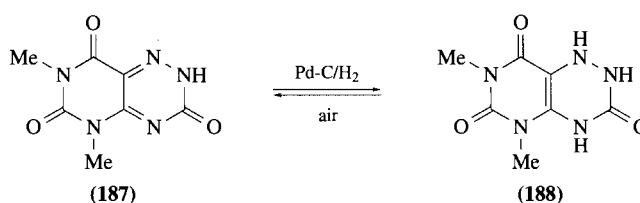
Pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) such as **(181)** may be alkylated with alkyl iodides <68JHC581, 78CPB3154, 80JHC869>. An alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate may also be used as an alkylating system <73TL1577>. In the isomeric pyrimido[4,5-*e*]-1,2,4-triazine (6-azapteridine) series, methylation of derivatives of type **(182)** with dimethyl sulfate gives selective N-5 methylated products <67EGP55032>. All three lactam nitrogen atoms in compound **(183)** can be methylated with methyl iodide and sodium hydride in DMF <70JOC3792, 75JOC2329>.



The toxoflavin **(185)** undergoes reduction with sodium dithionite to give the dihydro product **(184)** which is readily oxidized again by air, while dithionite reduction in the presence of formic acid gives the formyl dihydro derivative **(186)** (Scheme 8) <75CPB2001>. Hydrogenation of compound **(187)** gives the dihydro derivative **(188)** which is readily oxidized back to **(187)** in air (Scheme 9) <75JOC2329>.



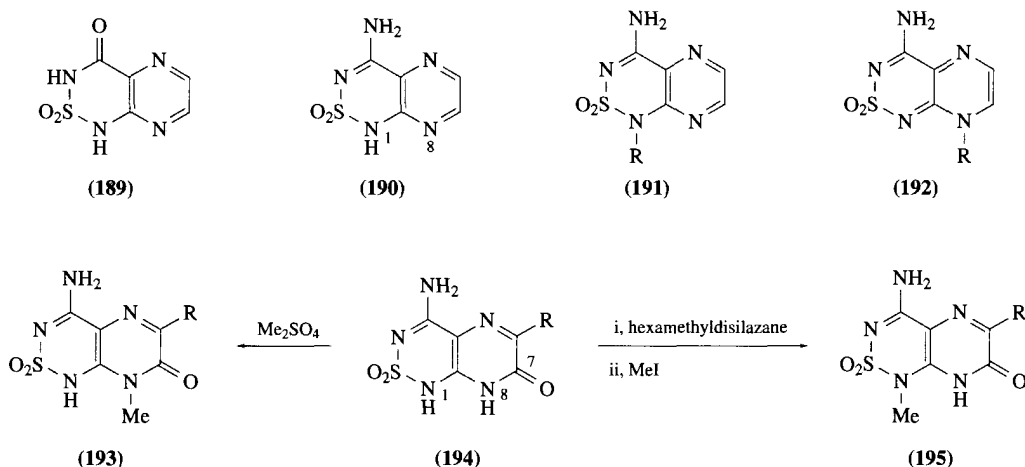
Scheme 8



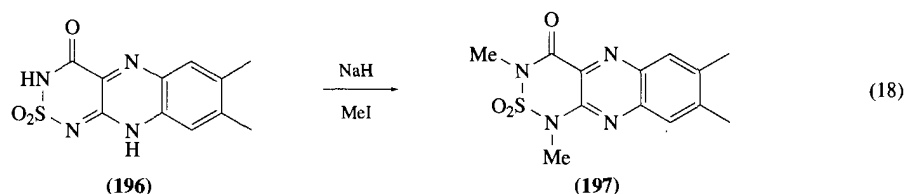
Scheme 9

7.20.6.2.2 Other ring systems

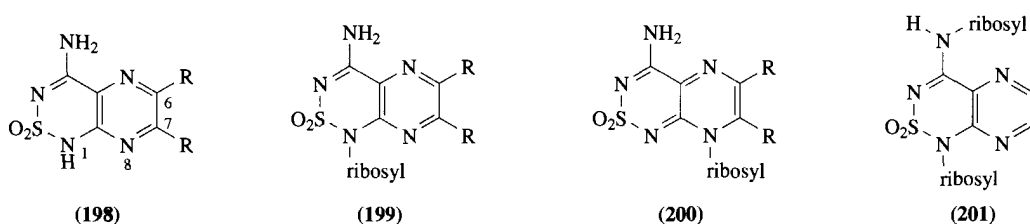
Pyrazino[2,3-*c*][1,2,6]thiadiazines (**19**) are known mostly in the form of their 2,2-dioxides, and interest in them stems from the fact that they are 2-thia analogues of pteridines. The powerful electron-attracting $\text{—SO}_2\text{—}$ group in the ring renders these molecules quite strongly acidic <88LA121>, and compounds of the 4-oxo series (**189**) show two acidic pKa values in the regions 1.20–1.99 and 5.50–6.25, and of the 4-amino series (**190**) a single acidic pKa value in the region 3.51–4.05 <84JHC861>. Alkylation of compounds of the 4-amino series (**190**) nearly always occurs on the N-1 nitrogen atom giving **(191)**, although, in certain cases, N-8 alkylated products **(192)** may also be formed <88H(27)2201, 90JHC785, 91LA301, 92JMC3977>. Methylation of the 4-amino-7-oxo-series (**194**) may give either N-1 or N-8 alkylated products, **(195)** or **(193)**, respectively (Scheme 10) <88LA121>, while methylation of the benzo fused system (**196**) gives the dimethyl product **(197)** (Equation (18)) <86AP(319)79>.



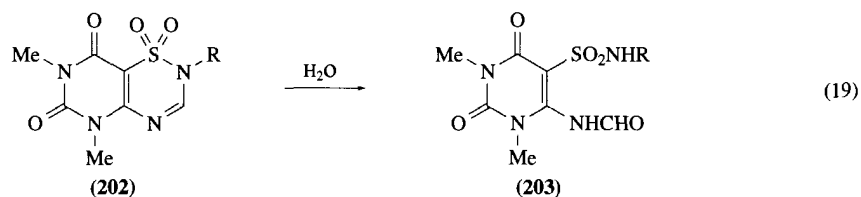
Scheme 10

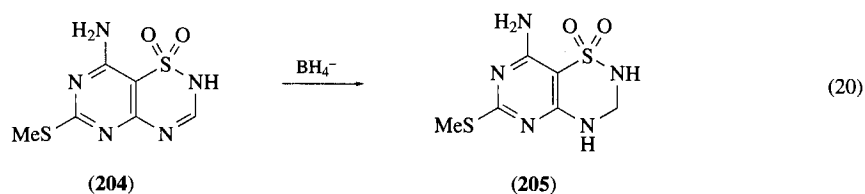


Related to these alkylation studies, it is possible to prepare both riboside and glucoside derivatives of (198) <86LA1872, 87LA961>. For example, silylation of (198) with hexamethyldisilazane and treatment of the resulting disilyl derivative with tetra-*O*-acetylribose and a Lewis acid catalyst yields ribosides. For 6,7-disubstituted starting materials, only N-1-monoribosides (199) are obtained. For 6,7-unsubstituted starting material (198; R = H), however, a mixture of compounds (199; R = H), (200; R = H) and (201) is formed. When a solution of the N-1 riboside (199; R = H) in dichloromethane containing boron trifluoride is allowed to stand at room temperature, the N-8 isomer (200; R = H) is formed, together with deribosylated material (198; R = H), suggesting that the N-8 product may be formed via the N-1 isomer. While the N-1 riboside is usually the major product, it is possible to choose reaction conditions so as to make the N-8 isomer predominate <88BSB867>.



A pyrimido[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide is shown in derivative (202), and the thiadiazine ring in this is readily cleaved by water to give the products (203) (Equation (19)). Compound (204) containing the same ring system is reduced with borohydride to the dihydro product (205) (Equation (20)) <63JOC1994>.

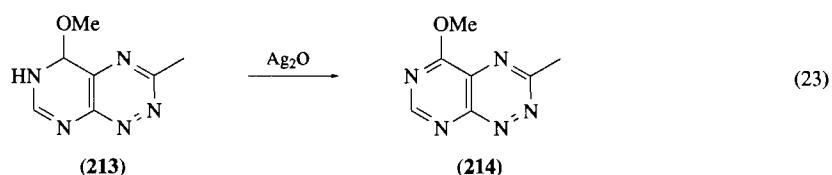
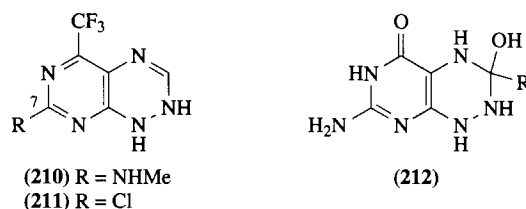
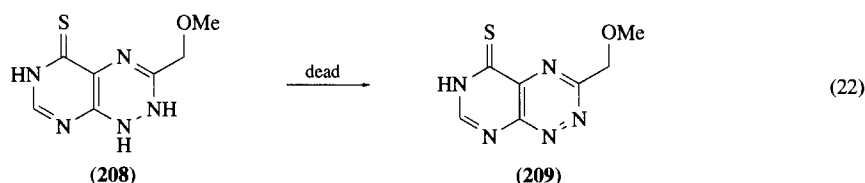
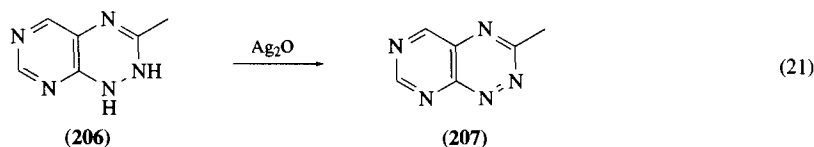




7.20.6.3 Non-isomers of Aromatic Compounds and Reduced Ring Systems

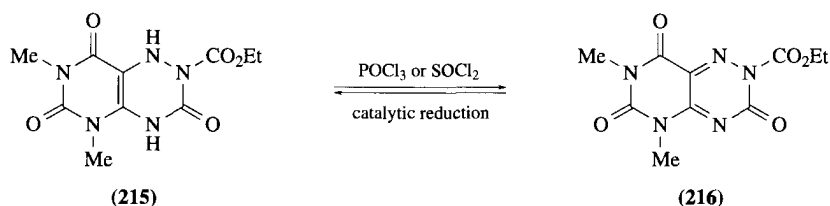
7.20.6.3.1 Pyrimidotriazines (azapteridines) (6) and (8)

Synthesis of pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) often gives the 1,2-dihydro derivatives in the first instance, for example (206) (see Section 7.20.9.3.2). These are usually oxidized very readily to the fully aromatic system, as in the oxidation of compound (206) to (207) (Equation (21)), and of (208) to (209) (Equation (22)) <69JOC3161, 71JOC2974, 72JCS(P1)237>. The substitution pattern of the rings, however, can have a marked effect on the ease of the oxidation. In the 5-trifluoromethyl series, compound (210) spontaneously oxidizes in air to the fully aromatic system, while the 7-chloro compound (211) resists oxidation by a variety of oxidizing agents, although it can be oxidized using 1-chlorobenzotriazole <71JCS(C)2475>. Compounds of the type (212) are also unusually difficult to oxidize <80JCR(S)278>. 5,6-Dihydropyrimido[5,4-*e*]-1,2,4-triazines are also common, being formed by covalent addition to the 5,6-carbon–nitrogen double bond (see Section 7.20.5.4). They are readily oxidized, usually with silver oxide, as in the conversion of (213) to (214) (Equation (23)) <70JCS(C)139>.

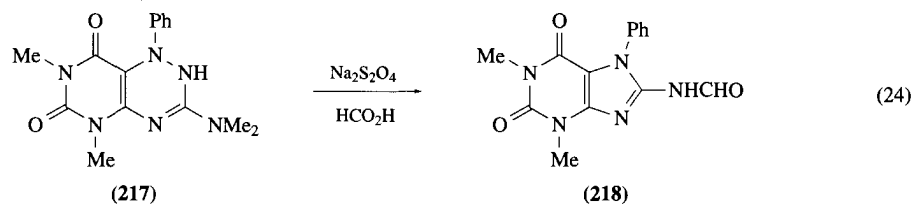


The isofervenurone derivative (215) can be dehydrogenated to (216) by refluxing in either phosphoryl chloride or thionyl chloride. Catalytic reduction readily converts the product (216) back to (215) (Scheme 11) <75JOC2329>. The reduced isofervenuin derivative (217) undergoes ring con-

traction of the triazine ring to give the purine (**218**) when treated with sodium dithionite in formic acid (Equation (24)) <74JA5607>.

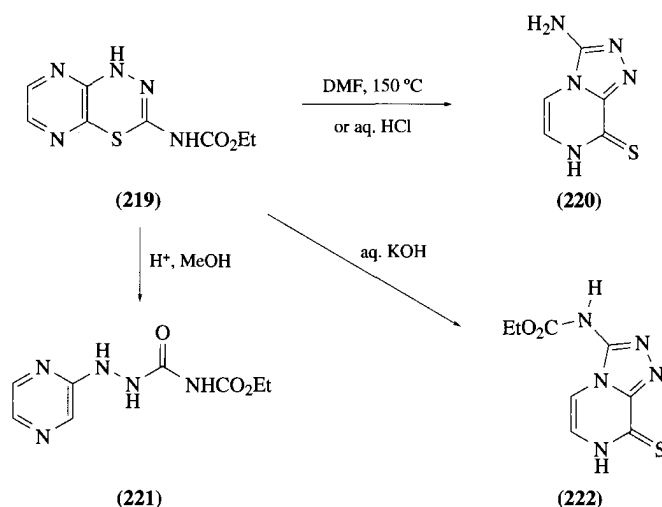


Scheme 11

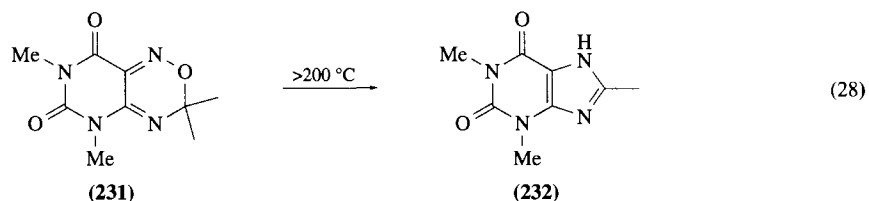
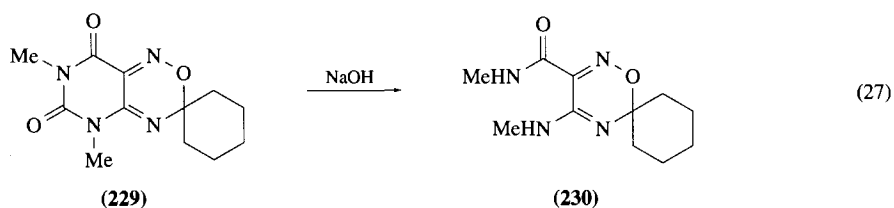
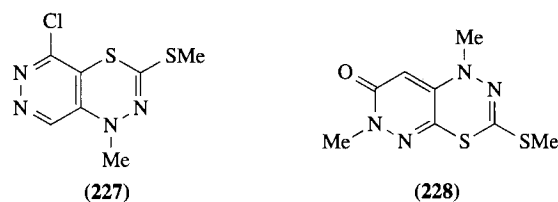
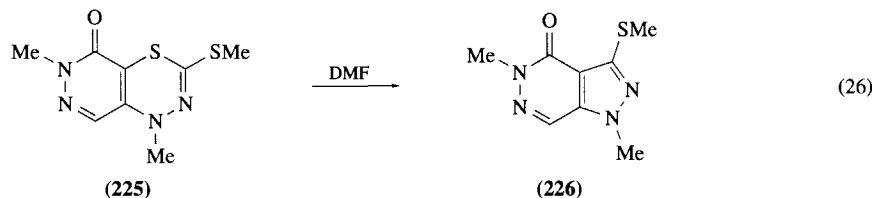
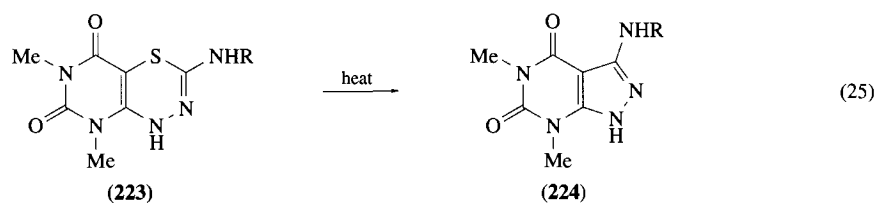


7.20.6.3.2 Other ring systems

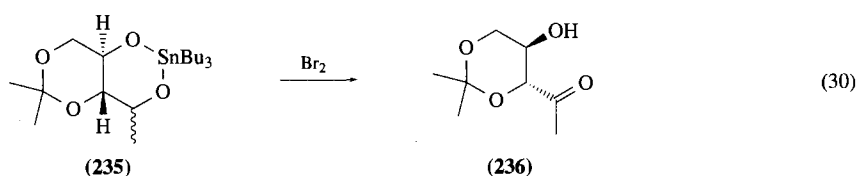
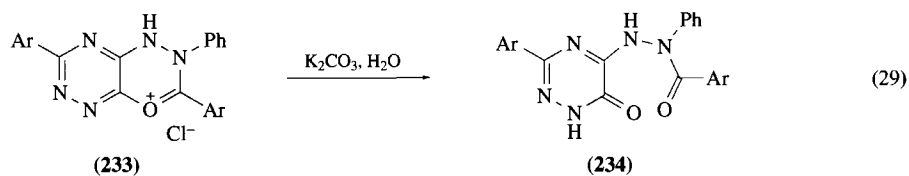
Many of the ring systems mentioned in this section have been little studied, and the amount of material extant is not great. A common reaction is the cleavage of one or other of the two fused rings, often followed by recyclization of the initially formed cleavage product. The carbon-sulfur bonds in the pyrazino[2,3-*e*][1,3,4]thiadiazine compound (**219**), for example, are easily broken, and in methanolic HCl complete loss of sulfur leads to the ring-cleaved product (**221**). Under other conditions ring cleavage is followed by recyclization on to a ring nitrogen atom giving either (**220**) or (**222**) <85H(23)913>. These reactions are shown in Scheme 12. Pyrimido[4,5-*e*][1,3,4]thiadiazines (**223**) lose sulfur on heating, to give ring-contracted products (**224**) (Equation (25)) <78MI 720-01, 78MI 720-02, 79CPB1965>. Similarly, pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives such as (**225**) undergo desulfurization to give ring-contracted products (**226**) (Equation (26)) <84H(22)479, 85JHC161>. Neither compounds (**227**) nor (**228**) undergo ring contraction with loss of sulfur <85JHC161>. The oxadiazine ring in the pyrimido[5,4-*c*][1,2,5]oxadiazine derivative (**229**) is stable to base, but the pyrimidine ring is cleaved, giving product (**230**) (Equation (27)). Both rings in compound (**229**) are stable to acid. On the other hand, the dimethyl analogue (**231**) loses a molecule of formaldehyde when heated, giving the ring-contracted product (**232**) (Equation (28)) <66LA(692)134>.



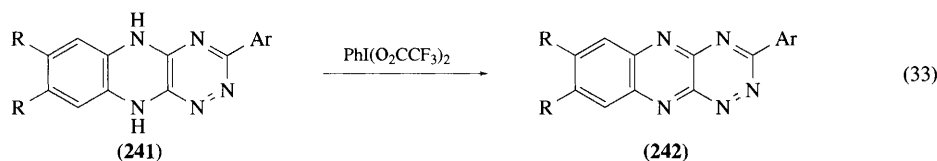
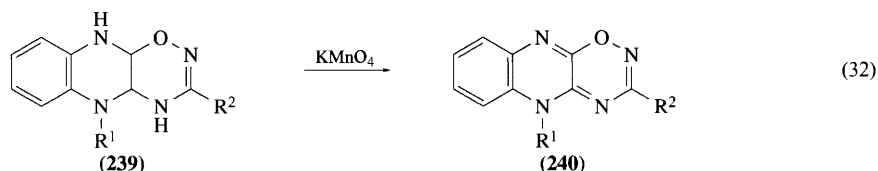
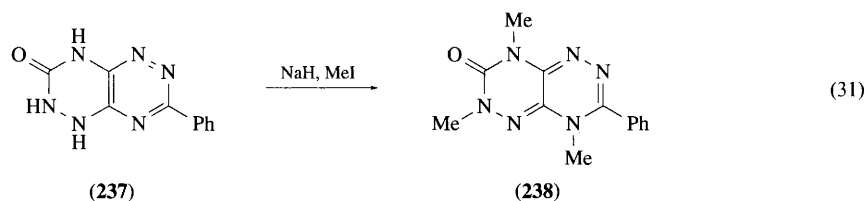
Scheme 12



Two reactions which involve cleavage at ring oxygen are the very ready hydrolysis of the [1,2,4]triazino[5,6-*e*][1,3,4]oxadiazine compound (233) giving (234) (Equation (29)) <87S128>, and the brominolysis of the tetrahydro[1,3]dioxino[5,4-*d*]-1,3,2-dioxastannin (235). The latter reaction is highly regiospecific, giving only the one hydroxyketone (236) in nearly quantitative yield (Equation (30)) <82JCS(P1)2131>.



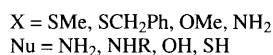
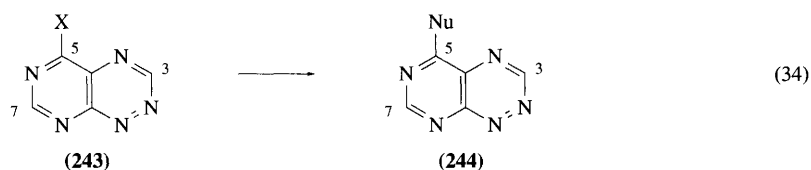
The [1,2,4]triazino[6,5-*e*]-1,2,4-triazine ring system is of interest as a 4,7-diazapteridine; compound (237) is an example. It undergoes trimethylation with methyl iodide and sodium hydride to give (238) (Equation (31)) <83TL1767>. Two dehydrogenations are mentioned: first, compounds of type (239) which are reduced benzo derivatives of the unusual ring system pyrazino[2,3-*e*]-1,2,4-oxadiazine (239) (which is more properly named as a [1,2,4]oxadiazino[5,6-*b*]quinoxaline) are dehydrogenated to derivatives (240) with potassium permanganate (Equation (32)) <87KGS1260>; and last, the benzo fused pyrazino[2,3-*e*]-1,2,4-triazine (241), a [1,2,4]triazino[5,6-*b*]quinoxaline, is aromatized to (242) by iodosobenzene bistrifluoroacetate (Equation (33)) <91S83>.

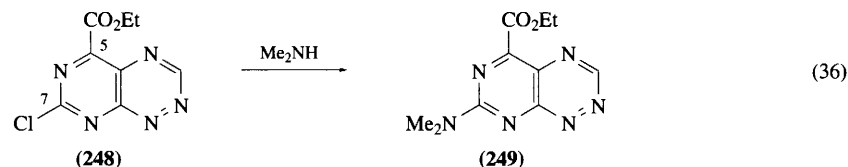
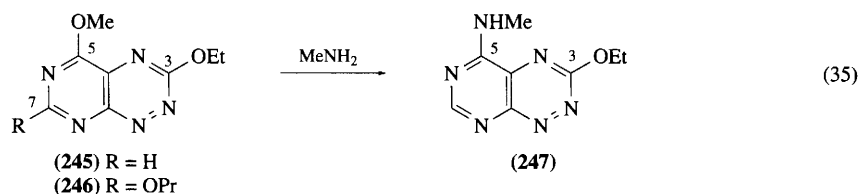


7.20.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

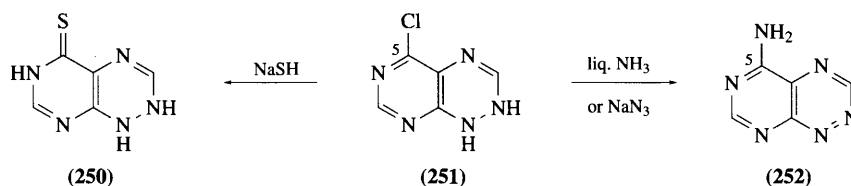
7.20.7.1 Pyrimidotriazines (Azapteridines) (6) and (8)

A leaving group at the 5-position of pyrimido[5,4-*e*]-1,2,4-triazines, as in (243), is particularly susceptible to substitution by nucleophiles, giving products of type (244) (Equation (34)) <75MI 720-01>. In contrast, there are very few examples of reaction at the 3- and 7-positions. Substitution can be achieved, but these positions are less reactive. Thus on treatment with methylamine under mild conditions, the 3-ethoxy group of (245) remains untouched while the 5-methoxy group is selectively replaced, giving (247) (Equation (35)). Trialkoxy compounds, for example (246), undergo successive substitution at the 5-, 3-, and 7-positions on treatment with methylamine, giving a mixture of the 5-, 3,5-, and 3,5,7-methylamino substituted products, depending upon the starting material and the severity of the reaction conditions <73AJC1689>. On the other hand, presence of a 5-ethoxycarbonyl group renders a 7-chlorine atom very reactive, and compound (248) on treatment with dimethylamine gives (249) almost instantaneously (Equation (36)) <74JCS(P1)1565>.

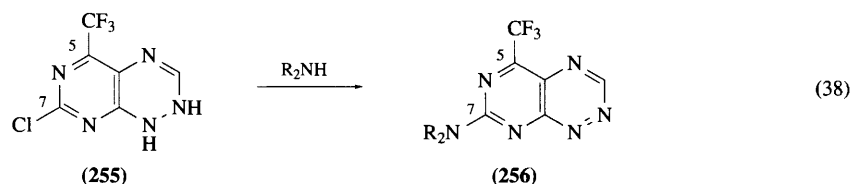
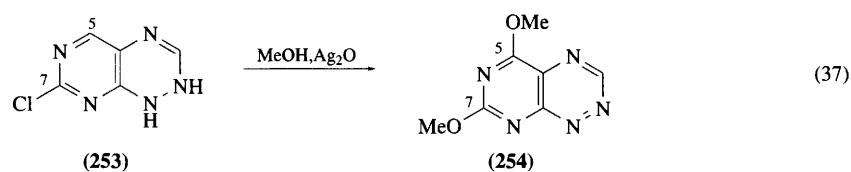




A chlorine atom at position-5 of a 1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazine (**251**) is also readily replaced by nucleophiles, and as a rule the fully aromatic product is obtained, <71JOC2974, 75JOC2205>, although with sodium hydrogen sulfide as the nucleophile the dihydrothione product (**250**) is isolated <69JOC3161>. Treatment of (**251**) with liquid ammonia causes replacement of the 5-chlorine atom with an amino group, giving (**252**), and the same product is obtained, rather than the 5-azido product, if sodium azide is used as the reagent <87JHC1657>. These reactions are shown in Scheme 13. A chlorine atom at position-7 of these dihydro systems may be similarly replaced, but the reaction becomes more complicated. A five substituent is nearly always introduced as well, probably by covalent addition to the 5,6-double bond followed by aerial oxidation. Thus, treatment of compound (**253**) with methanol and silver oxide gives the 5,7-dimethoxy product (**254**) (Equation (37)) <71JCS(C)2616>. 7-Chloro-1,2-dihydro-5-trifluoromethylpyrimido[5,4-*e*]-1,2,4-triazine (**255**) undergoes straightforward substitution of the chlorine with amines, however, to give the corresponding fully aromatic 7-amino-substituted product (**256**) (Equation (38)) <71JCS(C)2475>.

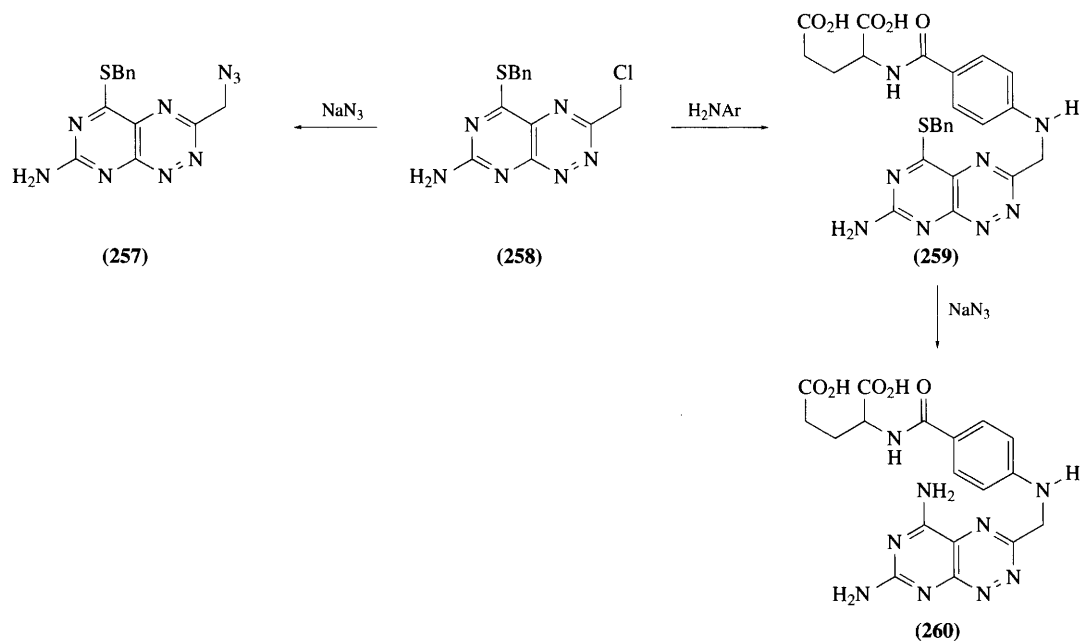


Scheme 13



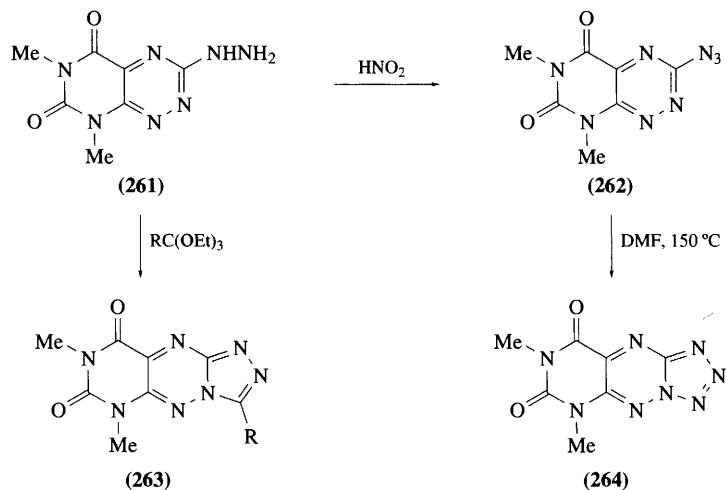
Surprisingly, the 5-benzylthio group in (**258**) is less reactive than the 3-chloromethyl group, and allows selective nucleophilic replacement of the chlorine atom in the latter with either azide ion or *p*-aminobenzoylglutamate, giving (**257**) and (**259**) respectively. The benzylthio group in (**259**) may be replaced subsequently with an amino group by treatment with sodium azide. The product obtained, (**260**), was used as an intermediate in the synthesis of 7-azafolic acid <75JOC2205>. These reactions are shown in Scheme 14.

The 3-hydrazino group in 3-hydrazinofervenuin (**261**) is converted into an azido group on treatment with nitrous acid, and the product (**262**) cyclizes to the tricyclic compound (**264**) on

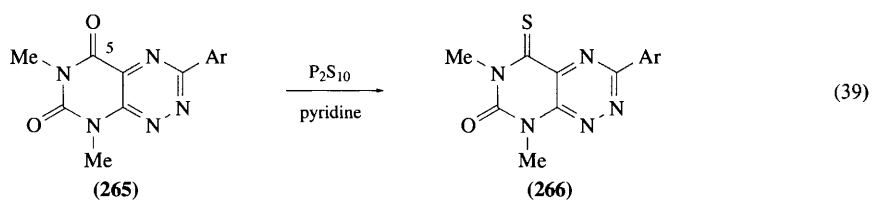


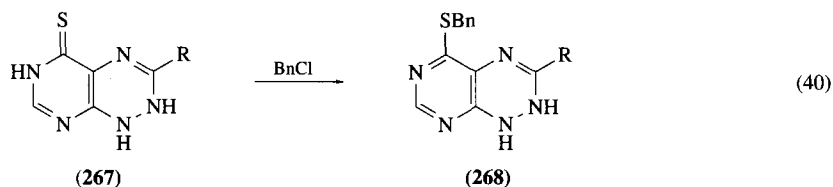
Scheme 14

heating in DMF. A different tricyclic system (263) is obtained on treating the same hydrazino compound (261) with an *ortho* ester (83JOC1628). These reactions are shown in Scheme 15. Other transformations of substituents attached to carbon in this series include the selective conversion of the 5-lactam carbonyl group in (265) into the corresponding thione (266) (Equation (39)) (73CPB926), and the alkylation of the sulfur atom in (267) to give (268) (Equation (40)) (69JOC3161, 71JOC2974, 71JOC3502).

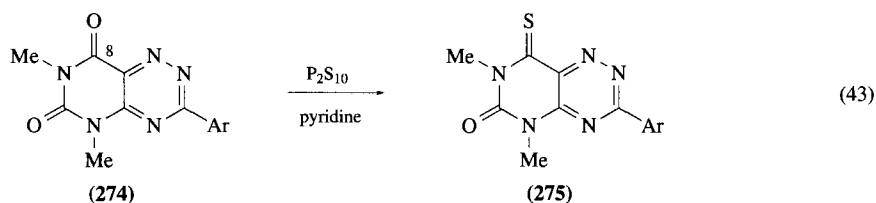
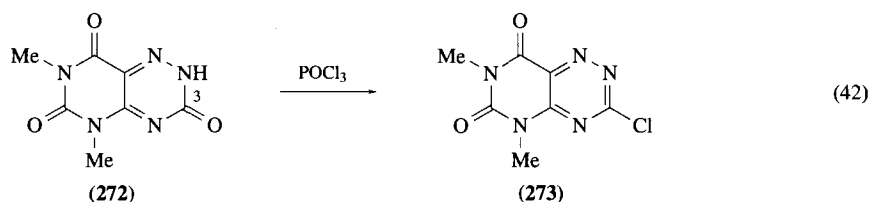
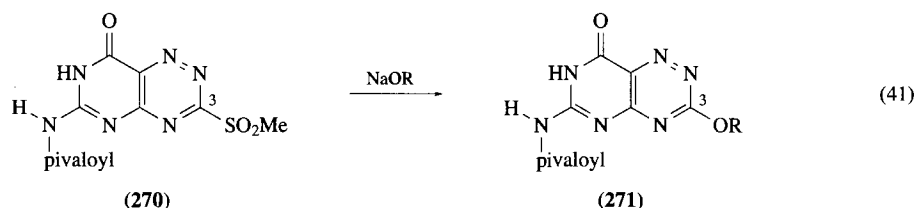
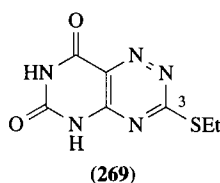


Scheme 15





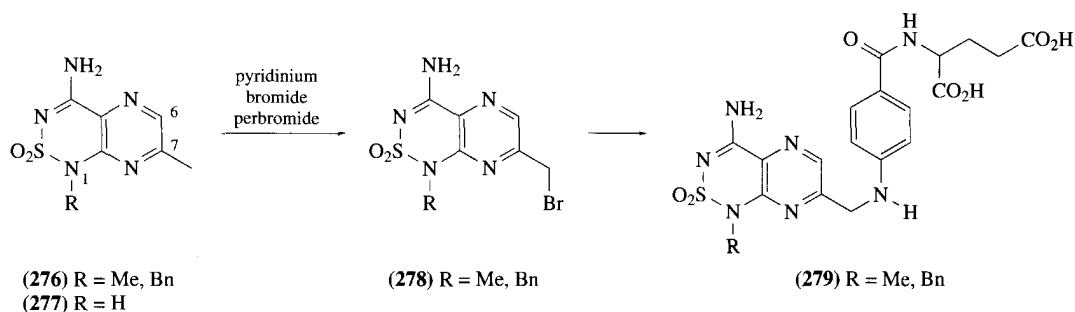
In the isomeric pyrimido[4,5-*e*]-1,2,4-triazine (6-azapteridine) series, substituents at the 3-position may readily be replaced nucleophilically. For example, the 3-ethylthio group of **(269)** may be replaced by amino or substituted amino groups <64CB5>. On the other hand, while the 3-methylsulfonyl group of **(270)** can be replaced by alkoxy or substituted amino groups, for example to give **(271)** (Equation (41)), the corresponding 3-methylthio compound is unreactive <88JOC800>. The 3-lactam oxygen in compound **(272)** may be replaced by chlorine on treatment with phosphoryl chloride, giving **(273)** (Equation (42)), in which the chlorine atom may then be replaced by hydrazine <75JOC2329>. And finally, just as in the pyrimido[5,4-*e*]-1,2,4-triazine series described above, the 8-lactam carbonyl group in **(274)** can be converted selectively into the corresponding 8-thione **(275)** with phosphorus pentasulfide (Equation (43)) <73CPB926>.



7.20.7.2 Other Ring Systems

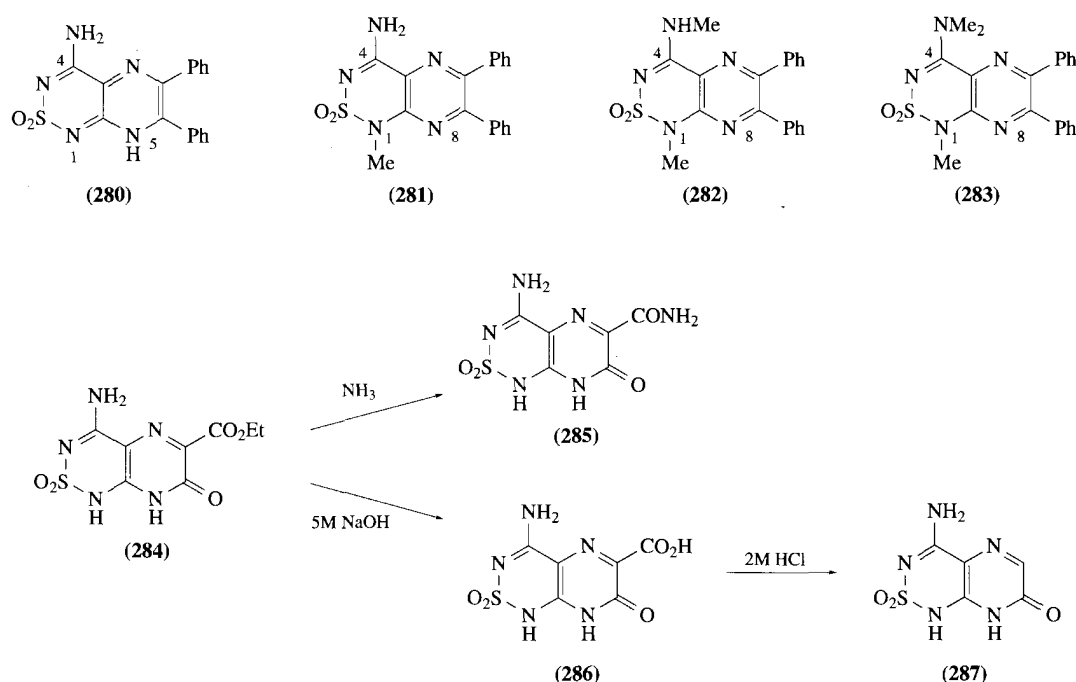
Pyrazino[2,3-*c*][1,2,6]thiadiazines are 2-thiapteridines, and their 2,2-dioxide derivatives **(276)** have been used in the preparation of 7-folic acid analogues **(279)**. The latter had no biological activity, however. In the synthesis, the 7-methyl group of derivatives **(276)** is first brominated with pyridinium

bromide perbromide, and the 7-bromomethyl product (**278**) is converted *in situ* into the 7-folate analogue (**279**) (Scheme 16). The corresponding 6-methyl compound does not brominate under similar conditions, nor can any bromomethyl product be obtained from the 1-H compound (**277**). Unfortunately, neither the methyl nor the benzyl groups in the final products (**279**) can be removed without at the same time removing the 7-side chain. <91LA301>.



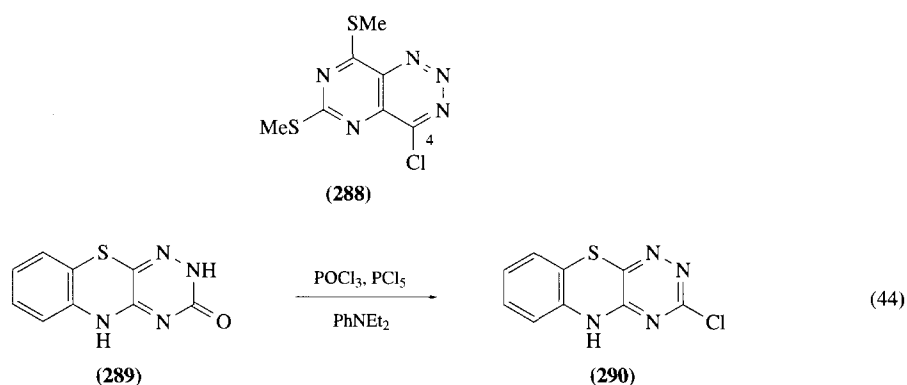
Scheme 16

While methylation of pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides normally occurs on ring nitrogen (see Section 7.20.6.2.2), and reaction of compound (**280**) with excess methyl iodide and one mole of potassium carbonate does give the N-1 monomethylated product (**281**), use of two or three moles of carbonate gives the di- and trimethylated products (**282**) and (**283**), respectively, in which the second and third methyl groups go onto the exocyclic 4-amino group. There is no N-8 methylated product <90JHC785>. Ester groups at position 6 of 7-oxo derivatives of this ring system behave normally. Compound (**284**) forms the amide (**285**) with ammonia, and is hydrolyzed by alkali to the carboxylic acid (**286**). The latter decarboxylates in 2 M HCl, giving compound (**287**) (Scheme 17) <88LA121>.



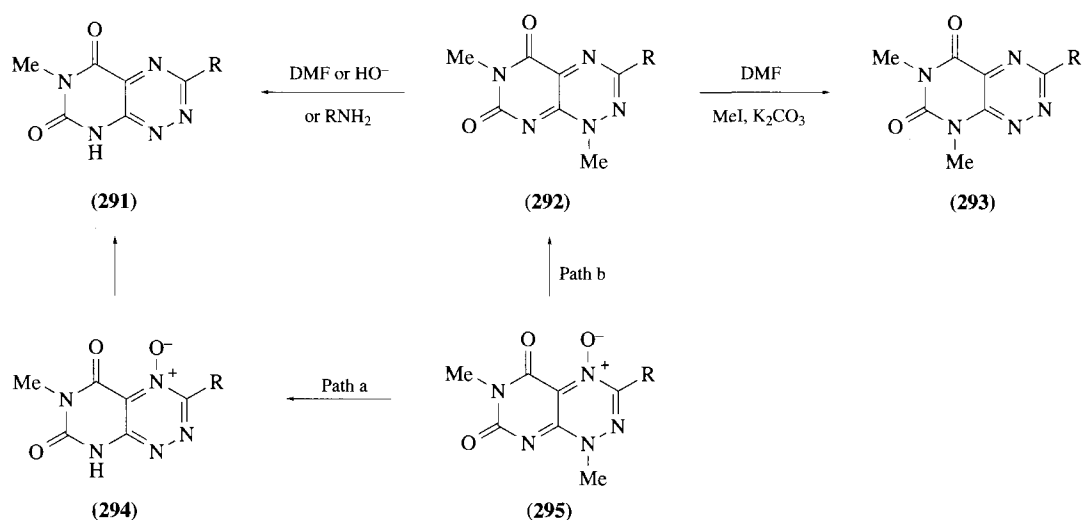
Scheme 17

Two other uncommon ring systems are mentioned. First, the 4-position of pyrimido[5,4-*d*]-1,2,3-triazines is very reactive towards nucleophilic attack, and the 4-chlorine atom in (**288**), for example, may be replaced nucleophilically without removal of either of the methylthio groups <65USP3213090, 84JCS(P1)1475>. Second, the rare [1,4]thiazino[3,2-*e*]-1,2,4-triazine ring system (**289**) undergoes normal chlorination of the lactam group to give the chloro derivative (**290**) (Equation (44)) <74JAP7448699>.



7.20.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

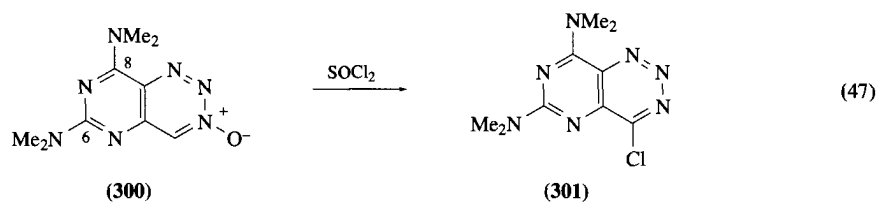
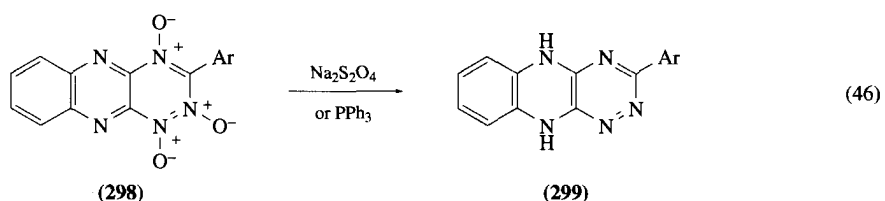
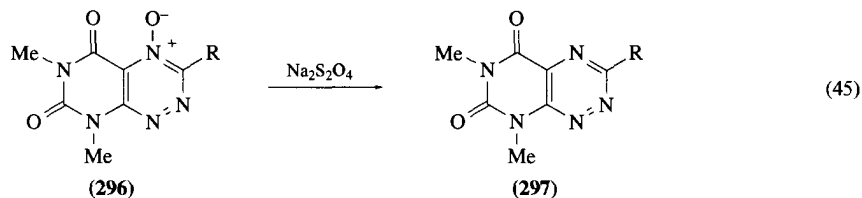
Probably the commonest substituent found attached to heterocyclic ring nitrogen is the methyl group, and an important reaction in the toxoflavin series is demethylation, since the reumycin formed is much less toxic and has potentially useful biological properties (see Section 7.20.12). Demethylation of toxoflavins (**292**) to reumycins (**291**) is effected by nucleophiles, and the use of amines and alkali for this purpose has been described in patents <80GEP2901537, 80JAP80102580, 81URP583613>. Another effective demethylating reagent is dimethylformamide <87JHC1373>, and stable intermediate radical anions have been detected during the conversion (**292**) $\rightarrow$ (**291**) with this reagent <73JA5735, 74JHC83>. Dimethylformamide can also convert a toxoflavin 4-*N*-oxide (**295**) into a reumycin (**291**) (Scheme 18). The first step here (path a) is demethylation to the reumycin *N*-oxide (**294**), which is then reduced to the reumycin (**291**). The alternative route involving initial reduction of the *N*-oxide does not seem to occur (path b), since electron spin resonance spectroscopy failed to detect any of the characteristic radical anions which would have been formed during demethylation of the intermediate toxoflavin (**292**) <75CPB2001>. If a toxoflavin (**292**) is treated with dimethylformamide and methyl iodide, a concomitant demethylation and methylation occurs and the fervenulin (**293**) can be obtained conveniently in one step. Other alkylating reagents may also be used in this reaction <74JHC271, 75BCJ2884>.



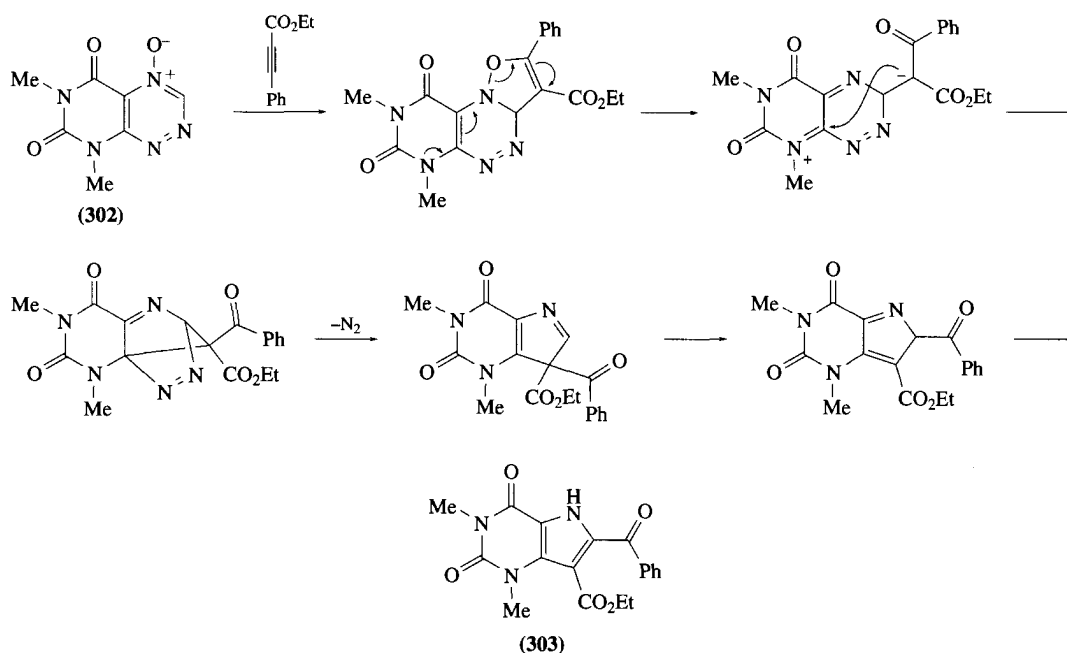
Scheme 18

The fervenulin 4-*N*-oxides (**296**) can be deoxygenated to the parent fervenulin (**297**) with sodium dithionite (Equation (45)) <73CPB448, 77JHC175, 82JHC1309>. With the same reagent, and also with triphenylphosphine, compound (**298**) loses its three *N*-oxide oxygen atoms, but suffers concomitant reduction of the pyrazine ring giving (**299**) (Equation (46)) <91S83>. Turning to another ring system, the *N*-oxides of pyrimidine[5,4-*d*]-1,2,3-triazines fail to give many of the usual *N*-oxide reactions,

probably due to the very high electron deficiency of the ring system, and also because of the ease with which the triazine ring can be cleaved. The 3-*N*-oxide (**300**), however, as well as the corresponding 6,8-di(methylthio) compound, may be converted into the 4-chloro derivative (**301**) on treatment with thionyl chloride (Equation (47)). The chlorine atom in compound (**301**) is highly reactive, and is readily replaced by nucleophiles <84JCS(P1)1475>.

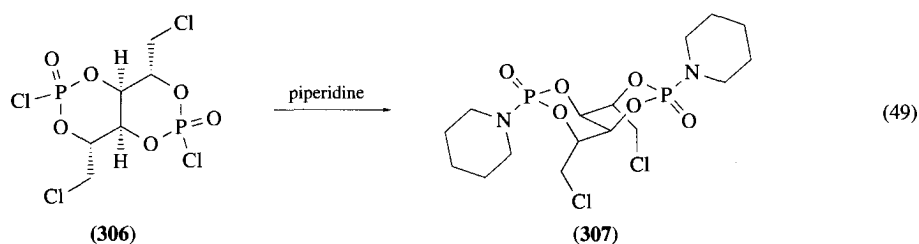
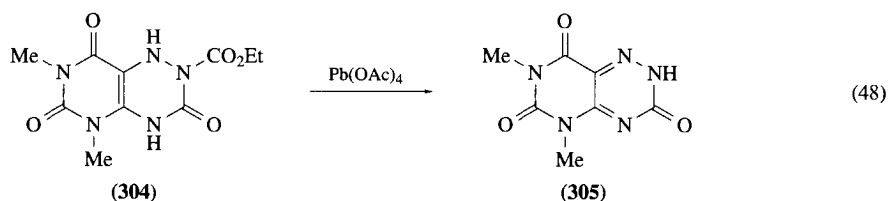


Fervenuin 4-*N*-oxide (**302**) acting as a 1,3-dipole can undergo cycloaddition with ethyl phenylpropiolate, leading ultimately to product (**303**). This interesting reaction involves a ring contraction with loss of nitrogen, and a possible mechanism is shown in Scheme 19 <85JOC2413>.



Scheme 19

Two other reactions may be mentioned: firstly, the reduced isofervenulone derivative (304) carries an ethoxycarbonyl group on the 2-nitrogen atom, and this is lost on oxidation with lead tetraacetate, giving (305) (Equation (48)) <75JOC2329>; and secondly, the reactive chlorine atoms attached to phosphorus in the [1,3,2]dioxaphosphorino[5,4-*d*]-1,3,2-dioxaphosphorin derivative (306) can be replaced by piperidine to give (307) (Equation (49)) <89IZV426>.



7.20.9 SYNTHESSES INVOLVING THE CONSTRUCTION OF A SECOND HETEROCYCLIC RING ONTO AN EXISTING MONOHETEROCYCLE

7.20.9.1 Introduction

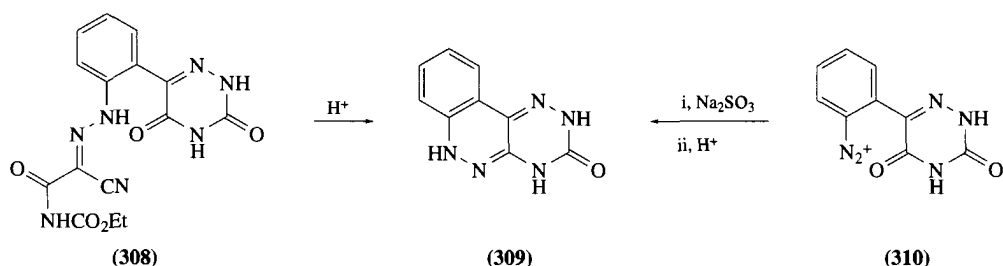
The arrangement of material in this section follows that adopted in CHEC-I. Syntheses in which a two-heteroatom ring is built on to an existing heteroatom ring are dealt with first, and classified according to whether the two heteroatoms in the new ring are disposed 1,2, 1,3, or 1,4 to the ring junction. Then come the syntheses of three-heteroatom rings, with the heteroatoms disposed either 1,2,3 or 1,2,4 to the ring junction. Depending upon the amount of material available, syntheses may be further subclassified as [6 + 0], [5 + 1], [4 + 2], or [3 + 3], referring to the number of atoms in the components which are brought together to form the new ring. This approach has the advantage that syntheses which are conceptually similar are grouped together. It means, of course, that syntheses for any particular ring system may be dealt with in more than one section.

7.20.9.2 Two Heteroatoms in the Ring being Formed

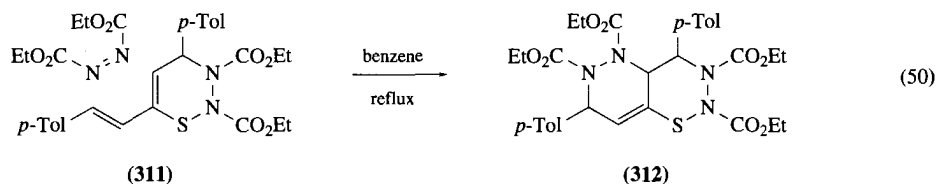
7.20.9.2.1 Two heteroatoms disposed 1,2 to the ring junction

This section covers syntheses in which a two-heteroatom six-membered ring is built onto an existing three-heteroatom six-membered ring, and in which the heteroatoms of the new ring are situated 1,2 to the ring junction. In fact, only two ring systems have been made using this approach. Compound (309) is a benzo fused pyridazino[3,4-*e*]-1,2,4-triazine (more correctly named as a 1,2,4-triazino[5,6-*c*]cinnoline), and may be prepared either by the acid-catalyzed cyclization of hydrazone (308), or by reduction of diazonium compound (310) followed by cyclization (Scheme 20) <79CCC2438>. The thione analogue of (309) may be similarly prepared <86MI 720-02>. Second, the

pyridazino[3,4-*e*]-1,2,3-thiadiazine derivative (**312**) is formed by the cycloaddition of diethyl azodicarboxylate to the thiadiazine (**311**) (Equation (50)) <90BCJ284>.

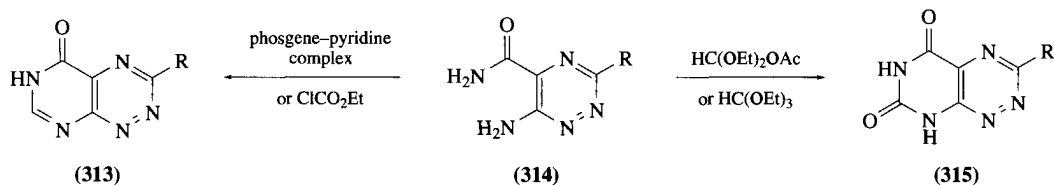


Scheme 20

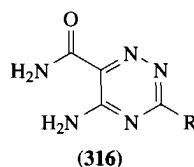


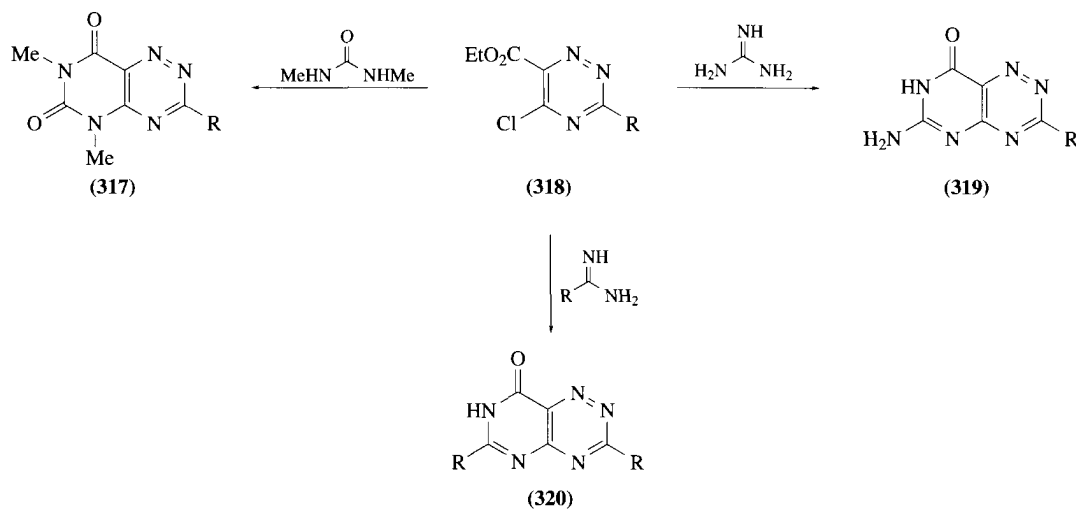
7.20.9.2.2 Two heteroatoms disposed 1,3 to the ring junction

All the syntheses described in this section involve the construction of a pyrimidine ring onto a triazine ring. One approach adopts a [5 + 1] component cyclization by treating a 6-amino-5-carbamoyl[1,2,4]triazine (**314**) with a variety of reagents which can supply the necessary single carbon atom to form pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) such as (**313**) or (**315**) (Scheme 21) <68JHC581, 69JOC2102, 74AJC1781>. In like manner, 5-amino-6-carbamoyl[1,2,4]triazines (**316**), and also 5-amino-6-cyano[1,2,4]triazines, can give the isomeric pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) <70JOC3792, 78HCA1175>. These latter may also be obtained by a [3 + 3] component cyclization, in which precursors of type (**318**) condense with urea, guanidine, or amidine reagents to give products (**317**), (**319**), or (**320**) (Scheme 22). The chlorine atom in (**318**) is very reactive due to the low electron density of the triazine ring <72LA(758)173, 85JOC2293, 87TL1977>.



Scheme 21

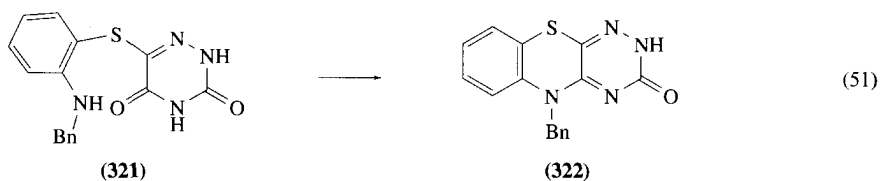




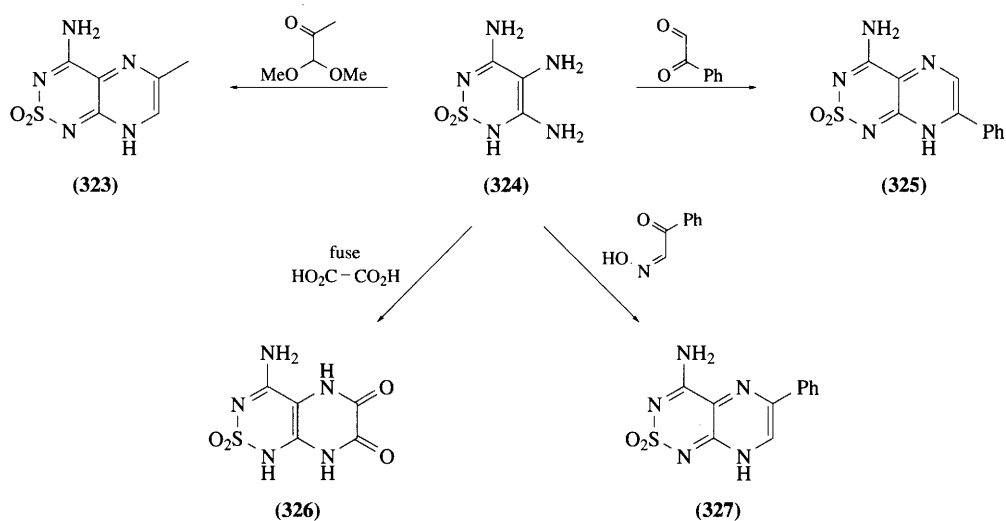
Scheme 22

7.20.9.2.3 Two heteroatoms disposed 1,4 to the ring junction

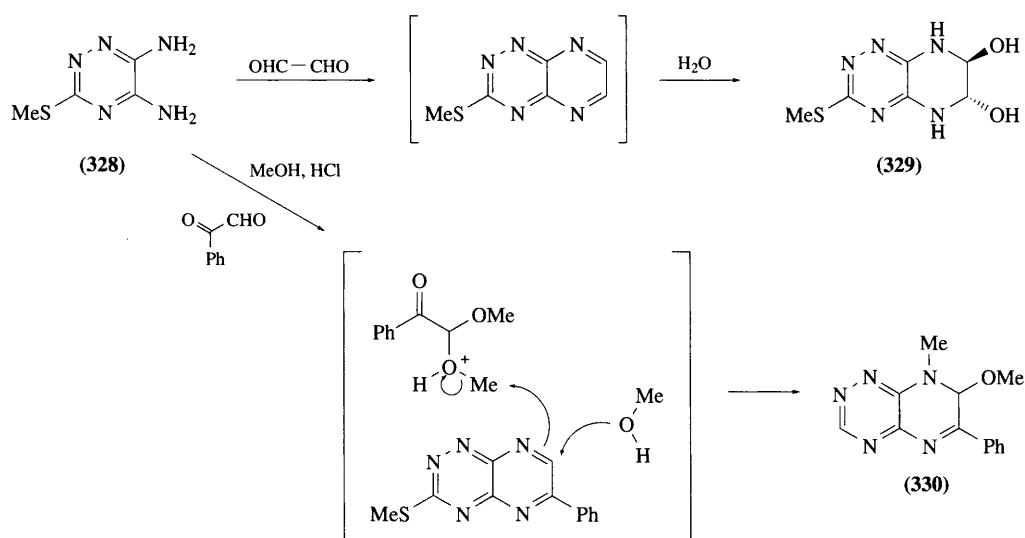
In the syntheses described in this section, a two-heteroatom ring is built onto an existing heterocyclic ring, the two heteroatoms in the newly constructed ring being 1,4 to the new ring junction. Most of the methods involve a [4 + 2] component cyclization, an exception being a [6 + 0] cyclization described in the Japanese patent literature for the preparation from (321) of a series of benzo-1,4-thiazino[3,2-*e*]-1,2,4-triazine compounds (322) (Equation (51)) <76JAP7605399>. Pyrazino-[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide derivatives such as (323), (325), (326), and (327) are conveniently prepared by a [4 + 2] component condensation involving two adjacent amino groups of compound (324) and two adjacent electrophilic carbon atoms in suitable reagents such as ketones or oximes (Scheme 23). By varying the reagent the regiochemistry of the reaction can be controlled, as for example in compounds (325) and (327) <85MIP531160, 88LA121, 88JST423, 90MI720-02, 92JMC3977>. Better yields may sometimes be obtained by reacting compound (324) with two molecules of an aromatic aldehyde, instead of with a benzil type 1,2-diketone <88JHC891, 88H(27)2201>.



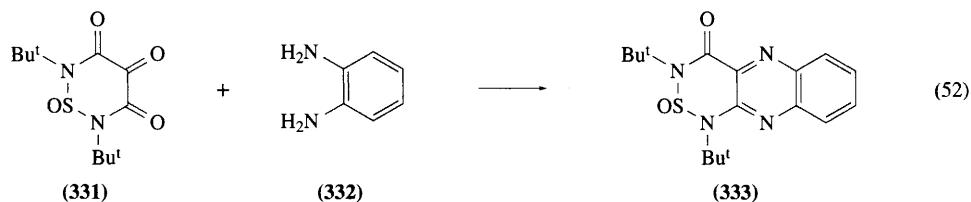
The same type of synthesis affords pyrazino[2,3-*e*]-1,2,4-triazines (329) and (330) from the diamino precursor (328), by reaction of the latter with glyoxal or phenylglyoxal, respectively. Product (329) is a dihydrate. The fully aromatic intermediate could not be isolated. Formation of (330) involves not only covalent solvation, but also an unusual *N*-methylation of the presumed first-formed intermediate, and the suggested mechanism is outlined in Scheme 24 <86JHC33, 93H(36)2577>. Reversing the order of polarities of the components allows [4 + 2] cyclization of pyrimidine (331) with *ortho*-phenylenediamine (332), giving the benzo fused pyrazino[2,3-*c*][1,2,6]thiadiazine (333) (a [1,2,6]thiadiazino[3,4-*b*]quinoxaline) (Equation (52)) <72ZN(B)1471>.



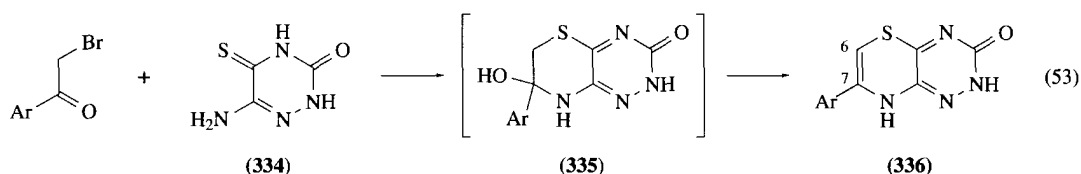
Scheme 23



Scheme 24



The 1,4-thiazino[2,3-*e*]-1,2,4-thiadiazine (336) is formed by a [4 + 2] component condensation of triazine (334) with an α -bromo ketone. This reaction involves an unexpected direction of dehydration in the presumed intermediate (335), leading to the product (336) with a 6,7 double bond, rather than the more fully conjugated isomer with a 7,8 double bond (Equation (53)) (93JHC293).



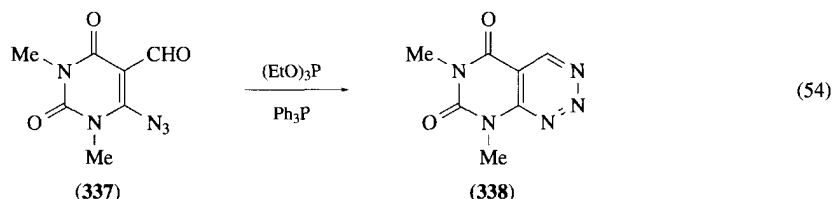
7.20.9.3 Three Heteroatoms in the Ring being Formed

7.20.9.3.1 Three heteroatoms disposed 1,2,3 to the ring junction

In this section, the three heteroatoms in the ring being formed are disposed 1,2,3 to the ring junction. Syntheses are classified according to the number of atoms in the components used to construct the new ring.

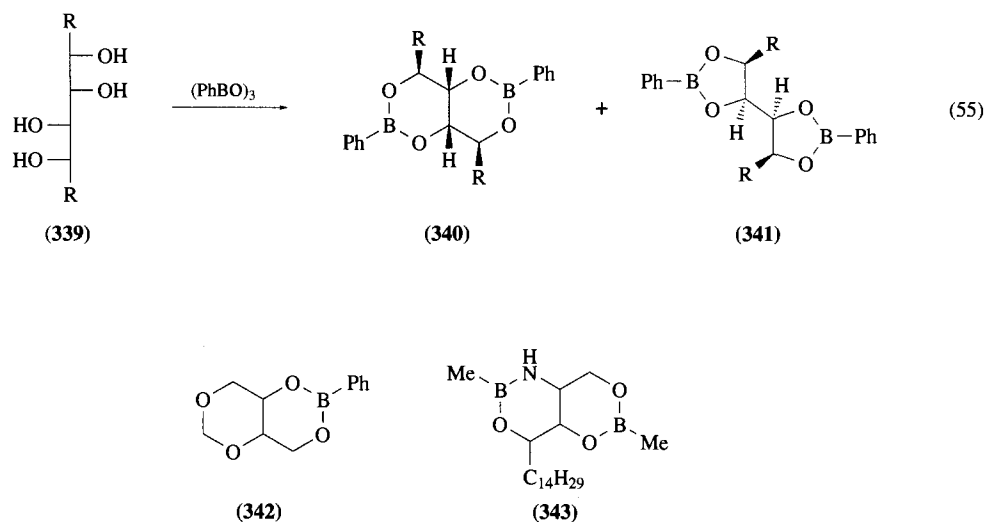
(i) [6 + 0] Component syntheses

Only one synthesis has been described using this approach. It involves cyclization of the 4-azidopyrimidine precursor (337) to give the pyrimido[4,5-*d*]-1,2,3-triazine (338) (Equation (54)) <83CPB3959>.

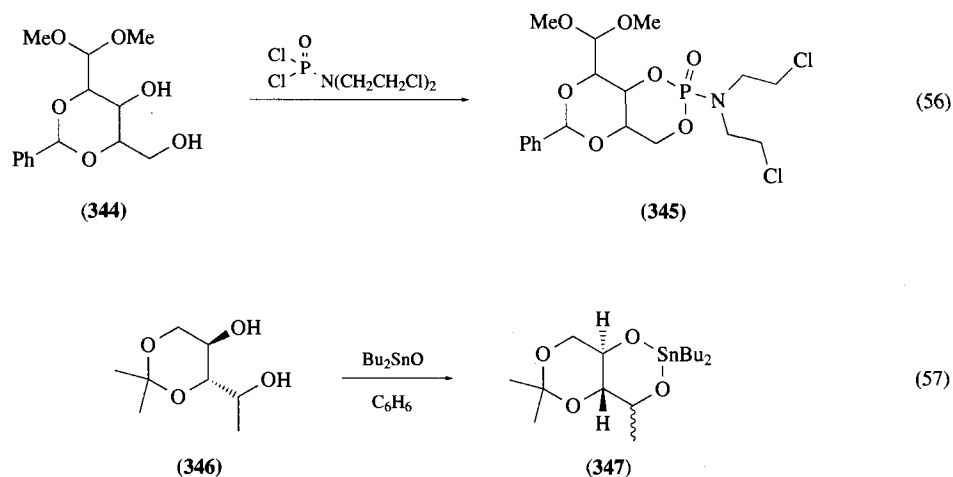


(ii) [5 + 1] Component syntheses

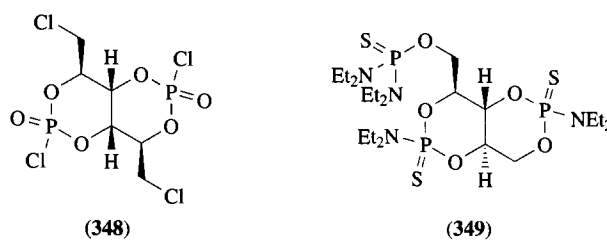
Sugars provide a ready source of 1,3-diols which may undergo [5 + 1] component cyclization to give 1,3,2-dioxaborins, -dioxaphosphorins, and -dioxastannins. When four hydroxyl groups are adjacent in the same sugar molecule, as in a 1,2,3,4-tetraol (339), and when they react as two 1,3 pairs with two molecules of benzenboronic anhydride, (PhBO)₃, then tetrahydro derivatives of the [1,3,2]dioxaborino[5,4-*d*]-1,3,2-dioxaborin ring system (340) are formed (Equation (55)). On the other hand, when the four hydroxyl groups react as two 1,2 pairs, bidioxaborolanes (341) are formed. A mixture of the two types of dibenzenboronate is usually obtained, and monobenzenboronates are not usually detected <79CAR(72)35>. Depending upon the relative configurations of the hydroxyl groups in the starting material, the two rings in the bicyclic products may be either *cis*-fused, as in (340), or *trans*-fused, and sometimes steric factors can be identified which allow the bicyclic product (340) to predominate over the bidioxaborolane (341). Similar products can be obtained from precursors containing five and six adjacent hydroxyl groups, although the number of possible isomers increases <80CAR(81)7, 80CAR(81)17>. Other reagents which react with diols to give these boron bicyclic compounds include diethyl(pivaloyloxy)borane <83CB3332>, triethylboroxin <80LA1176>, ethyl dimethoxyborane <80AG(E)548>, and butyl boronic acid <71MI 720-01>. Tetrahydro[1,3]dioxino[5,4-*d*]-1,3,2-dioxaborins (342) are simpler phenylboronate derivatives of sugars which have been known for a long time <65CAR(1)145, 65JCS7453>, and the bis-boronate (343) of hydroxysphinganine (a 2-amino-1,3-diol) incorporates a reduced form of the very uncommon 1,3,2-dioxaborino-[5,4-*d*][1,3,2]oxazaborine ring system <77OMS(12)651>.

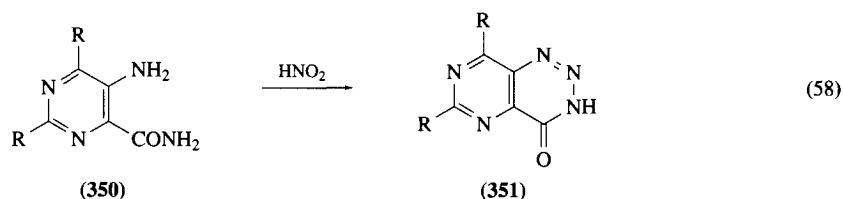


Analogous to these compounds are the tetrahydro[1,3]dioxino[5,4-*d*]-1,3,2-dioxaphosphorins such as compound (345), which was prepared as a nitrogen mustard from the ribose derivative (344) (Equation (56)) <62JOC3332>. Other examples of this ring system can be similarly prepared from sugars <83IZV329, 88ZOB2743>. The tetrahydro[1,3]dioxino[5,4-*d*]-1,3,2-dioxastannin (347), may be prepared from the 1-deoxypentitol (346) (Equation (57)) <82JCS(P1)2131>.



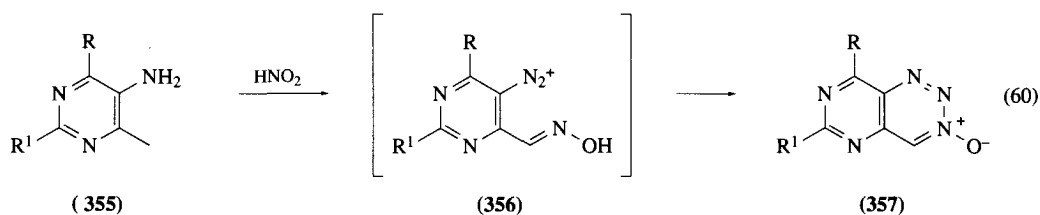
The only known bicyclic compounds having two phosphorus and four oxygen atoms in the rings are tetrahydro derivatives of the [1,3,2]dioxaphosphorino[5,4-*d*]-1,3,2-dioxaphosphorin ring system, prepared by a [5 + 1] synthesis from mannitol and ribitol <87IZV1193, 88ZOB699>. Two examples whose structures and conformations were proved by x-ray crystallography are compounds (348) and (349) <85IZV1550, 89IZV426>. The pyrimido[5,4-*d*]-1,2,3-triazine system, for example (351), may also be made by a [5 + 1] component cyclization, and many examples of it have been prepared and patented by treatment of a 5-amino-4-carbamoylpyrimidine (350) with nitrous acid (Equation (58)) <65USP3213090>.





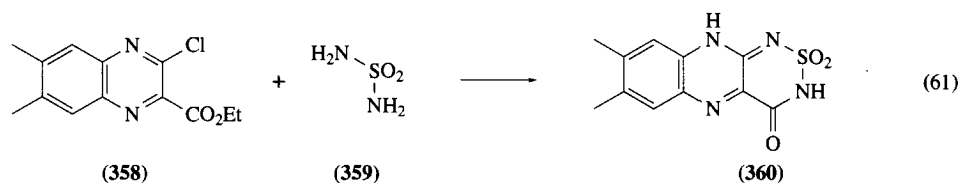
(iii) [4 + 2] Component syntheses

Construction of a 1,2,6-thiadiazine ring onto a pyrimidine ring may be achieved by the [4 + 2] component condensation of pyrimidine (352) with aminosulfonyl chloride (353), giving the 2,2-dioxide derivative (354) of the rare pyrimido[4,5-*c*][1,2,6]thiadiazine ring system (Equation (59)) <77HCA521>. Although strictly speaking it is not a [4 + 2] synthesis, a 1,2,3-triazine ring may be built onto a 4-alkyl-5-aminopyrimidine (355) by nitrosation of the latter. First described using 5-amino-4-methyluracil <63JOC1329>, the reaction was later extended to other pyrimidine starting materials, and both sodium nitrite and isoamyl nitrite can act as nitrosating reagents <84JCS(P1)1475, 84KGS268, 86CCC215>. Both the 4-methyl and the 5-amino groups of the derivatives (355) react with the nitrosating agent, leading to intermediate (356), which then cyclizes to the pyrimido[5,4-*d*]-1,2,3-triazine 3-*N*-oxide (357) (Equation (60)).



(iv) [3 + 3] Component syntheses

The cinnolino[2,3-*c*]-1,2,6-thiadiazine (360) may be synthesized by a [3 + 3] component cyclization of the precursors (358) and (359) (Equation (61)) <86AP(319)79>. It is a benzo derivative of a pyrazino[2,3-*c*][1,2,6]thiadiazine. Most examples of this latter ring system, however, have been prepared by constructing the pyrazine ring on to a 1,2,6-thiadiazine (see Section 7.20.9.2.3).

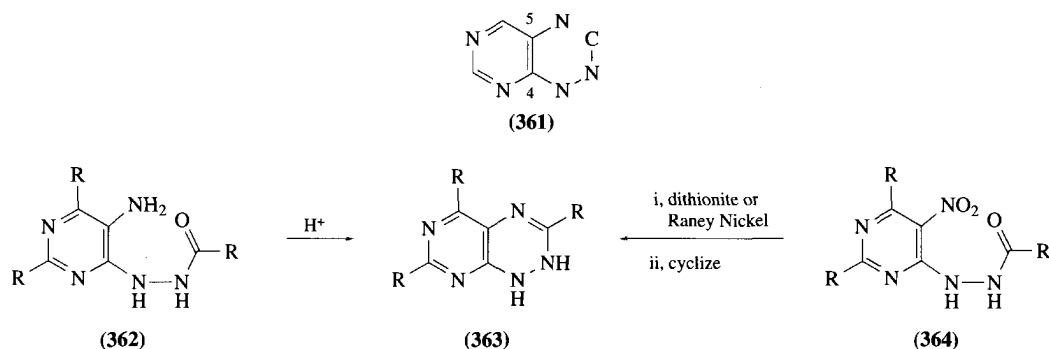


7.20.9.3.2 Three heteroatoms disposed 1,2,4 to the ring junction

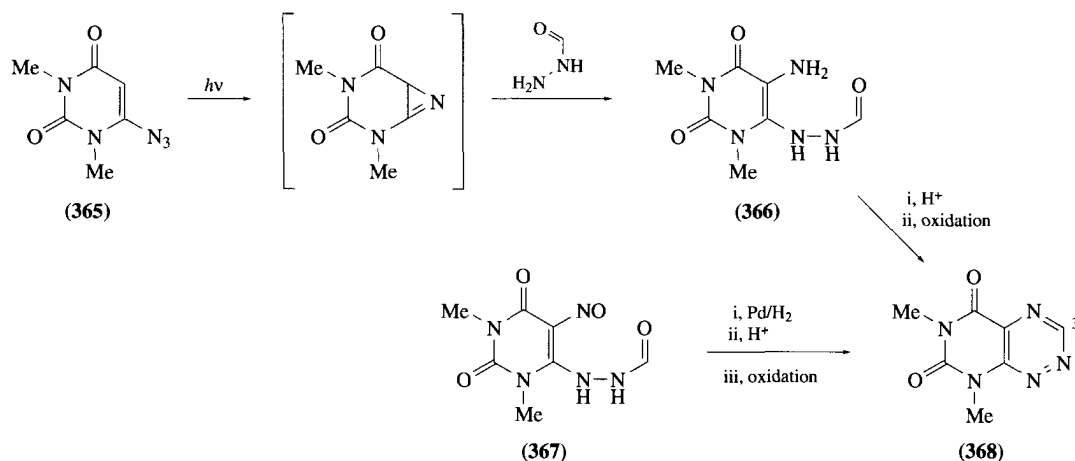
(i) [6 + 0] Component syntheses

(a) *Pyrimidotriazines (azapteridines) (6) and (8)*. The commonest [6 + 0] component approach to the synthesis of pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) employs a pyrimidine starting

material of the general type (361), in which the substituted hydrazino group at position four is readily introduced by the nucleophilic replacement of a chlorine atom. The 5-nitrogen substituent may be either an NH_2 group, or an NH_2 precursor such as NO , NO_2 , $\text{N}=\text{NAr}$, $\text{N}(\text{CO}_2\text{R})\text{NHCO}_2\text{R}$, or a fused furazan ring. It is possible to prepare 5-amino-4-acylhydrazinopyrimidines (362) and to cyclize them to the corresponding 1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazines (363) <64JCS4986, 71JCS(C)2475>. It is much easier, however, to generate the 5-amino group *in situ* by catalytic or dithionite reduction of the corresponding 5-nitropyrimidine, and precursors such as (364) offer a versatile route to a wide variety of pyrimido[5,4-*e*]-1,2,4-triazine derivatives (363) by reduction of the nitro group and subsequent cyclization, without isolation of the 5-amino intermediate <66JOC900, 70JCS(C)139, 70MI 720-01, 72JCS(P1)237, 80JCR(S)278>. These reactions are shown in Scheme 25. The initially formed dihydro products (363) are as a rule easily oxidizable to the fully aromatic compounds. While less common, reductive cyclization of 5-nitrosopyrimidine precursors proceeds similarly <74JCS(P1)1818>, and the first synthesis of fervenulin (368) was achieved by this method from (367) <58LA42, 61JOC5256>. An unusual route to fervenulin (368) and its 3-substituted derivatives involves photolysis of 6-azido-1,3-dimethyluracil (365) in the presence of an acylhydrazine. This reaction is believed to proceed via an unstable azirine, which suffers nucleophilic attack by the acylhydrazine, forming the desired 5-amino intermediate (366) <78JA7661>. These reactions are shown in Scheme 26. Finally, a 4,5-diaminopyrimine moiety may be generated by catalytic hydrogenolysis of a furazano[3,4-*d*]pyrimidine, and this reaction may be used for the synthesis of 5-aminopyrimido[5,4-*e*]-1,2,4-triazines, as in the preparation of (370) from (369) (Scheme 27) <73JOC2238>.

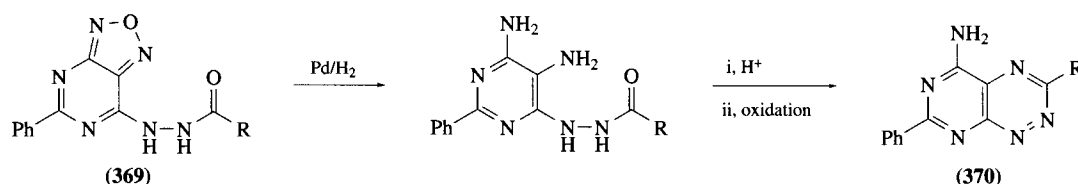


Scheme 25



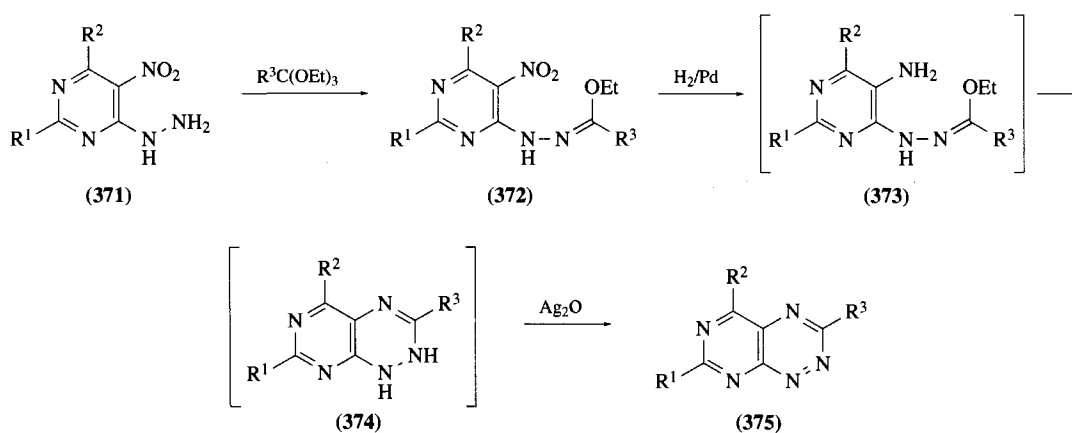
Scheme 26

Another important synthesis involves the reductive cyclization of 4-ethoxyalkylidenehydrazino-5-nitropyrimidines of type (372), which are obtained readily by reaction of 4-hydrazino-5-nitropyrimidines (371) with *ortho* esters. Catalytic reduction of the nitro group in (372) affords the 5-aminopyrimidine intermediate (373), which cyclizes *in situ* to the dihydro product (374). This may be oxidized without isolation to give the fully aromatic product (375). These reactions are shown in

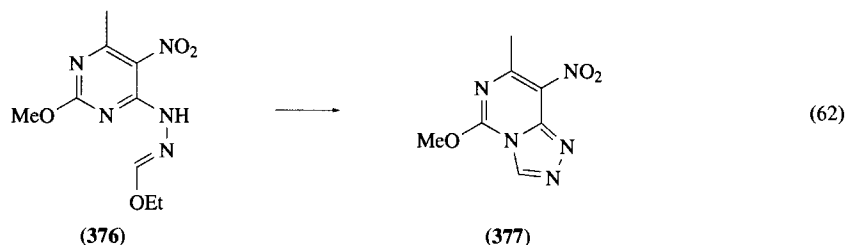


Scheme 27

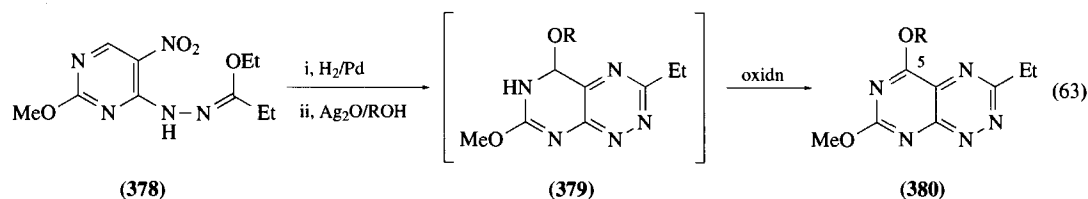
Scheme 28. The group R^3 in derivative (375) is dictated by the choice of *ortho* ester used, while R^1 and R^2 are dictated by the substitution pattern of the starting pyrimidine (371) <70JCS(C)139, 71AJC633>. Problems may arise occasionally during these reactions due to the ability of the 4-ethoxyalkylidenehydrazino group to cyclize onto a pyrimidine ring nitrogen atom. Thus, under vigorous reaction conditions, the triazolopyrimidine (377) was obtained from (376), precluding formation of the desired pyrimidotriazine (Equation 62) <71AJC633>.

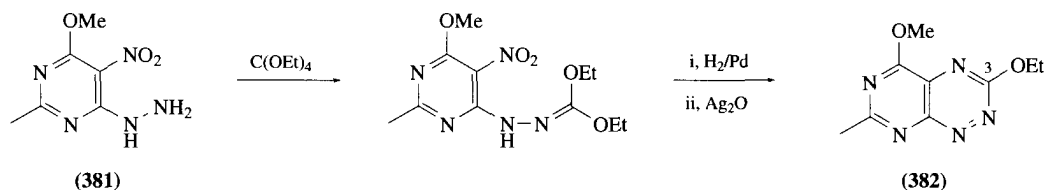


Scheme 28

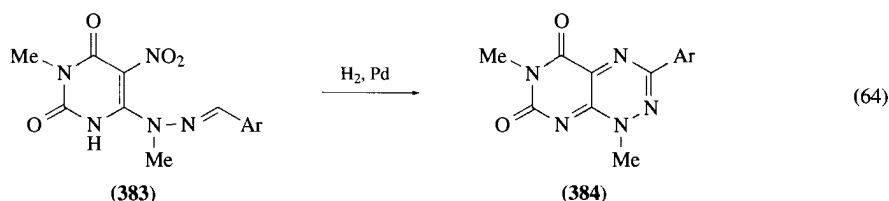


A useful variation for obtaining a 5-alkoxy-substituted product (380) is to start with a 6-unsubstituted pyrimidine precursor (378). After reduction of the nitro group and cyclization, the resulting dihydro intermediate is oxidized with silver oxide and alcohol to the fully aromatic system. This covalently adds a molecule of alcohol, giving intermediate (379), which is then oxidized again to the desired 5-alkoxy aromatic product (380) (Equation (63)) <72JCS(P1)2316> (see Section 7.20.5.4). A 3-alkoxy product may be prepared by another variation which uses an *ortho* carbonate instead of an *ortho* ester to react with the initial 4-hydrazinopyrimidine, as in the conversion (381) $\rightarrow$ (382) (Scheme 29) <73AJC1689>. Yet another variation is the reductive cyclization of the pyrimidine 5-nitro group onto an adjacent hydrazone functionality, and this may be used to prepare toxoflavin derivatives (384) from precursors (383) (Equation (64)) <75SI77>.

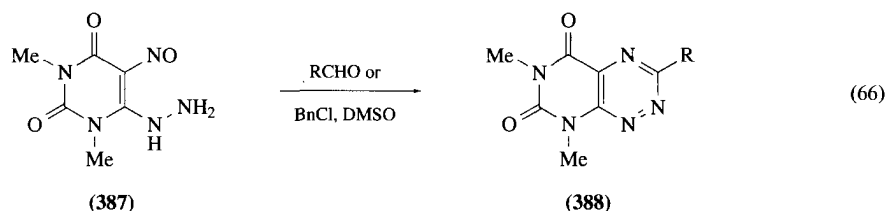
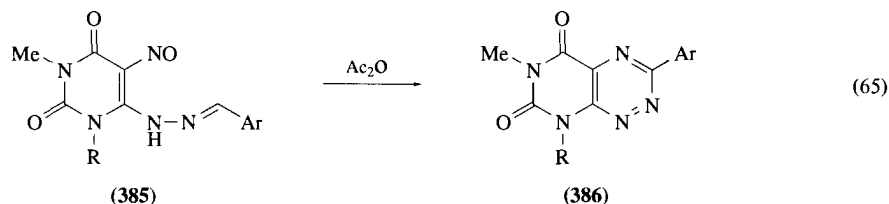




Scheme 29

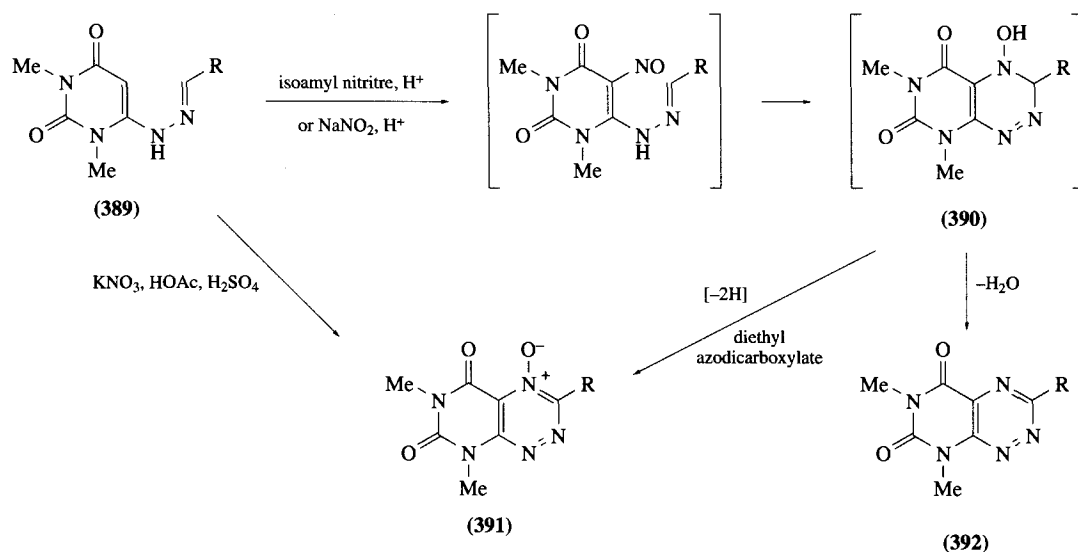


A different, nonreductive approach to triazine ring formation from a 5-nitrosopyrimidine precursor involves interaction of the nitroso group with an adjacent hydrazone functionality, and several pyrimido[5,4-*e*]-1,2,4-triazines have been prepared by this method, as in the conversion of (385) to (386) (Equation (65)) <78CPB3154, 80JHC869>. The hydrazone may be generated *in situ*, and cyclized without isolating it, by adding an aldehyde to the 6-hydrazino-5-nitrosopyrimidine (387), giving (388) (Equation (66)) <72CB3334, 84KFZ573>, or even by adding hydrazine and an aldehyde to 6-amino-1,3-dimethyl-5-nitrosouracil <88JOC3568>. Yet another variation is to treat the 6-hydrazino-5-nitroso-pyrimidine (387) with a benzylic chloride in the presence of DMSO, thus generating the aldehyde *in situ* <77H(6)1921>.

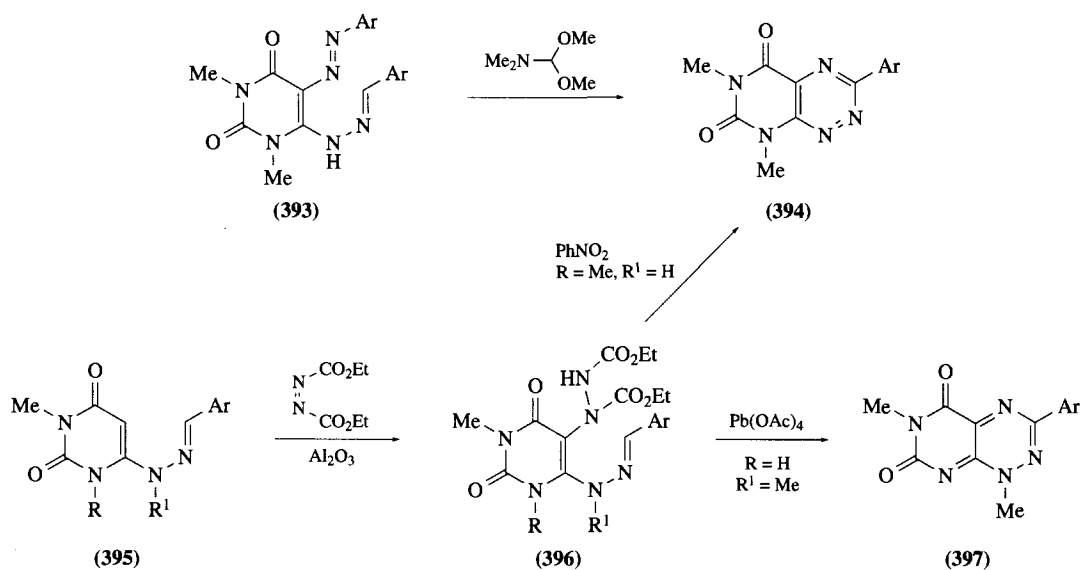


The 5-nitroso group may also be introduced and cyclized *in situ* <74JHC83, 92KGS219, 94H(37)1147>. While really a [5 + 1] component synthesis, this is so obviously related to the reactions just described above that it is more logically included here. 3-Substituted fervenulins (392), for example, may be made by the nitrosation of the derivatives (389) <72CB3334>. Sometimes the 4-*N*-oxide (391) is obtained in these cyclizations, depending upon whether the intermediate (390) undergoes dehydrogenation or dehydration <71TL851>. If the strong hydrogen-abstracting agent diethyl azodicarboxylate is added to the reaction, the 4-*N*-oxide (391) is the only product formed <76CC658, 76JCS(P1)713>. Closely related to these reactions is nitrative cyclization, which leads directly to a 4-*N*-oxide product. Thus treatment of derivatives (389) with potassium nitrate in strong acid gives fervenulin 4-*N*-oxides (391) <76CPB338>. All these reactions are shown in Scheme 30.

A related synthesis of 3-substituted fervenulins (394) uses an azo group at the 5-position of the pyrimidine precursor (393) instead of a nitroso group <81H(16)559>. Finally, yet another type of nitrogen functionality at the pyrimidine 5-position is that shown in (396), introduced by treatment of a pyrimidine (395) with diethyl azodicarboxylate. Cyclization of (396) using nitrobenzene or lead tetraacetate affords fervenulin (394) or toxoflavin (397) derivatives <76JCS(P1)2398>. All these reactions are shown in Scheme 31.

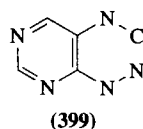
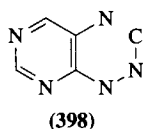


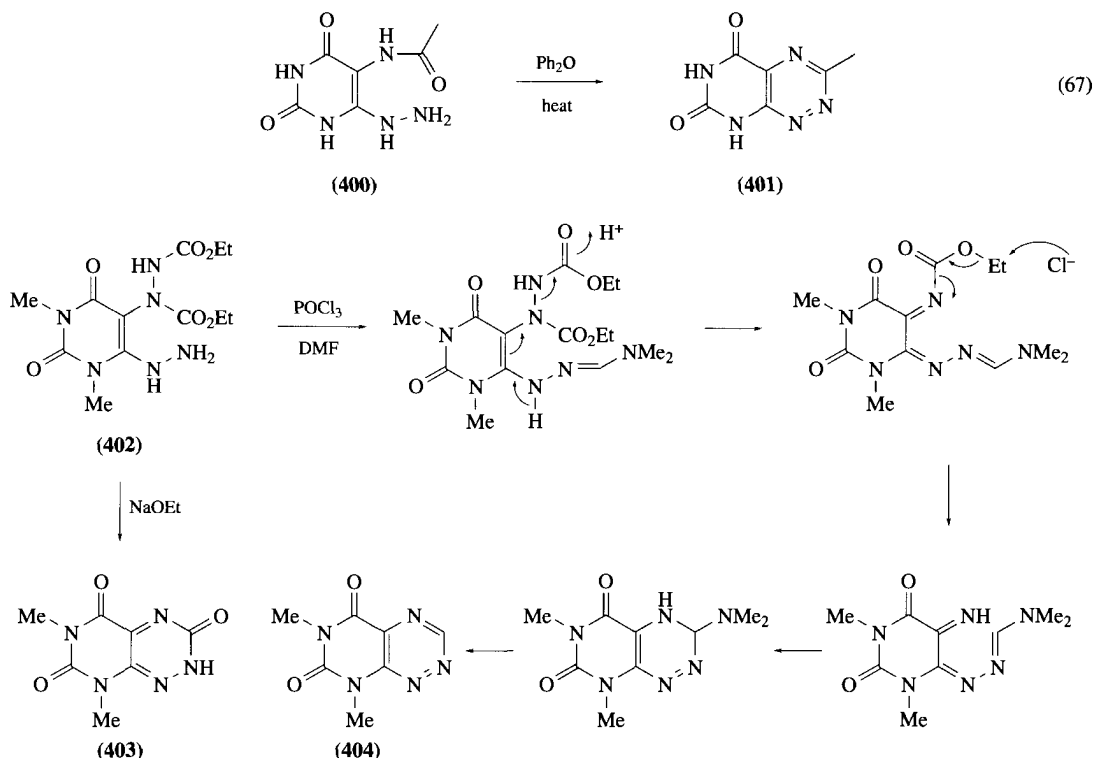
Scheme 30



Scheme 31

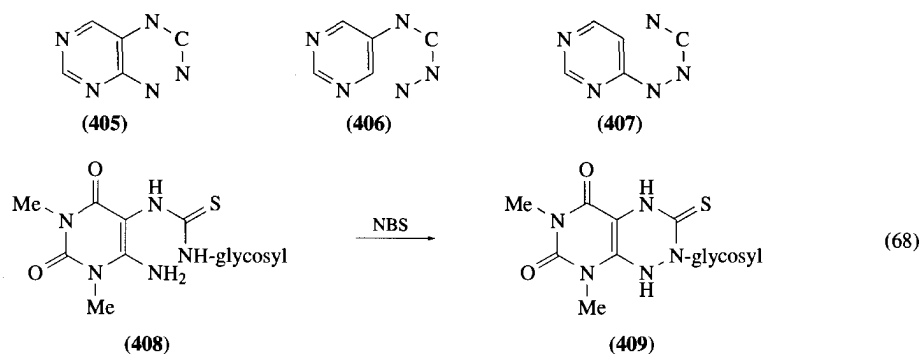
All the syntheses described above have involved the [6 + 0] ring closure of a pyrimidine precursor of the general type (398). There are a few [6 + 0] syntheses of pyrimido [5,4-*e*]-1,2,4-triazines which involve ring closure of a precursor of the general type (399). Thus pyrimidine (400) cyclizes to (401) on heating (Equation (67)) <68JMC1107>, and 7-azaxanthopterin may be synthesized by a closely related route <79JOC1125>. Pyrimidine (402) affords fervenulone (403) on treatment with ethoxide. On the other hand, in an unusual reaction, the same pyrimidine (402) gives fervenulin (404) on treatment with Vilsmeier's reagent, and the suggested mechanism is shown in Scheme 32 <75JOC2321>.



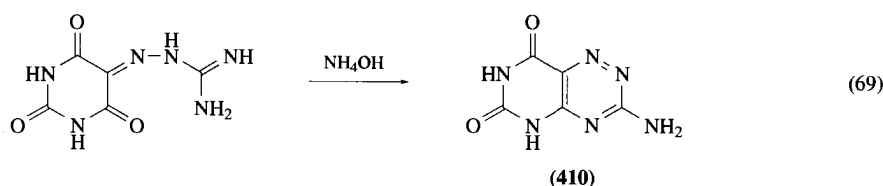


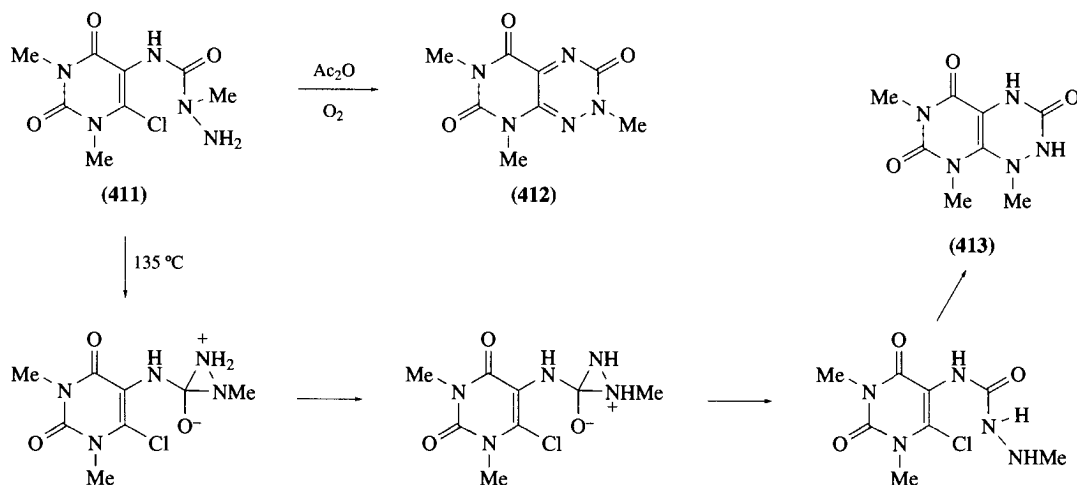
Scheme 32

[6 + 0] Syntheses from precursors of types (405) and (406) are rare, and of type (407) are unknown. One example of the first of these is the oxidative cyclization of pyrimidine (408) to the glycosyl pyrimidotriazine (409) (Equation (68)) <82MI 720-01>. An interesting example of the second type is the cyclization of the 6-chloropyrimidine (411). In the presence of air this affords 2-methylfervenulone (412) by straightforward intramolecular nucleophilic substitution of the chlorine atom. Pyrolytic cyclization of compound (411), however, affords the isomeric 1-methyl product (413), possibly via a diaziridine intermediate (Scheme 33) <75JOC2321>.

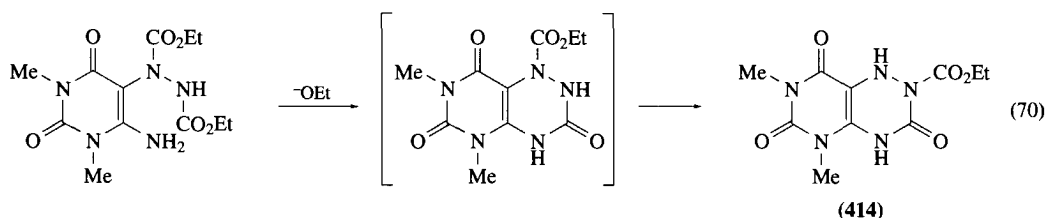


Syntheses of pyrimido[4,5-*e*]-1,2,4-triazines (6-azapteridines) by [6 + 0] component cyclization of pyrimidine precursors are uncommon. Two examples, however, are the preparation of compounds (410) and (414) (Equations (69) and (70)). Formation of the latter is interesting in that it involves an intramolecular acyl transfer of the ester group from one nitrogen atom to an adjacent one <65JA1976, 75JOC2329>.

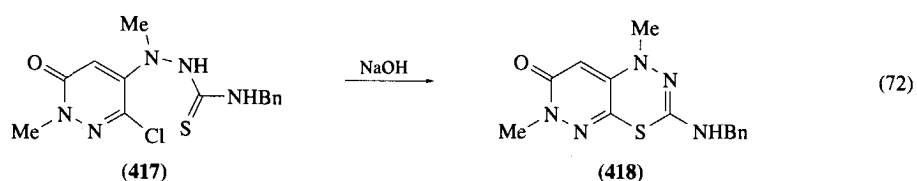
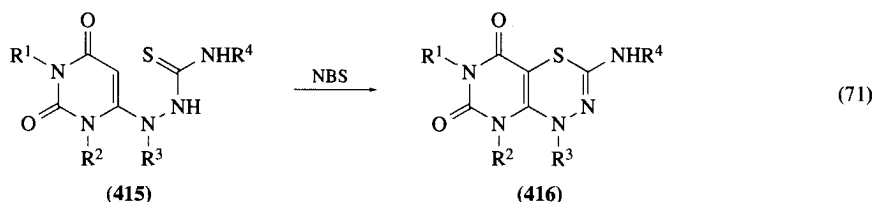


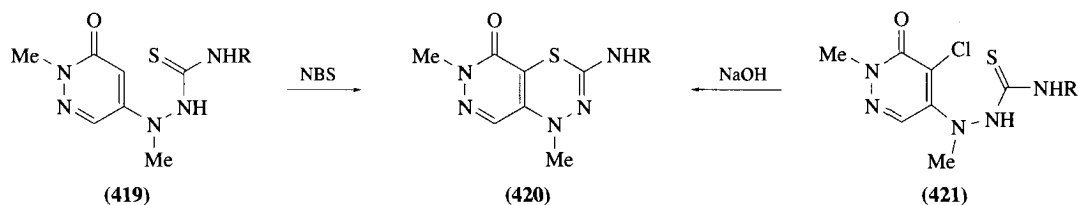


Scheme 33



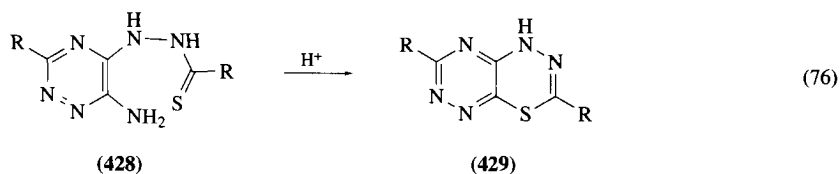
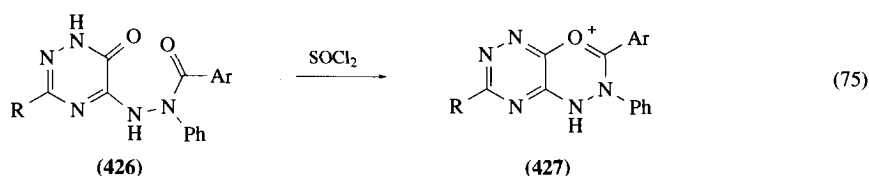
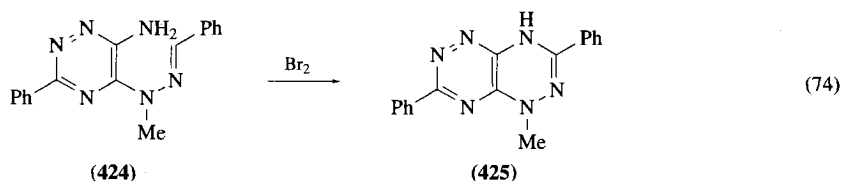
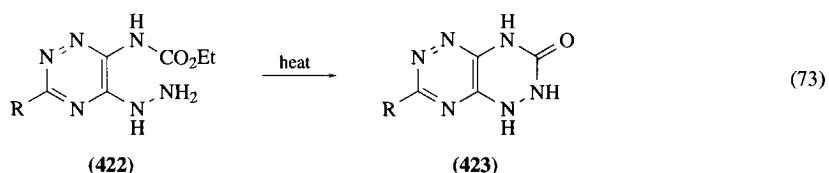
(b) *Other ring systems.* Intramolecular oxidative [6 + 0] ring closure of sulfur onto the 5-position of a pyrimidine ring may be used to prepare a wide variety of substituted pyrimido[4,5-*e*] [1,3,4]thiadiazines (416) from precursors (415), using *N*-bromo- or *N*-chlorosuccinimide as oxidant (Equation (71)) <78JAP7828192, 78MI 720-01, 78MI 720-02, 79CPB1965>. The same ring closure may also be used to prepare pyridazino[4,5-*e*] [1,3,4]thiadiazines (420) from (419) <85JHC161>, and improved results are sometimes obtained using diethyl azodicarboxylate as reagent (Scheme 34) <90S1020>. Intramolecular nucleophilic replacement of chlorine may be used to synthesize the pyridazino[4,3-*e*] [1,3,4]-thiadiazine ring system (418) from a chloropyridazine precursor (417) (Equation (72)), and the same type of reaction does give the isomeric pyridazino[4,5-*e*] [1,3,4]thiadiazine (420) from (421) (Scheme 34). In the latter case, however, the initially formed product (420) may suffer desulfurization under the basic reaction conditions used, leading to a pyrazolo[3,4-*d*]pyridazine as a major by-product <85JHC161>.





Scheme 34

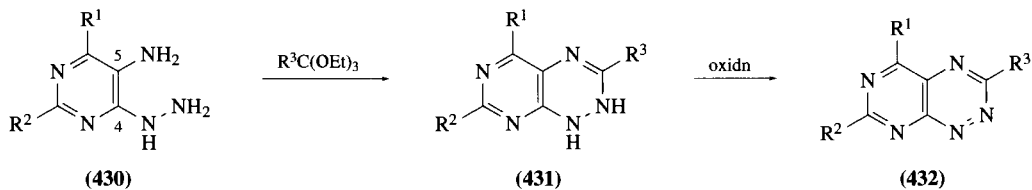
Three six-heteroatom ring systems have been synthesized by [6 + 0] component ring closure reactions. The first of these is the [1,2,4]triazino[6,5-*e*]-1,2,4-triazine system (a diazapteridine) and is accessible either by heating (422) to give (423) (Equation (73)), or by treating (424) with bromine to give (425) (Equation (74)) <83TL1767>. The second is a [1,2,4]triazino[5,6-*e*][1,3,4]oxadiazine derivative (427) and is obtained by thionyl chloride treatment of (426) (Equation (75)) <87S128>. The third is a [1,2,4]triazino[5,6-*e*][1,3,4]thiadiazine (429), formed by acid-catalyzed cyclization of (428) (Equation (76)) <88S778>.



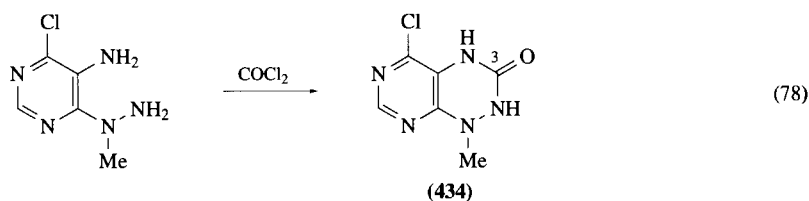
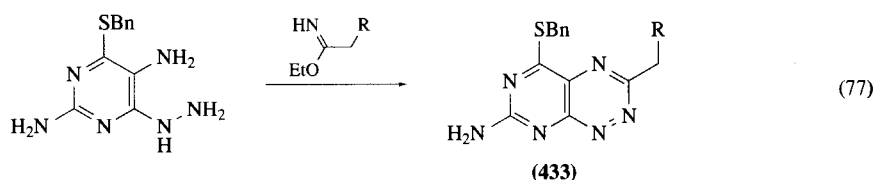
(ii) [5 + 1] Component syntheses

(a) *Pyrimidotriazines (azapteridines) (6) and (8)*. All the useful [5 + 1] component methods for preparing pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) start with a 4-hydrazinopyrimidine carrying either an amino or a nitroso group at position 5. A variety of reagents may supply the necessary one carbon atom. To some extent the classification of these reactions as [5 + 1] is arbitrary, since in most cases the new ring will be formed by a [6 + 0] cyclization of an (unisolated) intermediate, and some of the reactions described here are closely related to those described in Section 7.20.9.3.2(i)(a).

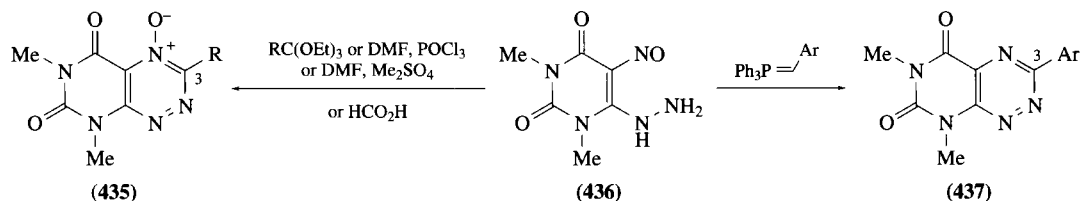
5-Amino-4-hydrazinopyrimidines (**430**) may be cyclized with *ortho* esters, affording 1,2-dihydro-pyrimido[5,4-*e*]-1,2,4-triazines (**431**), which as a rule are easily oxidized to the fully aromatic compounds (**432**) (Scheme 35). The substituent R^3 in the product (**432**) is dictated by the *ortho* ester used <63JOC923, 69JOC3161, 70JCS(C)139, 71JCS(C)2475, 71JOC2974, 71JOC3502, 74JCS(P1)1565>. Cyclization may also be achieved using an imidic ester, generated *in situ*, giving a product such as (**433**) (Equation (77)) <85JHC1369>, and 7-azafolic acid can be synthesized using this method <73JHC889>. Finally, cyclization with phosgene gives a 3-oxo product (**434**) (Equation (78)) <63JOC2677>. Cyclization has been effected with formic acid, but this procedure is sometimes complicated by purine formation <60JA4592, 61JOC4961>.



Scheme 35

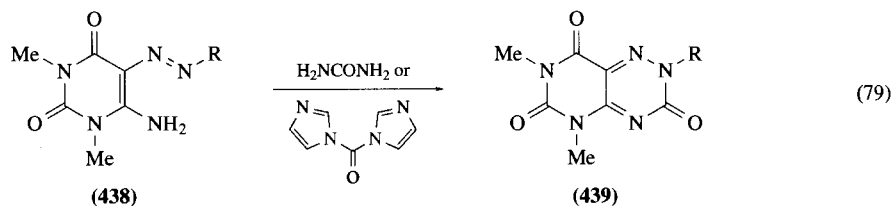


6-Hydrazino-5-nitrosopyrimidines of type (**436**) may also be cyclized, and $RC(OEt)_3$, DMF/ $POCl_3$, DMF/ Me_2SO_4 , and HCO_2H can all convert (**436**) into fervenulin 4-*N*-oxides (**435**) <78JOC469>. The *ortho* ester is the more versatile reagent, since it can give different 3-substituted products, depending upon the *ortho* ester used. Treatment of the same starting material (**436**) with a Wittig reagent gives 3-arylfervenulins (**437**) <78H(9)29>. These reactions are shown in Scheme 36.



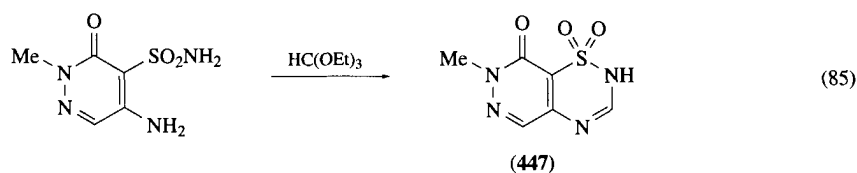
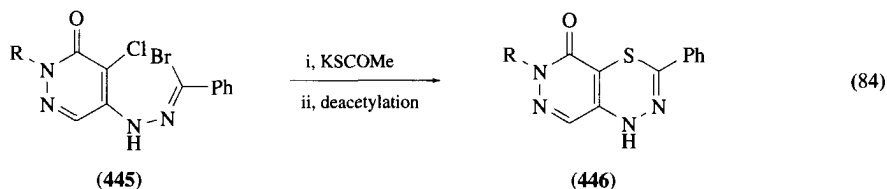
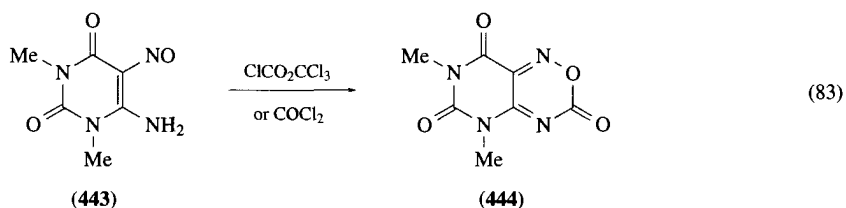
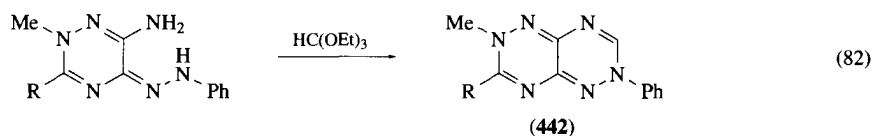
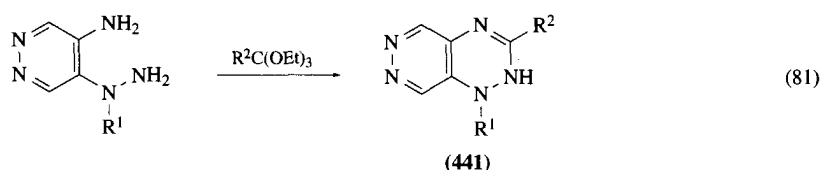
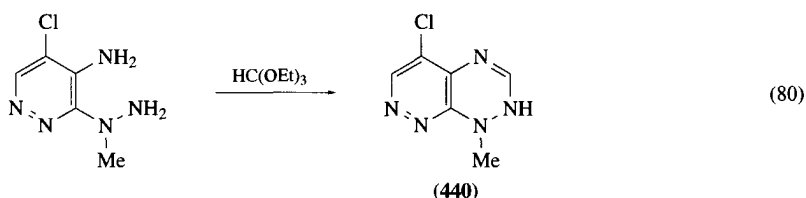
Scheme 36

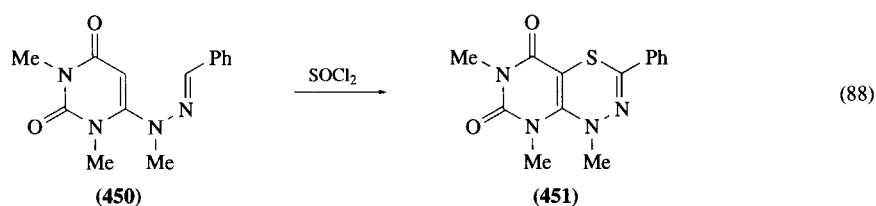
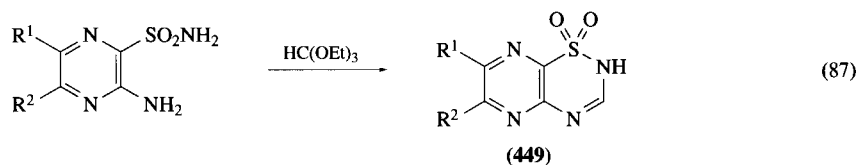
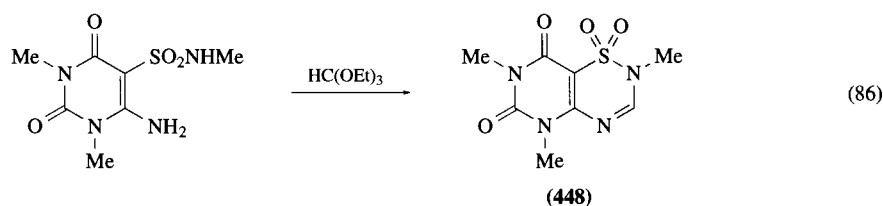
3-Oxo derivatives (**439**) of the isomeric pyrimido[4,5-*e*]-1,2,4-triazine ring system (6-azapteridines) can be prepared by cyclization of the amines (**438**) with either urea or *N,N'*-carbonyldiimidazole (Equation (79)) <80JHC1365>.



(b) *Other ring systems.* Apart from the pyrimidotriazine (azapteridine) syntheses described in the previous section, the use of a [5 + 1] component cyclization for the construction of a new 1,2,4-heteroatom ring onto an existing heterocycle is rare. While eight other ring systems have been prepared this way (one of them containing six heteroatoms), most of them are covered by just a single report in the literature.

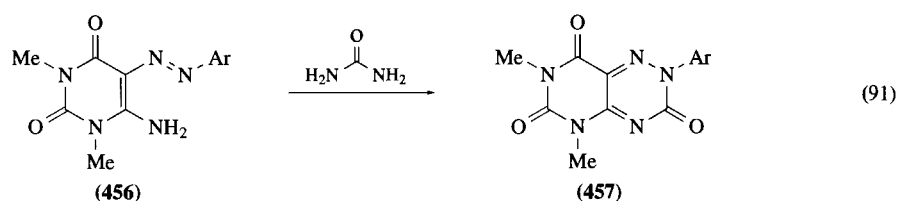
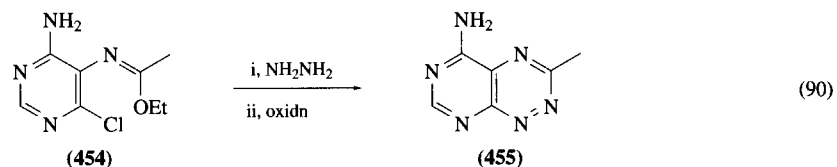
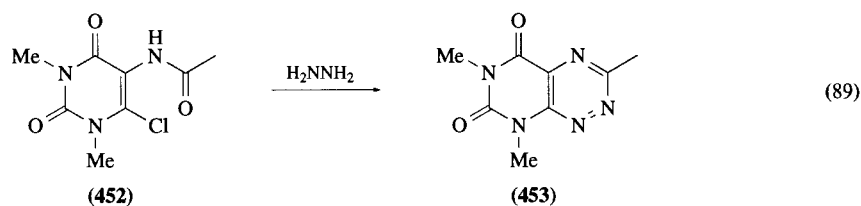
Ortho ester cyclization of adjacent amino and hydrazino groups leads to the isomeric ring systems pyridazino[4,3-*e*]-1,2,4-triazine (**440**) (Equation (80)) and pyridazino[4,5-*e*]-1,2,4-triazine (**441**) (Equation (81)) <74JHC167>, and the [1,2,4]triazino[6,5-*e*]-1,2,4-triazine (**442**) can be obtained using a similar reaction (Equation (82)) <88S877>. The nitrosoaminopyrimidine (**443**) is cyclized by trichloromethyl chloroformate <86JHC1661>, and also by phosgene <70CB908>, forming a pyrimido-[5,4-*c*][1,2,5]oxadiazine (**444**) (Equation (83)), while a 1,5-dihalogen system (**445**) may be cyclized with potassium thioacetate to give a pyridazino[4,5-*e*][1,3,4]thiadiazine (**446**) (Equation (84)) <84CPB4437>. Adjacent sulfonamido and amino groups can be cyclized with *ortho* esters giving the isomeric ring systems pyridazino[4,5-*e*]-1,2,4-thiadiazine (**447**) (Equation (85)) <69JHC407>, pyrimido[4,5-*e*]-1,2,4-thiadiazine (**448**) (Equation (86)) <63JOC1994>, and pyrazino-[2,3-*e*]-1,2,4-thiadiazine (**449**) (Equation (87)) <73BCJ1890>. Finally, thionyl chloride cyclization of (**450**) gives the pyrimido[4,5-*e*]-1,2,4-thiadiazine (**451**), albeit in low yields (Equation (88)) <85JHC381>.



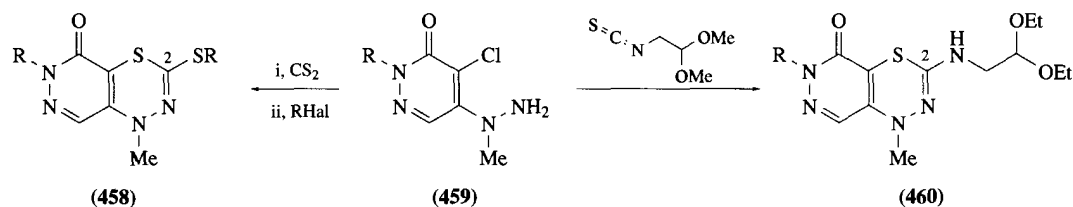


(iii) [4 + 2] Component syntheses

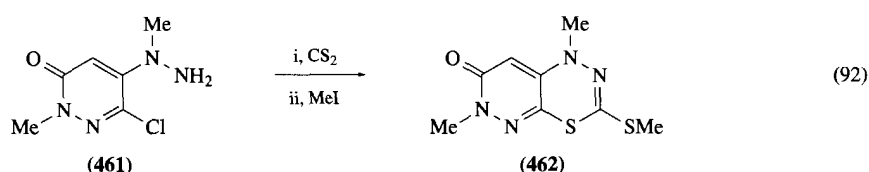
Fourteen different ring systems, most of them uncommon, have been synthesized by the [4 + 2] component syntheses described in this section. Reaction of a hydrazine as the two-atom component with a 5-amido-4-chloropyrimidine such as (452) may be used as a route to pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) (Equation (89)) (453) <66JOC900, 78CC367, 87JHC1373>, and the first synthesis of toxoflavin was achieved by this method <62JA1724>. A 5-alkoxyalkylideneamino group may be used instead of an amido group in the starting material, as in the preparation of (455) from (454) (Equation (90)) <63JOC3038>. The isomeric pyrimido[4,5-*e*]-1,2,4-triazine (6-azapteridine) ring system (457) can be made by reaction of urea as the two-atom component with a 5-arylazopyrimidine (456) (Equation (91)) <78H(9)1387>.



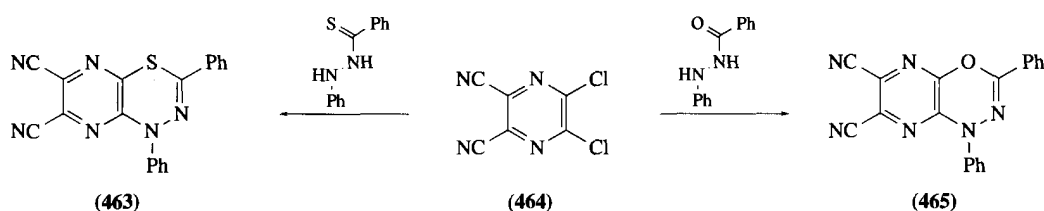
Pyridazino[4,5-*e*][1,3,4]thiadiazines such as (458) and (460) may be prepared by the cyclization of a 4-chloro-5-hydrazinopyridazine (459) using reagents containing a carbon-sulfur double bond (Scheme 37). The nature of the 2-substituent in the product is controlled by the sulfur reagent used <85JHC161, 92JHC825>. The isomeric pyridazino[4,3-*e*][1,3,4]thiadiazine ring system (462) is formed from precursor (461) using the same carbon disulfide cyclization (Equation (92)) <85JHC161>.



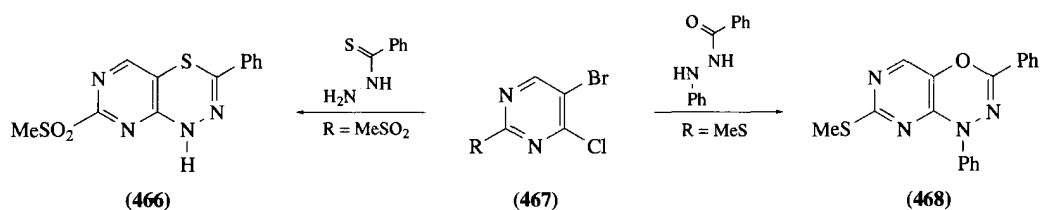
Scheme 37



Reaction of a 1,2-dihalo heterocycle, such as compounds (464) and (467), with a suitable acylhydrazine or thioacylhydrazine leads to derivatives of four different ring systems, namely pyrazino[2,3-*e*][1,3,4]thiadiazine (463), pyrazino[2,3-*e*][1,3,4]oxadiazine (465), pyrimido[4,5-*e*][1,3,4]thiadiazine (466), and pyrimido[4,5-*e*][1,3,4]oxadiazine (468) (Schemes 38 and 39) <80JOC3677, 81JHC799, 91IJC(B)936>.

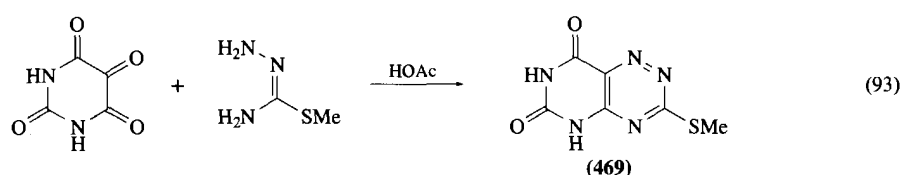


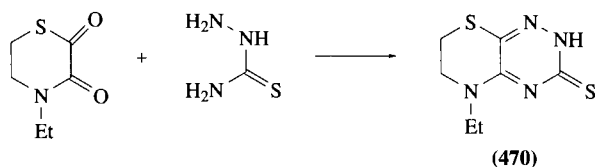
Scheme 38



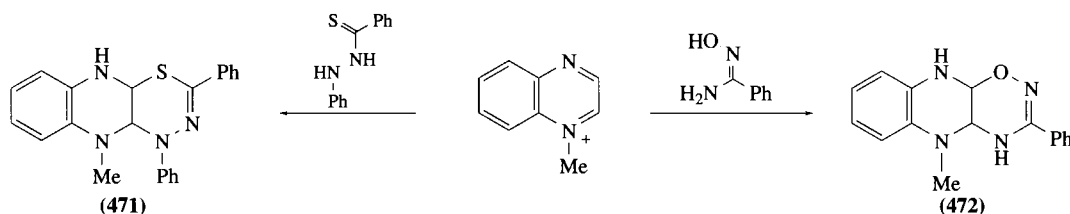
Scheme 39

Reaction of adjacent carbonyl groups on a heterocycle with 1,2-diamino reagents has been very little used as a synthetic method in the present context. The first 6-azalumazine (469) was prepared like this, however (Equation (93)) <64CB5>, and so was compound (470) containing the rare [1,4]thiazino[3,2-*e*]-1,2,4-triazine ring system <92MI 720-01>.

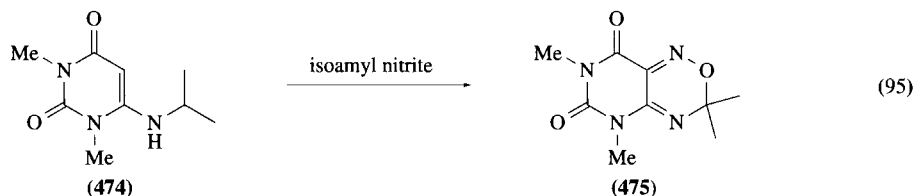
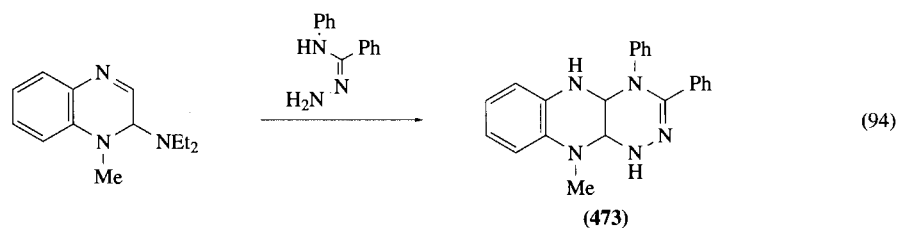




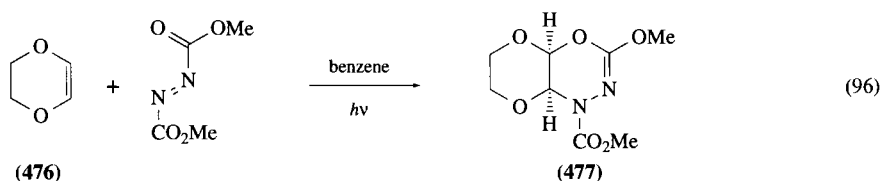
Bifunctional nucleophilic compounds can add to *N*-alkylpyrazinium salts, and the benzo fused pyrazino[2,3-*e*][1,3,4]thiadiazine (471) as well as the benzo fused pyrazino[2,3-*e*]-1,2,4-oxadiazine (472) can be made by this method (Scheme 40). A closely related reaction is exemplified by the preparation of the pyrazino[2,3-*e*]-1,2,4-triazine (473) (Equation (94)) <87KGS557, 87KGS1118>. The pyrimido[5,4-*c*][1,2,5]oxadiazine (475) can be prepared by treatment of the uracil derivative (474) with isoamyl nitrite (Equation (95)). Presumably the reaction proceeds by cyclization of an initially formed 5-nitrosopyrimidine intermediate <64ZC454>.

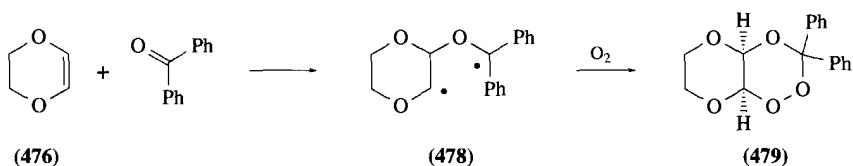


Scheme 40



1,4-Dioxene (476) offers a starting point for [4 + 2] syntheses of dioxino ring systems. For example a 1,4-cycloaddition reaction may be used to prepare the [1,4]dioxino[2,3-*e*][1,3,4]oxadiazine (477) (Equation (96)). Although carried out under irradiation at 3500 Å in benzene solution, the cycloaddition is probably thermal, with the irradiation being required to produce the *cis* azodiformate which reacts faster than the *trans* isomer <70JOC1155>. And finally, synthesis of the reduced [1,4]dioxino[2,3-*e*]-1,2,4-trioxin derivative (479) has been achieved by argon ion laser irradiation of 1,4-dioxene (476) with benzophenone in chloroform in presence of oxygen. The reaction proceeds via the diradical intermediate (478) which reacts with molecular oxygen to give the *cis*-fused bicyclic product (479) (Scheme 41) <86TL2953>.

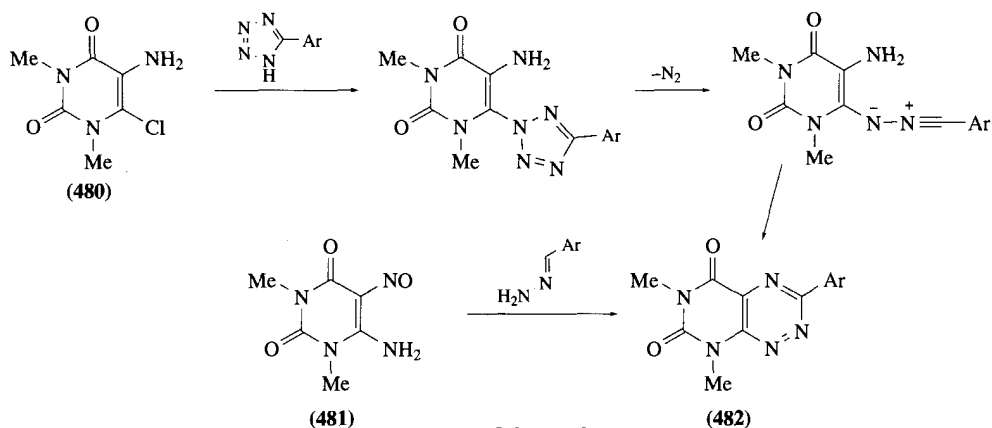




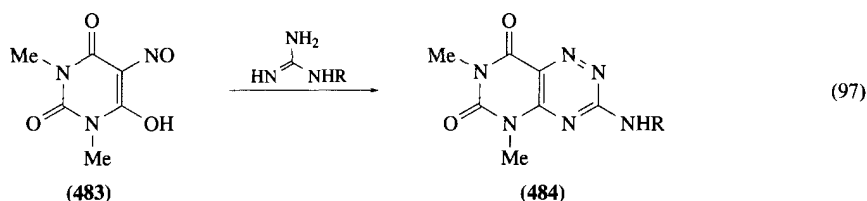
Scheme 41

(iv) [3 + 3] Component syntheses

Only a few reactions are known in which a [3 + 3] component cyclization is used for the construction of a 1,2,4-heterocycle onto an existing heterocycle, and they all lead to pyrimidotriazines (azapteridines). Perhaps the most important is that between the 6-amino-5-nitrosopyrimidine (**481**) and an aldehyde hydrazone, which was developed as a route to 3-substituted fervenulins (**482**). This reaction could also be considered as a [6 + 0] type synthesis since 6-hydrazino-5-nitroso intermediates have been isolated and cyclized $\langle 78\text{CPB}3154, 80\text{JHC}869 \rangle$. 3-Substituted fervenulins (**482**) are also formed in an unusual reaction of the 5-amino-6-chloropyrimidine (**480**) with a 5-aryltetrazole $\langle 81\text{H}(15)285 \rangle$. These reactions are shown in Scheme 42. Finally, the pyrimido[4,5-*e*]-1,2,4-triazine compounds (**484**) may be prepared by reaction of 1,3-dimethyl-5-nitrosobarbituric acid (**483**) with a substituted guanidine (Equation (97)). This reaction does not work with unsubstituted 5-nitrosobarbituric acid $\langle 75\text{BCJ}725 \rangle$.

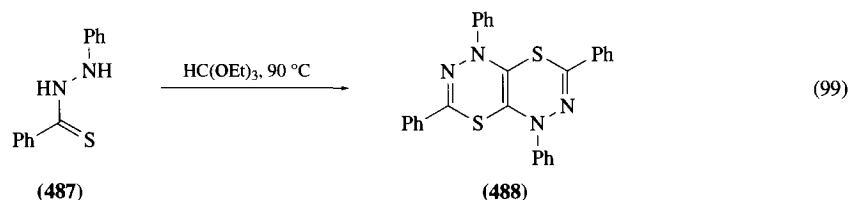
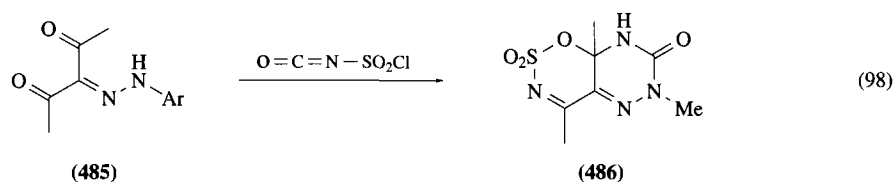


Scheme 42

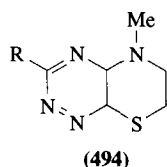
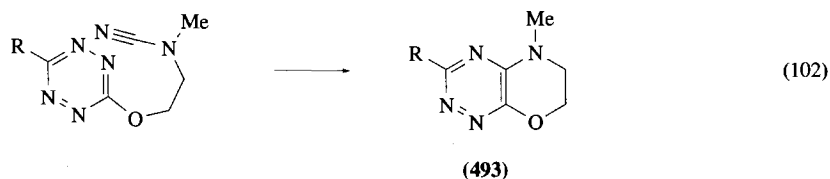
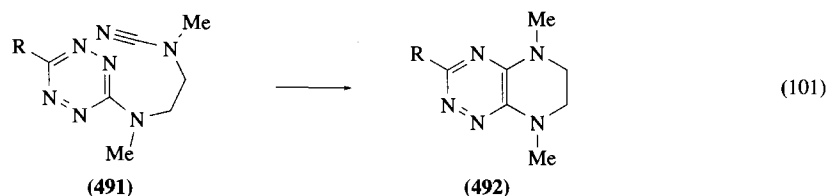
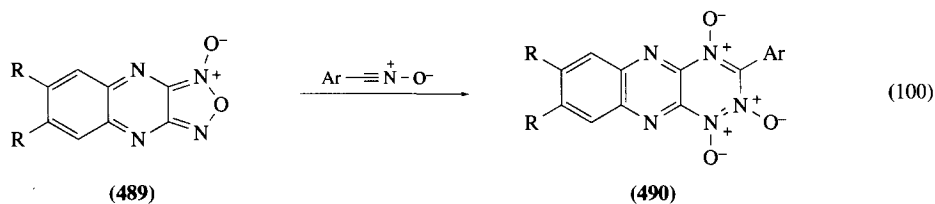


7.20.10 SYNTHESIS FROM ACYCLIC PRECURSORS OR INVOLVING TRANSFORMATION OF AN EXISTING HETEROBICYCLIC RING SYSTEM

There are only two examples in which a heterobicyclic ring system is synthesized in a one-pot procedure from acyclic precursors. The first involves formation of the rare [1,2,4]triazino[6,5-*e*]-1,2,3-oxathiazine ring system (**486**) by condensation of the aryl hydrazone (**485**) with chlorosulfonyl isocyanate (Equation (98)) $\langle 91\text{SC}1695 \rangle$. The second involves formation of the [1,3,4]thiadiazino[6,5-*e*][1,3,4]-thiadiazine (**488**) as a minor by-product when (**487**) is heated with triethyl orthoformate (Equation (99)) $\langle 71\text{TL}4985 \rangle$.

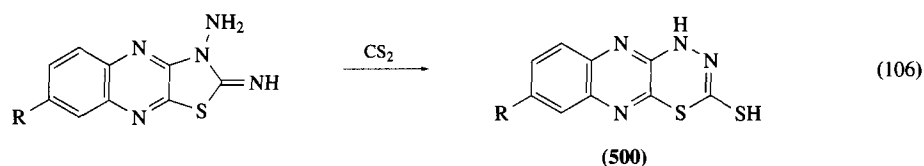
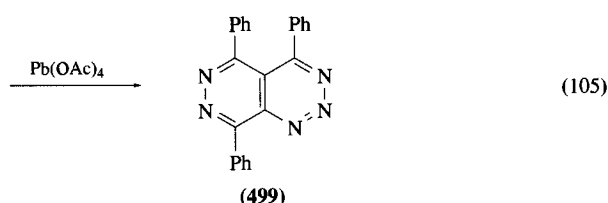
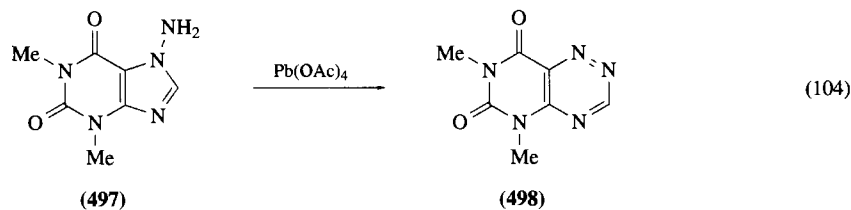
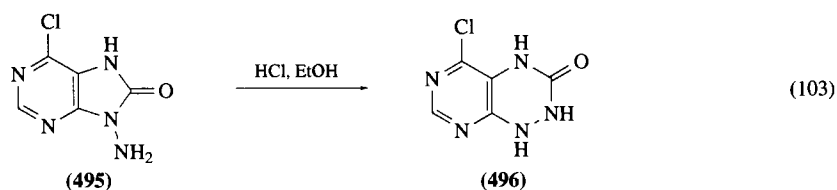


Two quite different cycloaddition reactions have been employed as routes to pyrazino[2,3-*e*]-1,2,4-triazines. In the first, cycloaddition of a nitrile oxide across the two nitrogen atoms of the furoxan ring in (489) causes expansion of the latter to the triazine tri-*N*-oxide ring (490) (Equation (100)) <91S83>. In the second, product (492) may be obtained from (491) in a reaction which probably proceeds through intramolecular cycloaddition of the terminal nitrile group across the two carbon atoms of the tetrazine ring, followed by loss of nitrogen (Equation (101)). The same reaction may be used to prepare [1,4]oxazino[3,2-*e*]-1,2,4-triazines (493) (Equation (102)), and also [1,4]thiazino[3,2-*e*]-1,2,4-triazines (494) <91AP(324)803>.

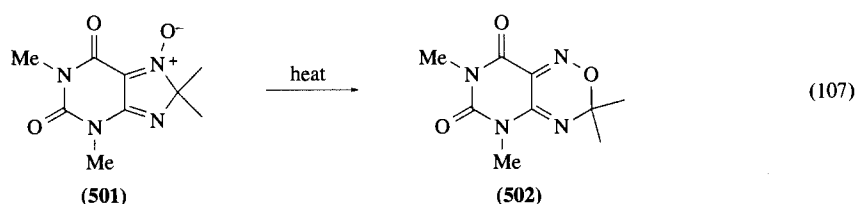


All the remaining syntheses described in this section involve ring enlargement reactions. The 9-aminopurine (495), for example, gives the pyrimido[5,4-*e*]-1,2,4-triazine (496) on treatment with acid (Equation (103)) <63JOC2677>, and 7-aminotheophylline (497) with a variety of oxidizing agents gives the pyrimido[4,5-*e*]-1,2,4-triazine (498) (Equation (104)) <83KGS1564, 89KGS95>. Similar reactions may be used to prepare the pyridazino[4,5-*d*]-1,2,3-triazine (499) (Equation (105))

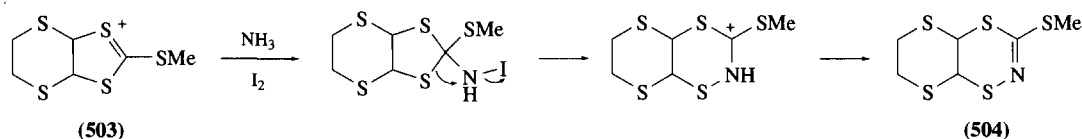
<75JCS(P1)1747>, and also the benzo fused pyrazino[2,3-*e*][1,3,4]thiadiazine (**500**) (Equation (106)) <89JIC124>, more properly named as a thiadiazine[5,6-*b*]quinoxaline.



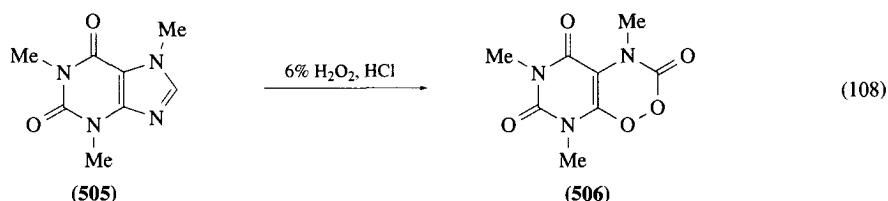
In like manner, the oxygen atom of a purine 7-*N*-oxide may be incorporated into an expanded ring, and theophylline 7-*N*-oxides (**501**) give rise to pyrimido[5,4-*c*][1,2,5]oxadiazines (**502**) on heating (Equation (107)) <66LA(692)134, 66LA(699)145, 67FRP90508>.



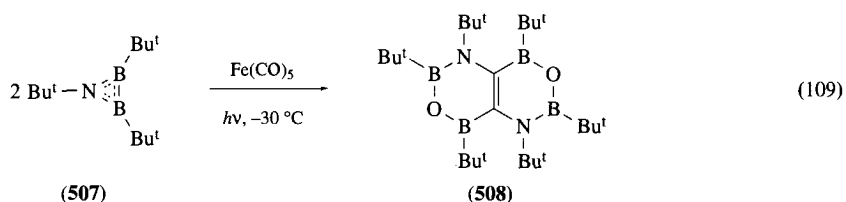
The extra atom necessary for incorporation into the five-membered ring may also come from an added reagent. A molecule of ammonia, for example, supplies the necessary nitrogen atom for the conversion of the salt (**503**) to the tetrahydro[1,4]dithiino[2,3-*e*]-1,4,2-dithiazine (**504**) (Scheme 43) <92JCS(P1)2295>. In a more unusual reaction, the pyrimido[5,4-*e*]-1,2,4-dioxazine (**506**) may be obtained, together with other products, by treating caffeine (**505**) with H_2O_2 in hydrochloric acid (Equation (108)) <90JHC667>.



Scheme 43



An uncommon ring system formed by an unusual reaction, and the only ring system dealt with here which has eight heteroatoms in its two rings is represented by the [1,3,2,6]oxazadiborino[5,4-*d*][1,3,2,6]-oxazadiborine derivative (**508**) which is formed when two molecules of the three-membered ring precursor (**507**) are irradiated in presence of iron pentacarbonyl at -30°C <90AG(E)900>.



7.20.11 SYNTHESSES OF PARTICULAR CLASSES OF COMPOUNDS

More methods have been developed for the preparation of pyrimido[5,4-*e*]-1,2,4-triazines (7-azapteridines) (**8**) than for any other ring system in this chapter, and a summary of the various strategies which have been used for their synthesis is given in Tables 1, 2, and 3.

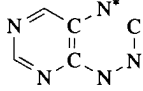
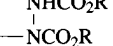
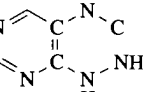
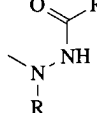
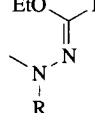
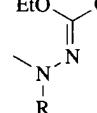
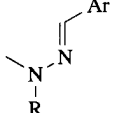
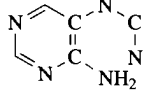
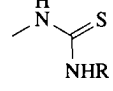
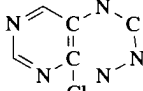
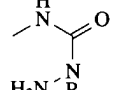
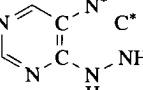
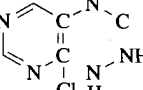
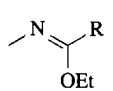
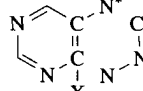
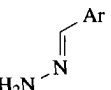
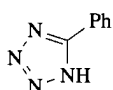
7.20.12 IMPORTANT COMPOUNDS AND APPLICATIONS

No outstandingly important applications have been associated with any of the ring systems dealt with in this chapter. Nevertheless there are a few reports which are worthy of mention, even if some of them are described only in isolated patents, or mentioned with few accompanying details in published papers.

The pyrimido[5,4-*e*]-1,2,4-triazine or 7-azapteridine ring system (**8**) stands out as by far the most important in this context, and earlier work on it has been covered in a comprehensive review <75MI 720-01>. Toxoflavin (**509**) was first isolated in 1933 from "bongkreng", which is a native food eaten on the island of Java and made by incubating a coconut preparation with a certain mold. Contamination of the preparation, however, sometimes led to outbreaks of fatal food poisoning, and the toxic contaminant was shown to be toxoflavin. Its chemical structure (**509**) was established later, with publication of its x-ray crystal structure and its total synthesis <61RTC307, 62JA1724>. Toxoflavin is also known as xanthothricin, and its production by a culture method has been patented <80JAP80102395>. It acts as an antibiotic but its usefulness as a clinical agent is limited by its toxicity <92MI 720-02>. Its demethylated derivative called reumycin (**510**) is less toxic, however, and is an antitumor agent. It is active against carcinoma, melanoma, and carcinosarcoma, though not against leukemia <81MI 720-01>. Reumycin has an oral bioavailability of 50% <85MI 720-01>, and ³¹P NMR studies showed that it affects the consumption of creatine phosphate in hepatoma 22a cells in culture <85DOK(281)180>. It has been tested on patients with brain and kidney tumors as well as on mice <80GEP2901537, 85MI 720-02>. Two other related compounds which occur naturally, and which exhibit broad spectrum antibiotic properties, are fervenulin (**511**), an isomer of toxoflavin, and 2-methylfervenulone (**512**), also called MSD-92. Derivatives of fervenulin have been prepared and studied for antiinflammatory, analgesic, and antimicrobial activity <88KFZ560, 92JAN1795>. Fervenulin itself (**511**) has been associated with bacterial grain rot of rice, and has been shown to reduce the growth of the leaves and roots of rice seedlings <89MI 720-02>. Other 7-azapteridines have been shown to have activity as antiinflammatory or diuretic agents <73GEP2233242>, as herbicidal agents <85USP4494981>, or as antibacterial or antifungal agents <93CPB362>, while 6-azapteridines (**513**) have been found to have analgesic and antiinflammatory activity <80URP742432, 81KFZ50>.

Some pyridazino[4,5-*e*]-1,2,4-triazine derivatives of the type (**514**) can act as photosynthetic

Table 1 Synthesis of 7-azapteridines (8) from pyrimidine precursors.

Precursor(s)	Functional groups on precursor				Section
 [6+0]	 	—NH ₂ —NO —NO ₂ —N=NAr	  		7.20.9.3.2(i)(a)
 [6+0]		  			7.20.9.3.2(i)(a)
 [6+0]					7.20.9.3.2(i)(a)
 [6+0]					7.20.9.3.2(i)(a)
 [5+1]	 	—NH ₂ —NO R · C(OR) ₃ DMF/POCl ₃ R · C(=NH)OEt DMF/Me ₂ SO ₄ COCl ₂ HCO ₂ H Ph ₃ P=CHAr			7.20.9.3.2(ii)(a)
 [4+2]					7.20.9.3.2(iii)
 [3+3]	  	—NH ₂ —NO —NH ₂ —Cl  			7.20.9.3.2(iv)

inhibitors. They show a broad herbicidal activity against many weeds without damage to crops such as rice, corn, barley, wheat, or soybeans (84JAP84116201, 86JAP8607278, 87MI 720-02).

Various types of fused-ring thiadiazines, including pyrimido[4,5-*e*][1,3,4]thiadiazines (515), pyrazino[2,3-*e*][1,3,4]thiadiazines (516), and the rare pyrimido[5,4-*e*][1,3,4]thiadiazines (517) and pyridazino[3,4-*e*][1,3,4]-thiadiazines (518), may be useful for the coloring of polyester fibers

Table 2 Synthesis of 7-azapteridines (**8**) from triazine precursors.

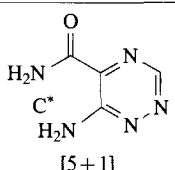
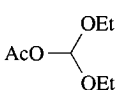
Precursors	Functional groups on precursor	Section
 [5+1]	 Cl · CO ₂ Et COCl ₂ , pyridine H · C(OR) ₃	7.20.9.2.2

Table 3 Synthesis of 7-azapteridines (**8**) by ring expansion.

$$\xrightarrow[\text{MeOH}]{\text{HCl}}$$

Section
7.20.10

(509) toxoflavin

(510) reumycin

(511) fervenulin

(512)

(513)

(514)

(515)

(516)

(517)

(518)

(519)

(520)

(521)

<77USP4025510>. Other pyrimido[4,5-*e*][1,3,4]thiadiazines of type (**519**) have been found useful as hypotensives, diuretics, antiinflammatory, or antigastric ulcer agents <78JAP7828192>. In the early 1990s, *N*-substituted pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides were reported as a new class of diuretics <92JMC3977>, with compound (**520**) being the most active of a series of compounds of

this type which was synthesized. A substituent on the ring nitrogen appears necessary for diuretic activity, and simple alkyl groups at positions six and seven of the heterocycle are also required. The relative positioning of these can be critical. Compound (**521**), for example, has no diuretic activity at all. Other substituted pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides may find application either as antihelmintic agents <93AF163> or as dyestuffs <89MIP2009198, 94MI 720-01>.

7.21

Tricyclic Systems: Central Carbocyclic Ring with Fused Five-membered Rings

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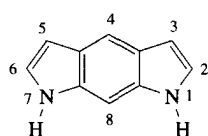
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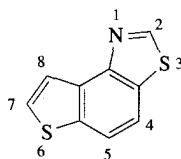
7.21.1 INTRODUCTION

This chapter includes a large number of systems where account is taken of the size of the central carbocyclic ring, the relative orientation of the five-membered heterocyclic rings, the types of heteroatoms, their number, and, in rings with two or more heteroatoms, their relative situations. The field as a whole has not been previously reviewed, but some general reviews contain references to members <86HAC226>, and some reviews exist of limited areas, for example of some benzofuroxans <81AHC(29)251>, benzodipyrroles <91H(32)41>, and some benzodipyrrole antitumor agents such as CC-1065 (**155**), and the phosphodiesterase inhibitors PDE-I and PDE-II (**154**) <87H(25)701> (see Section 7.21.12). This last review presents many significant approaches to both the heterocyclic and carbocyclic rings.

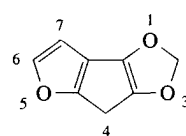
The nomenclature used here corresponds to that used in *Chemical Abstracts*, which employs the style cyclobuta-, cyclopenta-, benzo- etc. di(heterocycle), if the rings are similar. Otherwise the form of "heterocycle[cyclobuta- etc.] heterocycle" is used. Thus the compound (**1a**) is described as a benzodipyrrole, rather than as a pyrroloindole, the correct name being benzo[1,2-*b*:5,4-*b'*]dipyrrole. Compound (**1b**) is named as a thieno[3,2-*e*]benzothiazole, and the compound (**1c**) is named as a furo[3',2']cyclopenta[1,2-*d*]-1,3-dioxole.



(1a)



(1b)



(1c)

7.21.2 THEORETICAL METHODS

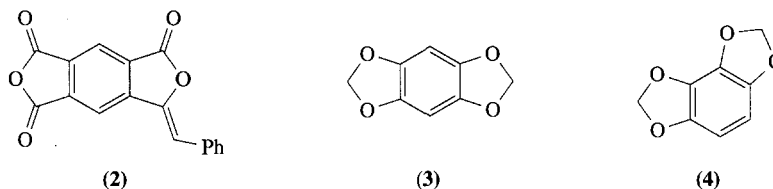
For some angular [*b*:*b'*]benzodithiophenes, the Hückel method was used to calculate the localization energies and π electron densities $\langle 83\text{JCS(P2)813} \rangle$. In earlier work, an LCAO-MO-SCF-CI method was applied to various benzodifurans, benzodithiophenes, and furobenzothiophenes. The calculated π electron densities were in good agreement with the observed UV spectra $\langle 71\text{ZN(B)1235} \rangle$. The effects of charge variations in some benzodithiophenes were considered, using different modes of sulfur bonding. The sulfur atom appears to act as a π donor $\langle 74\text{JJC589} \rangle$.

MO calculations on benzo[1,2-*b*:4,5-*b'*]- and benzo[1,2-*b*:4,3-*b'*]dipyrroles predicted the greatest reactivity to electrophilic substitution in the 3,7 and 1,8 positions, respectively $\langle 83\text{KGS1086} \rangle$. Also, calculations on the first excited state of some 1,2-diheterocyclic-substituted ethenes $\langle 75\text{RTC239} \rangle$ supported Wynberg's hypothesis $\langle 67\text{JOC3093} \rangle$ on their ability to undergo photoinduced cyclization to dihydrobenzodiheterocycles, and an MNDO calculation of state correlation diagrams for the process was used to design compounds capable of irreversible photocyclization $\langle 90\text{CA(113)221161} \rangle$.

A CNDO study on benzo[1,2-*c*:4,5-*c'*]dithiophene predicted that it would be more polar than thieno[3,4-*c*]thiophene, and that excess electron density would be distributed at the bridgehead carbon atoms. A singlet ground state was also predicted $\langle 75\text{ACR139} \rangle$. The heats of atomization, charge densities, and resonance energies of a series of benzodithiophenes were calculated $\langle 80\text{T2711} \rangle$. A [*c*] fusion led to less resonance stabilization of a system than a [*b*] fusion.

For a series of carbonyl systems, one of which was a benzodifuran derivative (**2**), the energies of the first five singlet and triplet excited states were calculated by CNDO/S-CI methods. For compound (**2**), three *quasi* degenerate low-lying $n\pi^*$ states were proposed, and the effects of NH_2 , OH , and CN substituents were determined $\langle 85\text{ZN(A)859} \rangle$.

The hyperfine splitting constants for all protons of the two benzo[*d*:*d'*]bis-1,3-dioxoles (**3**) and (**4**) and benzo[*d*:*d'*:*d''*]tris-1,3-dioxole were calculated by INDO and HMO methods. The magnitudes of the experimental splitting constants of the hydrogen atoms were explained by applying perturbation theory to interaction between the aromatic and heterocyclic ring π MOs $\langle 82\text{ZN(A)680} \rangle$.



Investigations of heterocyclic systems with potential for electrical conductivity have stimulated an investigation of thiophenes using an *ab initio* method $\langle 90\text{SM327, 91CC1268} \rangle$. For other polymer applications, a CNDO/2 calculation was used to determine the order of protonation and proton binding in polybenzobisoxazoles $\langle 83\text{CA(98)35076} \rangle$, and the AM1 method for conformations of polybenzobisthiazoles and benzobisoxazoles $\langle 90\text{MM2410} \rangle$. Polyphenylene benzobis-oxazoles and thiazoles have been investigated by molecular mechanics and CNDO/2 methods $\langle 83\text{JMAS1119} \rangle$. Both geometrical isomers had virtually identical energy profiles for conformation energy against torsion angle, but the polybenzobisthiazole had smaller energy differences than the polybenzobisoxazole. An *ab initio* method was used to investigate materials based on polymeric thiophenes, including one derived from a cyclobuta[*c*:*c'*]dithiophene, that might exhibit a sufficiently low fundamental bandgap to allow electrical conductivity $\langle 90\text{SM327} \rangle$.

Ab initio calculations, using a 4-31G basis set, have been used to predict intramolecular interactions of sulfur lone-pair electrons in two benzo[*c*:*d'*]dithiophenes $\langle 87\text{CL257} \rangle$. On some cyclooctatetraenes with fused hetero rings these calculations suggested an increase in the length of the fused bond $\langle 91\text{JOC5426} \rangle$.

Calculation of the first and second $\text{p}K_a$ values of benzo[1,2-*d*:4,5-*d'*]- and benzo[1,2-*d*:3,4-*d''*]diimidazole in the ground and excited states suggested that excitation increases the electron density in the heterocyclic rings $\langle 81\text{CA(94)29952} \rangle$. An *ab initio* calculation of a benzodiborole gave the geometry of ground states, and an electronic spectrum calculated by VESCF methods was in good agreement with experimental data $\langle 75\text{JA752} \rangle$.

7.21.3 EXPERIMENTAL STRUCTURAL METHODS

7.21.3.1 X-ray, Neutron, and Electron Diffraction

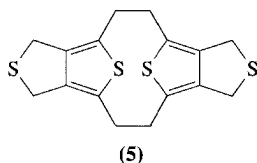
Little data has been reported on x-ray structural methods. In a study of benzo[1,2-*c*:3,4-*c'*]bis-thiadiazole and a monoselenium analogue, S—N bond distances of the order of 1.62 Å were found and attributed to the heterocyclic rings being *quasi* aromatic, but with severe distortion of the aromatic character of the carbocyclic ring <84ZN(B)485>.

X-ray methods have been used to examine the structure of the antitumor agent CC-1065 (see Section 7.21.12), and portions thereof <81JA7629, 88JOC4610>.

A determination of the structure of the cyclododecathiophene (**5**) established that the saturated and unsaturated thiophene rings were almost co-planar, by 11.3° <87AG(E)763>.

The structures of polymers containing benzobisthiazole and benzobisoxazole have been determined. These form rigid rod-like polymers with high specific strength <81MM935>. For some bis-selenadiazolo analogues of tetracyanoquinodimethane x-ray methods established the presence of extensive intermolecular interactions <87CL2285>.

No studies using neutron or electron diffraction methods have been reported.



7.21.3.2 Photoelectron Spectroscopy (PES)

The PE spectrum of tetrahydrobenzo[1,2-*c*:4,5-*c'*]dithiophene and tetrahydrobenzo[1,2-*c*:3,4-*c'*]dithiophene have been examined. Splitting of peaks below 10 eV was attributed to remote interaction of sulfur lone pairs of electrons <87CL257>. Little other data has been recorded.

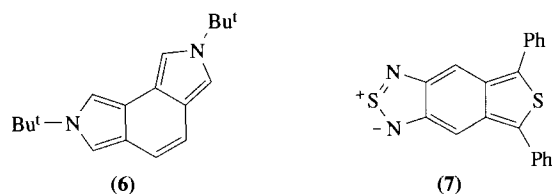
7.21.3.3 IR Spectroscopy

Infra red methods have been little used, other than for routine structural confirmation. They have been employed to distinguish between linearly and angularly fused systems; adjacent hydrogens on angularly fused systems demonstrate an out-of-plane deformation band at 810 cm⁻¹ <76CCA319>.

7.21.3.4 UV and Visible Spectroscopy

Few studies are concerned only with UV spectra. Cyclopentadithiophenes have maxima in the range 217–255 nM <68T3381>. Most of the simple conjugated benzodiheterocycles do not absorb in the visible spectrum. The data for benzodifurans, benzodithiophenes, and furobenzothiophenes have been recorded, and show a series of absorptions below ~330 nM <67JOC3093, 71ZN(B)1235, 86CB3198>. The [*c*:*c'*] angularly fused benzodipyrrole (**6**) has four maxima below 305 nM, while the [*c*:*c'*:*c''*] trisfused system absorbs below 341 nM <88ZN(B)125>. Some dihydro angularly fused benzodipyrroles, dithiophenes, and selenophenes have maxima in the visible range, between 530 and 620 nM, depending on substitution <90JOC2592>. More conjugated systems, especially those where the bonding may have a 1,3-dipolar character (e.g. certain sulfur compounds) absorb in higher ranges. Thus, hexaphenylbenzo[1,2-*c*:3,4-*c'*]dithiophene absorbs at 793 and 871 nM, tetraphenylthienobenzopyrazole at 602 nM and the thienobenzothiadiazole (**7**) at 645 nM <75ACR139>.

The geometrical preference of a conjugated benzo[1,2-*d*:4,3-*d''*]bisthiazole depends on the size of the group on the nitrogen atoms, and affects the position and intensity of λ_{max} <82ZOR199>.



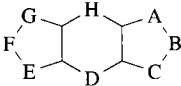
7.21.3.5 Mass Spectrometry

In the great majority of examples, mass spectral data have been used only to establish the molecular ions, or for elemental analyses. The collision activated mass spectra of $(M + 1)^+$ ions from three bis(benzothieno)benzenes give patterns consistent with the loss of SH radicals $\langle 82\text{ANC}574 \rangle$. The mass spectrum of an oxazolobenzisoxazole does not show rearrangements comparable to simpler benzisoxazoles $\langle 81\text{OMS}(16)552 \rangle$. The cyclododecadithiophene (**5**) shows a doubly charged parent ion $\langle 87\text{AG}(E)763 \rangle$.

7.21.3.6 NMR Spectroscopy

The ^1H NMR data for some simple angular and linear benzodiheterocycles are tabulated (Tables 1 and 2). Most of the papers referred to in this chapter contain some ^1H data and many also contain ^{13}C data.

Table 1 The chemical shifts (δ) for the methine protons of selected linearly fused benzodiheterocycles.

								
<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E</i>	<i>F</i>	<i>G</i>	<i>H</i>	<i>Ref.</i>
7.51	7.72	S	8.47	7.51	7.72	S	8.49	86CB3198
6.92	7.12	S	7.85	S	6.92	7.12	7.85	86CB3198
S	N	Me	8.44	Me	N	S	8.32	86CB3198
Me	N	S	8.44	8.44	Me	N	S	86CB3198
Me	N	NH	7.2	NH	N	Me	8.0	88JMC2034
Me	N	NMe	7.95	NMe	N	Me	7.29	88JMC2034
S	7.47	7.86	8.55	S	7.47	7.86	8.55	790PP247

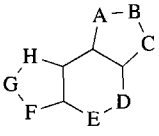
^a Measured in d_6 -acetone solution.

7.21.3.6.1 Proton NMR Spectroscopy

The $J_{1,2}$ values of protons in $[b]$ fused thiophenes are greater than those for the corresponding furans $\langle 72\text{JCS}(P2)101 \rangle$. The long-range coupling of heterocyclic to aromatic protons in angular benzodithiophenes and benzodifurans has also been investigated. In thieno[1,2-*b*:4,3-*b'*]benzofuran the magnitude of a five-bond coupling between protons on the heterocyclic ring and the carbocyclic ring is 0.6 Hz. The methylene protons in cyclopentadithiophenes absorb at approximately $\delta = 6.36$ –6.52 ppm $\langle 68\text{TL}3381 \rangle$.

The ^1H NMR spectrum of benzo[1,2-*c*:4,3-*c'*]bisthiazole and benzo[2,1-*c*:3,4-*c'*]bisthiazole in the nematic phase of *N*-(4-ethoxybenzylidene)-4-*N*-butylaniline was examined. It was concluded that the molecules are planar, with considerable bond fixation in the latter $\langle 84\text{MCLC}285 \rangle$. The chemical shifts and coupling constants have been determined for the antifungal agent tjipanazole A (see Section 7.21.12) $\langle 91\text{T}7739 \rangle$.

Table 2 The chemical shifts (δ) for the methine protons of selected angularly fused benzodiheterocycles.

								Solvent	Ref.
A	B	Methine Chemical Shift (ppm) or Heteroatom/Substituent C	D	E	F	G	H		
7.90	7.77	S	7.94	7.94	S	7.77	7.90	d ₆ -acetone	77CS57
S	7.54	7.45	7.78	7.78	7.45	7.54	S	d ₆ -acetone	77CS57
S	7.52	7.43	7.73	7.83	S	7.67	7.55	d ₆ -acetone	77CS57
7.83	S	7.58	7.10	7.10	7.58	S	7.83	d ₆ -acetone	77CS57
S	7.68	7.68	7.53	7.53	7.82	7.20	O	d ₆ -acetone	67JOC3093
O	7.10	7.87	7.49	7.49	7.87	7.10	O	d ₆ -acetone	67JOC3093
N	S	9.26	7.76	7.67	S	N	Me	CDCl ₃	91JHC347
S	N	Me	7.60	7.68	9.25	S	N	CDCl ₃	91JHC347
S	N	Me	7.89	7.89	Me	N	S	CDCl ₃	91JHC347
S	N	Me	7.97	7.90	S	N	Me	CDCl ₃	91JHC347
N	S	8.9	7.25	7.25	8.9	S	N	CDCl ₃	80JHC533
9.5(8.8)	S	N	7.4	7.4	8.8(9.5)	S	N	CDCl ₃	80JHC533
9.2	S	N	7.65	7.65	N	S	9.2	CDCl ₃	80JHC533
6.9	7.68	O	7.43	7.43	O	7.68	6.9	CCl ₄	72JCS(P2)101
7.44	7.44	S	7.65	7.45	O	7.62	6.96	CCl ₄	72JCS(P2)101
7.11	NBu ^t	7.26	6.96	6.96	7.26	NBu ^t	7.11	CDCl ₃	88ZN(B)125
7.78	O	7.97	—CH=CH—CH=CH—	7.97	O	7.78	7.78	CDCl ₃	80TL3831
6.73 ^a	7.18 ^a	NH	OMe	OMe	NH	7.18 ^a	6.73 ^a	CDCl ₃	86JA2110
^b	^b	NBz	^b	^b	O	^b	^b	CDCl ₃	87JOC19
^c	^c	NBz	^c	^c	S	^c	^c	CDCl ₃	87JOC19
NH	7.10	6.46	7.30	7.12	NH	7.18	6.66	d ₆ -acetone	82KGS206
NH	8.04	Ac	8.12	7.32	NH	7.31	6.74	d ₆ -acetone	82KGS206
NH	Ac	7.34	7.38	7.23	NH	7.27	6.97	d ₆ -acetone	82KGS206

^aThese values may be reversed. ^bThe carbocyclic and heterocyclic protons are a series of singlets and multiplets between 6.72 and 7.66 ppm. ^cThe carbocyclic and heterocyclic protons are a series of singlets and doublets between 6.84 and 7.66 ppm.

7.21.3.6.2 Carbon-13 NMR Spectroscopy

The ¹³C spectra of various cycloalkane tetracarboxylic acid anhydrides have been examined. In the cyclobuta-fused compounds, the carbonyl carbon atoms appear at relatively higher values than in larger systems <92CA(116)83109>.

An examination of the ¹³C and ¹⁵N magnetic resonances of a nitrobenzo[*d*:*d'*]bis-2,1,3-oxadiazole and a benzo[*d*:*d'*:*d''*]tris-2,1,3-oxadiazole concluded that these compounds did not exhibit valence tautomerism. The *N*-oxide nitrogen resonated at approximately 24 ppm, whereas the other nitrogen atoms resonated in the range -0.2 to 8.6 ppm <90CA(112)197462>.

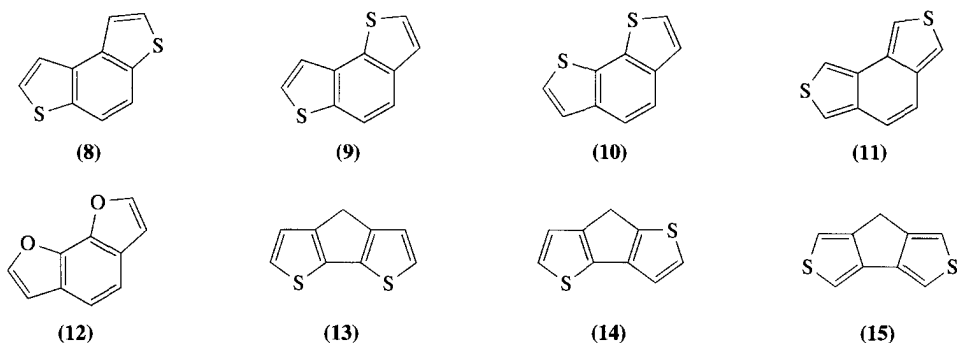
In staurosporine (**170**), a benzodipyrrole derivative having protein kinase C activity (see Section 7.21.12), the conformational energy changes with protonation have been determined by NMR methods <91CC182>.

7.21.4 THERMODYNAMIC ASPECTS

Given the diversity of systems, trends are difficult to correlate. Fully conjugated benzo systems, and those with cyclobuta and cyclopenta systems are planar. The fully conjugated systems are also aromatic and have typical aromatic properties corresponding to simpler (e.g. benzo-fused) heterocycles.

The melting points of some fused dithiophenes, based on limited data, correlate with the symmetry of the system and with perhaps the ability of the sulfur atoms to form intermolecular interactions. Thus, benzo[1,2-*b*:4,3-*b'*]dithiophene (**8**) has m.p. 112°C, whereas benzo[1,2-*b*:3,4-*b'*]dithiophene (**9**) has m.p. 39.5°C, benzo[2,1-*b*:3,4-*b'*]dithiophene (**10**) has m.p. 45–46°C and benzo[1,2-*c*:3,4-*c'*]dithiophene (**11**) has m.p. 112°C. Benzo[2,1-*b*:3,4-*b'*]difuran (**12**) (m.p. 39–40°C) is slightly lower than the thiophene analogue (**10**) <67JOC3093, 77CS57>.

This trend is evident too with cyclopentadithiophenes. The symmetrical [2,1-*b*:3,4-*b'*]dithiophene (**13**) has m.p. 74–75°C, whereas the unsymmetrical [1,2-*b*:3,4-*b'*]compound (**14**) has m.p. 46.5–47.2°C. The [1,2-*c*:3,4-*c'*]compound (**15**) has m.p. 114–115°C <68T3381>.



7.21.5 REACTIVITIES OF FULLY CONJUGATED RINGS

7.21.5.1 Reactions of the Carbocyclic Ring

7.21.5.1.1 Thermal and photochemical reactions that are unimolecular

An allyloxybenzobisthiadiazole undergoes a Claisen rearrangement to an allylhydroxybenzobisthiadiazole <92H(33)791>.

7.21.5.1.2 Electrophilic attack

While electrophilic attack on suitable π excessive heterocycles should be feasible, few examples are reported. Benzo[1,2-*c*:5,4-*c'*]dipyrazole undergoes nitration and bromination in the carbocyclic ring <88JMC2034>.

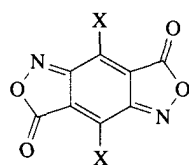
7.21.5.1.3 Nucleophilic attack

Dichloro- or diethoxybenzobisisoxazolones (**16a,b**) react with alkoxides with displacement of a substituent <85ZN(B)429>, and the dihydroxy compound (**16c**) is converted to the dichloro compound by PCl_5 <81JHC1409>. Halogen substituents on benzobisthiadiazoles (e.g. (**17**)) are also displaced <92H(33)791>, suggesting that the heterocyclic ring has an electron-withdrawing character. Various cyclopentadithiophene ketones or 1,4-quinones have typical carbonyl reactivity and are attacked by amines, reactive methylene compounds, and ylides etc. <86CC1779, 88JHC1917, 90HCA1948, 91CC1268, 92CC1137>. The cyclopentadithiophene ketone (**18**) undergoes opening of the carbocyclic ring by base to form a dithienyl-2-carboxylic acid <83LA2029>.

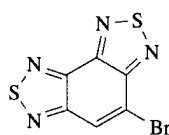
The 1,2- and 1,4-quinones (**19**) and (**20**) can also be reduced to phenols <86CB3198, 87JA2711>, but certain types accept electrons to form anion radicals <87BCJ3459, 88PS(39)235>.

7.21.5.1.4 Reactions with a cyclic transition state

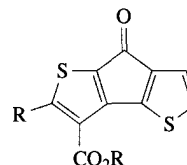
Linear thieno[*c*:*d*]benzothiadiazoles dimerize by linking at the carbocyclic *peri* positions <75ACR139>. While most [*c*] fused heterocycles add dienophiles across the heterocyclic ring, the thieno[1,2-*c*:4,5-*c'*]benzisoisothiazole (**21**) added ethyl azodicarboxylate across the benzenoid ring <86CB3158>.



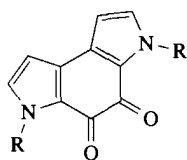
(16a) X = Cl
 (16b) X = OEt
 (16c) X = OH



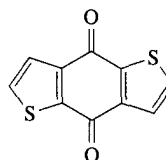
(17)



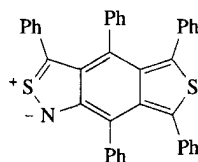
(18)



(19)



(20)



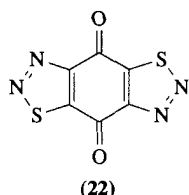
(21)

7.21.5.2 Reactions of the Heterocyclic Rings

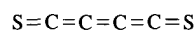
7.21.5.2.1 Thermal and photochemical reactions

An intramolecular reaction of an isocyanate on a benzo[1,2-*b*:4,3-*b'*]difuran constructed a fused pyridine ring, probably via a pericyclic reaction <86JHC1637>. Photolysis of the bistiadiazoquinone (22) resulted in rupture of the whole molecule, with loss of carbon monoxide to form the cumulene (23) <91CB2617>.

Furazans, i.e. benzo-2,1,3-oxadiazole-*N*-oxides, undergo isomerism and the rate is influenced by the benzo fusion of another heterocyclic ring <81AHC(29)251>.



(22)



(23)

7.21.5.2.2 Electrophilic attack at nitrogen

While this should be a common reaction, as with simpler nitrogen heterocycles, few examples are reported. Benzodiiisoxazoles, benzodipyrazoles, and benzodiimidazoles are alkylated on nitrogen <81JHC1409, 82ZOR199, 91M371>, and anions of dibenzopyrazoles react with iodomethane to give *N*-alkylated products <88JMC2034, 91H(32)41>.

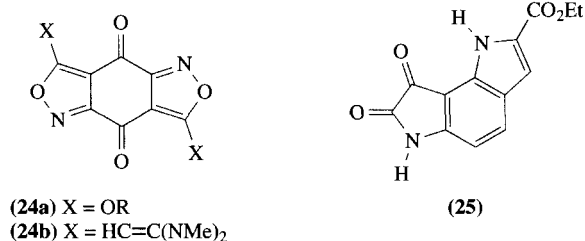
7.21.5.2.3 Electrophilic attack at carbon

Benzodipyrroles, difurans, and dithiophenes all undergo electrophilic attack at the heterocyclic ring carbon, including halogenation, nitration, and Vilsmeier formylation <78EJM435, 87CA(107)211476, 88CA(108)131629>. With benzodipyrroles there is some preference for β -substitution, but with the

difurans and dithiophenes the preference appears to be for α -substitution. The electrophilic substitution in the three angular [$b:b'$]dithiophenes, as measured by rates of detritiation, indicate that the order of reactivity is; hetero α position > hetero β position > aromatic ring <83JCS(P2)813>.

7.21.5.2.4 Nucleophilic attack at carbon

Surprisingly few examples are reported, but the alkoxy substituents on the benzodiisoxazoles (**24a**) are displaced by enediamines to form the compounds (**24b**) <85ZN(B)429>. The isatin analogue (**25**) undergoes ring opening by base <88TL3709>, and in some benzobis-1,3-dithioles, the heterocyclic rings are hydrolyzed by base to 1,2-dithiols <90T1553>.

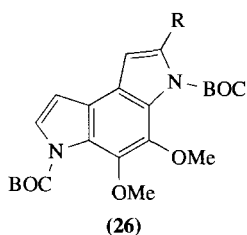


7.21.5.2.5 Nucleophilic attack at sulfur

Benzobis-1,3-dithioles are converted by sulfur in liquid ammonia to benzobis-1,2,3-trithioles. This probably results from a nucleophilic attack at sulfur <88TL6291>.

7.21.5.2.6 Deprotonation

Benzo[1,2-*b*:4,5-*b'*]dithiophene undergoes metallation at the 2-position, allowing formylation with dimethylformamide <83MAC627>, and treatment of a benzo[1,2-*b*:4,3-*b'*]dipyrrole (**26a**) with LITMP and excess methyl chloroformate afforded a 2-carboxylic ester (**26b**) <87H(25)701>.

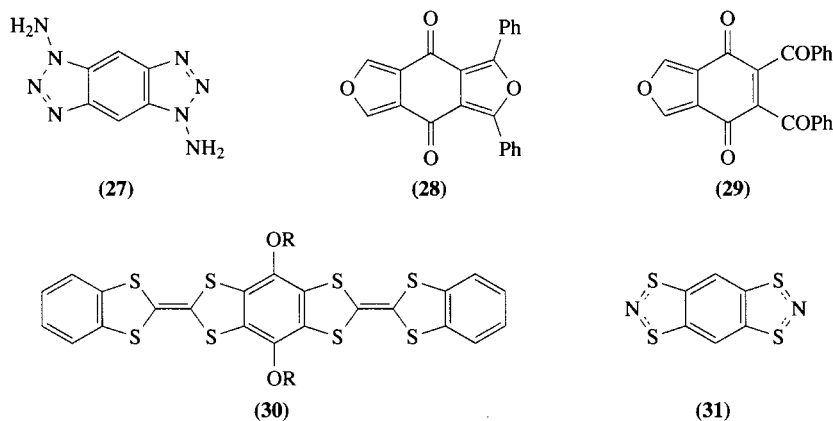


7.21.5.2.7 Reduction

The heterocyclic rings may be reduced. Thus, a protonated form of a benzo[1,2-*b*:4,3-*b'*]dipyrrole was selectively reduced at the 2-3 bond with cyanoborohydride <87JA2706> and this is useful in an approach to CC-1065 (**155**). However reaction with dissolving metals can lead to substituted benzenes or benzoquinones by total reduction and rupture of both heterocyclic rings, and this is more commonly observed <85ZN(B)429, 86URP1227633, 89BCJ3127, 90HCA2147, 92H(33)791>. A conjugated benzopyrrole dication was reduced by sodium metal in liquid ammonia <87AG1068>, with the conversion of the aromatic ring into a *p*-benzoquinodimethane form. Some dihalo-substituted benzodithiophene quinone analogues have been proposed as Wurster-type electron acceptors <83CL905>.

7.21.5.2.8 Oxidation

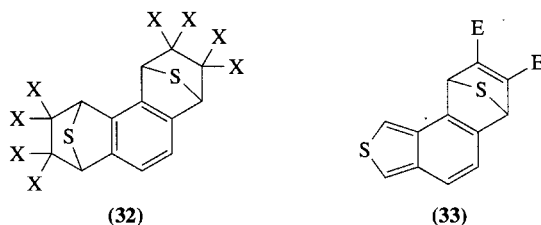
1,5-Diaminobenzobis-1,2,3-triazole (**27**) was oxidized by lead(IV) species to form 1,2,3,4-tetrahydrobenzene, which formed adducts with furan and 2,4-cyclohexadienes <86JOC979, 87JOC3835>. With cerium(IV) the benzo[*c*:*c'*]difuranquinone (**28**) was ruptured to a dibenzoyl compound (**29**) <89BSF708>, and a benzo[1,2-*b*:4,5-*c'*]dipyrrole readily underwent ring opening of the [*c*] fused ring on exposure to air <78JCR(S)39>. A benzobis-1,3-dithiole derivative (**30**) on electrochemical oxidation gave a tetracationic species <89SM15>, and also formed a charge transfer complex with 2,3-dichloro-5,6-dicyanobenzoquinone. The benzobis-2,1,3-thiadiazole system (**31**) can exist in three stable oxidation states (a diradical, a radical cation, and a dication) <86SM233, 86SM239>.



7.21.5.2.9 Reactions with cyclic transition states

The 2,2'-linking of a benzobis-1,3-dithiole-2-thione can be viewed as initially involving a [2 + 2] dimerization, but other couplings involve ionic mechanisms <90CC1624, 90T1553>. Heterocycles with [*c*] ring fusion usually react with various dienophiles by addition across the heterocyclic ring. Thus both 5,7-diphenyl-1-methylbenzo[1,2-*b*:4,5-*c'*]dipyrrole and hexaphenylbenzo[*c*:*c'*]dithiophene formed 1:1 adducts with *N*-phenylmaleimide by reaction at a heterocyclic ring. Two [*b*:*c*] fused angular benzodithiophenes failed to react with maleic anhydride, but did react with DMAD across the [*c*] fused ring <77CS57>.

Thieno[*c*:*d'*]benzothiadiazoles react preferentially with *N*-phenylmaleimide at the thiophene ring rather than at the thiadiazole ring <75ACR139, 78JCR(S)39>. The angular benzo[*c*:*c'*]dithiophene (**11**) reacted with tetracyanoethylene to form a diadduct (**32**; X = CN) via charge transfer complexes <84JOC1027>. With DMAD, a monoadduct (**33**; E = CO₂Me) was obtained. Azodicarboxylic ester added to a thienobenz[*c*:*c'*]isothiazole across the thiophene ring <86CB3158>. Tetramethyldihydrobenzene also added to benzo[*c*:*c'*]dipyrroles and tripyrroles <88ZN(B)125>, and activated alkynes added to related furans and *N*-substituted pyrroles <74BSF2105, 78JCR(S)39>.



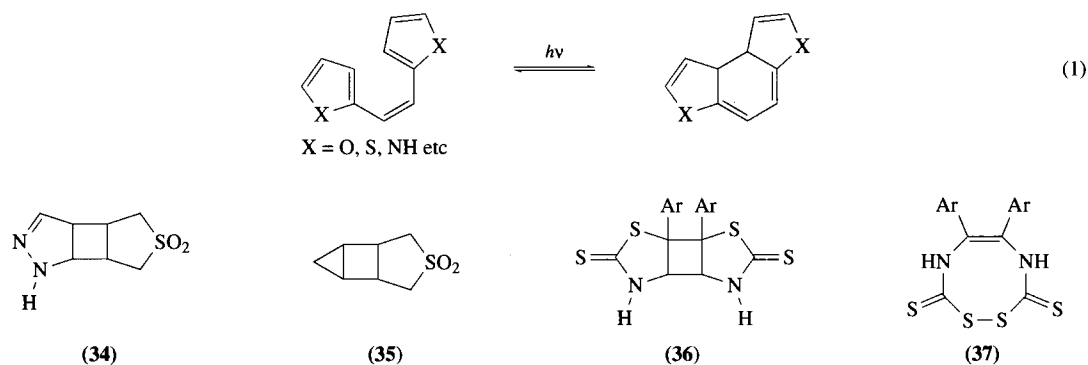
7.21.6 REACTIVITIES OF NONCONJUGATED RINGS

Where the reactivity involves both a carbocyclic ring and a heterocyclic ring it is discussed under the former.

7.21.6.1 Reactions of the Carbocyclic Ring

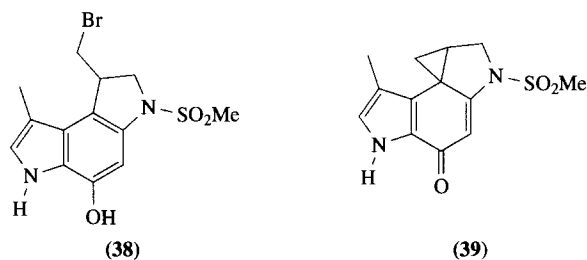
7.21.6.1.1 Thermal and photochemical reactions

Various dihydrobenzo[2,1-*b*:3,4-*b'*]dithiophenes and related selenophenes and pyrroles interconvert with acyclic forms under irradiation (Equation (1)) <90JOC2592>. As with simpler adducts of diazomethane and alkenes, the thienocyclobutapyrazole (34) photochemically extruded nitrogen to form a cyclopropacyclobutathiophene (35) <82CC1164>. A cyclobuta[*d*:*d'*]bisthiazole (36) rearranged at 30° to a dithiadiazacyclooctene (37) <86CC1030>.



7.21.6.1.2 Reaction with carbenes

Treatment of the bromo compound (38) with Hunig's base caused intramolecular attack of a substituent on the carbocyclic ring, with formation of the cyclopropane ring in compound (39) <81JA5621> and this was used in another approach to CC-1065 (155) (see Section 7.21.12). A similar reaction was achieved by treatment of a related mesylate with dbu <83CC1198>.



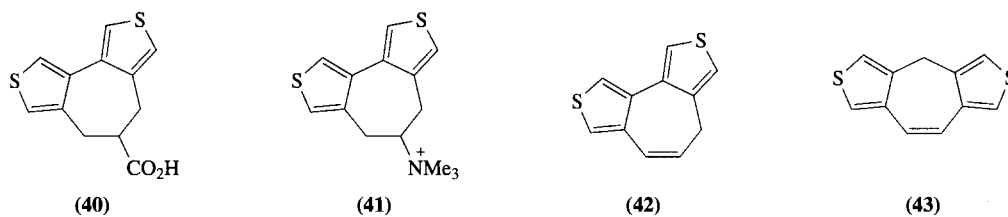
7.21.6.1.3 Nucleophilic attack at carbon

The nitrogen atom of the pyrrolidine moiety in a dihydrobenzothiazole internally displaced the bromine on the carbocyclic ring, forming a pyrrolbenzothiazole with a fused aziridine ring <83CPB1518>.

7.21.6.1.4 Dehydrogenation

The carbocyclic ring in dihydrobenzodipyrroles, benzodithiophenes, and benzodipyrroles may be aromatized by palladium on carbon <84IJC(B)918, 87JOC1521, 91H(32)41>.

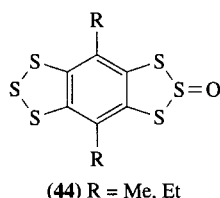
The oxidative decarboxylation of a cyclohepta[*c*:*c'*]dithiophene (40), or the elimination of the trimethylammonium group in the salt (41) gave the fused cycloheptatriene (42) <82CS53>. However, in contrast to the isomeric system (43), a tropylium ion could not be formed from compound (42) <81JCS(P1)2904>.



7.21.6.2 Reactions of the Heterocyclic Rings

7.21.6.2.1 Thermal and photochemical reactions

The light-catalyzed interconversions of dihydrobenzodithiophenes have been covered above under the reactions of the carbocyclic ring (see Section 7.21.6.1.1). 4,8-Dialkylbenzo[1,2-*d*:4,5-*d'*] benzobis-1,2,3-trithiolane-2-oxides (**44**) rearranged to the 1-oxides on photolysis <93TL673>. The flash vacuum pyrolysis of a furocyclobutathiophene-*S,S*-dioxide ruptured the thiophene ring with eventual formation of phthalic anhydride. Likewise, a cyclobutadithiophene-*S,S'*-tetraoxide formed styrene <83CC725>.

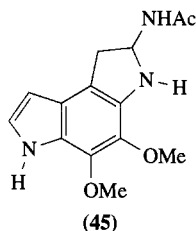


7.21.6.2.2 Electrophilic attack at carbon

No examples have been observed.

7.21.6.2.3 Electrophilic attack at nitrogen

An intramolecular reaction, which could be viewed as an electrophilic attack on nitrogen, is mentioned under the reactions of the carbocyclic ring (see Section 7.21.6.1.3) <83CPB1518>. The dihydrobenzodipyrrole (**45**) was acylated on the pyrrolidine nitrogen atom <87CC1406>. The oxidation of some benzodipyrroles, e.g. compound (**6**), and related tripyrroles, to their *N*-oxides can be viewed as an electrophilic attack on nitrogen.

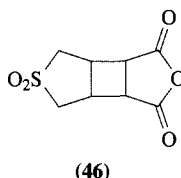


7.21.6.2.4 Electrophilic attack at sulfur

Few reactions of this type are reported, but benzobis-1,2,3-trithioles are oxidized to the 2-oxides (**44**) by MCPBA <93TL673>. Similarly, some tetrahydrobenzodithiophenes are oxidized to *S,S'*-dioxides with periodate. Dehydration of these over alumina afforded aromatic conjugated systems such as the benzodithiophene (**11**) <84JOC1027>.

7.21.6.2.5 Nucleophilic attack at carbon

Attack by nitrogen or carbon nucleophiles displaced halogen on a hexachlorobenzo[*c*:*c'*]dipyrrole <87AG1068>. Also, the trivial example of the anhydride (46) being converted to an ester is an example of a nucleophilic attack at a carbon atom <85CC1775>. The formation of cyclic imides from cyclic anhydrides are examples of nucleophilic attack at carbon by nitrogen nucleophiles (see Section 7.21.9.1). The acetolysis of *N*-oxides of tetrahydrobenzo[*c*:*c'*]dipyrroles aromatized the heterocyclic rings <88ZN(B)125>, and can be viewed as a type of deprotonation on carbon.



7.21.6.2.6 Oxidation

Apart from the oxidations on sulfur and nitrogen described above, various benzobisdioxoles can be converted to radical cations <82ZN(A)680>.

7.21.7 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.21.7.1 In Conjugated Systems

7.21.7.1.1 On the carbocyclic ring

Thiol groups on central benzenoid rings are alkylated <87SUL135>, and hydroxy groups may be oxidized to quinones, converted to ethers, or esterified <83MAC627, 91CB2613>.

7.21.7.1.2 On the heterocyclic rings

Intramolecular attack by an isocyanate group on a benzodifuran led to a new fused ring <86JHC1637>.

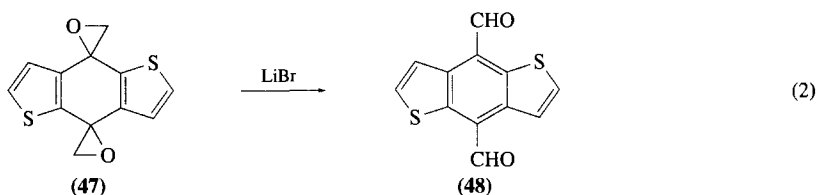
The aldehydes of benzodifurans, dipyrroles, and benzodithiophenes have typical reactivity, reacting with Wittig reagents, and other carbanions <83MAC627, 83ZOB441, 84KFZ1452>, and pyrrolecarboxylic acids readily decarboxylate <82KGS504>. Also, as with simpler monocyclic systems, benzodifuran-2-carboxylic acids decarboxylate readily <78EJMC435>.

Halogens on a benzodithiophene quinone analogue can be metallated by lithium. The resulting lithio compounds react with borate esters, eventually allowing conversion to the unhalogenated system <83CL905>.

Methyl groups on cationic rings can readily form carbanions, and condense with carbonyl reagents, for example trimethinecyanines can be formed by appropriate condensations <83URP1024962, 84URP1082786>.

7.21.7.2 In Nonconjugated Systems

Spirobisoxiranes (47), formed from benzodithiophene quinones, rearrange to dialdehydes (48) by treatment with lithium bromide (Equation (2)) <88JHC1917>.



7.21.8 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Few examples of this type have been described. Various tetrahydrobenzo[*c:c'*]dipyrrole-*N,N'*-dioxides dehydrate, with aromatization of the heterocyclic rings <88ZN(B)125>. 1- and 2-Substituted benzobistriazoles isomerize via an ionic mechanism. Three isomers are possible, with the 1,3'-isomer being the most favored in an equilibrium mixture. The thermodynamic and kinetic parameters for the reaction have been established <90JPO289>. *N*-Aminobenzo[*d:d'*]bistriazoles are oxidized to bisdehydrobenzene equivalents, presumably via nitrene intermediates <87JOC3835>, and *N*-acyl groups in pyrrole moieties are removed by hydrolysis. Some benzobis-1,2,3-trithiole-2-oxides rearrange photochemically to 1-oxides (44) <93TL673>.

7.21.9 RING SYNTHESIS

The syntheses of the systems below are classified according to the size of the central carbocyclic ring, as well as by the number and nature of bonds formed. Where the only bond formed is that at the fusion of the carbocyclic ring, it is covered under the synthesis of the carbocyclic ring, rather than of the heterocyclic ring. Compounds with a central six-membered ring, being usually derived from substituted benzenes, are the most common. This chapter will only deal with syntheses where the two heterocyclic rings are constructed virtually simultaneously, or where a second heterocyclic ring is constructed on an initially formed cycloalka-heterocycle. For the synthesis of the first heterocyclic ring, the appropriate chapter elsewhere in this work should be consulted. Most of the heterocyclic syntheses are analogous to those for simple or benzo-fused monocyclic heterocycles.

7.21.9.1 Synthesis of Compounds with a Central Four-Membered Ring

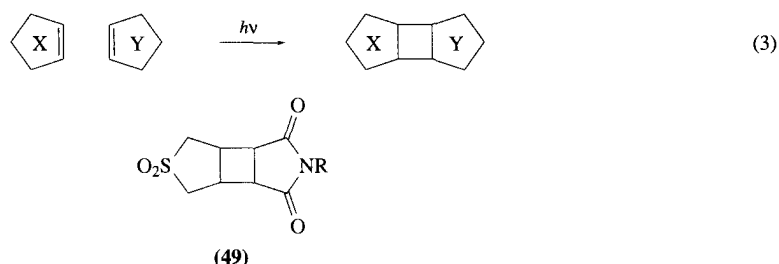
7.21.9.1.1 Compounds with one heteroatom in each heterocyclic ring

(i) Synthesis of the heterocyclic ring by formation of two bonds

(a) *Two C—N bonds.* The most common situation is that of cyclic imide (cyclobuta[*c:c'*]dipyrrole) formation from cyclobutanetetracarboxylic acids and anhydrides (cyclobuta[*c:c'*]difurans). This is widely used in polymer applications, especially for polymers for imaging purposes <82USP4340715, 82USP4358579, 82USP4366302, 87EUP249881, 88EUP259761, 88JAP(K)63249127, 88JAP(K)63259515, 89CA(110)76187, 90CA(113)6913, 90JAP(K)02219827, 91CA(114)196193, 91JAP(K)03153786, 92JAP(K)0413724, 92USP5129727>. Other syntheses of this type are uncommon.

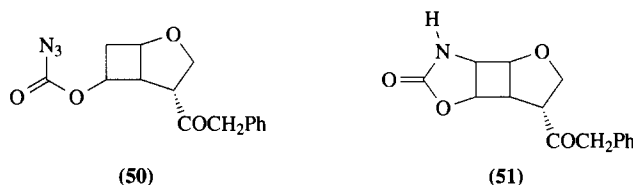
(ii) Synthesis of the carbocyclic ring by formation of two bonds

The most common method here is the photodimerization of furans, pyrroles, or thiophenes or their dihydro derivatives (Equation (3)). Thus furans, and various 2,3- or 2,5-dihydrofurans under photolysis form tetrahydro- and octahydro-cyclobutadifurans respectively with a head-to-head geometry <85JOC4707, 89JOC140, 91AG(E)1354>. 2,5-Dihydrofurans, 2,3-dihydropyrroles, and thiophenes also form head-to-head or head-to-tail dimers <84HCA1402, 89HCA1817, 89T1667, 90JOC5691>. Mixed systems too are accessible. Thus, maleimide and 2,5-dihydrothiophene-1,1-dioxide formed the thienocyclobutapyrrole (49) <91USP5053508>.

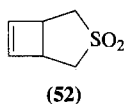


7.21.9.1.2 Compounds with two heteroatoms in one heterocyclic ring and one in the other*(i) Synthesis of the heterocyclic ring by formation of one bond*

(a) *A C—N bond.* The furocyclobutaoxazole (**51**) was formed by thermolysis of the carbamyl azide (**50**) <85JCS(P1)391>.

*(ii) Synthesis of the heterocyclic ring by formation of two bonds*

(a) *A C—C and a C—N bond.* The cyclobuta[*c*]thiophene (**52**) reacted with diazomethane to form the thieno[1,2-*c*:3,4-*c'*]cyclobutapyrazole (**34**) <82CC1164>.



(b) *A C—C and a C—O bond.* The cyclobuta[*c*]thiophene (**52**) reacted with nitrile oxides to form thieno[1,2-*c*:3,4-*d'*]isoxazoles <82CC1164>.

7.21.9.1.3 Compounds with two heteroatoms in both heterocyclic rings*(i) Synthesis of the heterocyclic ring*

No examples have been reported.

(ii) Synthesis of the carbocyclic ring

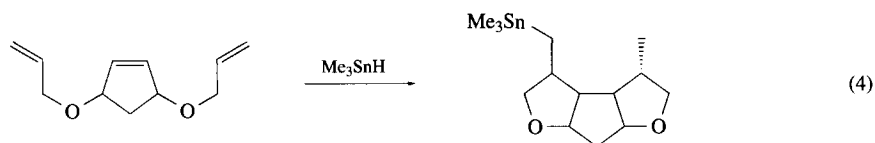
A photodimerization approach has been applied here. Thus photolysis of 4-(4-chlorophenyl)-thiazoline-2-thione forms the head-to-head dimer (**37**) <86CC1030>. Under radical conditions 1,3-dioxole forms two geometrical isomers of cyclobutabis-1,3-dioxolane <85CC1088>.

7.21.9.1.4 Compounds with more than two heteroatoms in either ring

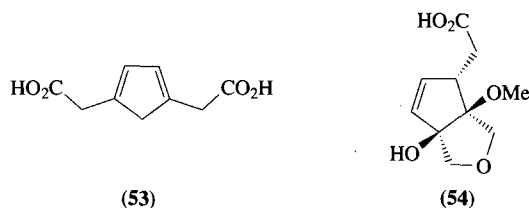
No examples have been reported.

7.21.9.2 Synthesis of Compounds with a Central Five-membered Ring**7.21.9.2.1 Compounds with one heteroatom in each heterocyclic ring***(i) Synthesis of the heterocyclic ring by formation of one bond*

(a) *A C—C bond.* The radical cyclization of some allylic trienyl ethers gives simultaneous construction of the two five-membered heterocyclic rings, leading to cyclopenta[*b*:*b'*] difurans (Equation (4)) <92JA3115>. In a related reaction, the heterocyclic and carbocyclic rings were constructed simultaneously <92BCJ1550>.



(b) A C—O bond. The acid-catalyzed cyclization of suitable diols gives cyclopenta[*b*:*c*]difurans <85JOC958>, and the cyclization of dicarboxylic acids of the type (53) gives cyclopentadifurans <86TL5437>, in a reaction related to the iodine-catalyzed cyclization of the alkenic acid (54) to a cyclopenta[*b*:*c*]difuran <88H(27)1557>.



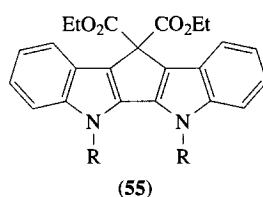
(ii) *Synthesis of the carbocyclic ring by formation of one bond*

Few examples of this approach have been described but the oxidative ring closure of dilithio-dithienyls by CuCl_2 has provided all seven cyclopentadithiophenes <68T3381>. A variation of this method is the internal coupling of dithienyl Grignard reagents by nickel complexes <89PS(42)63>. The internal coupling of 2,2'-diiodo-3,3'-dithienylmethanes, or of 3,3'-diiodo-2,2'-dithienylmethanes, with copper gave cyclopenta[1,2-*b*:3,4-*b'*]- and cyclopenta[1,2-*b*:4,3-*b'*]dithiophenes respectively <70JCS(C)273>.

Cyclopenta[1,2-*b*:3,4-*b'*]dithiophenes were formed by the internal attack of dithienyl carbenes <84ACS(B)533, 84JCS(P1)571>.

(iii) *Synthesis of the carbocyclic ring by formation of two bonds*

Two heterocyclic rings can also be linked by electrophilic substitution reactions. Thus, the cyclopentadiindole (55) is formed by the treatment of a 2,2'-diindolyl with diethyl mesoxalate <92AP(325)353>, and 3,5-dithienylthiophene-2,2'-dicarboxylic acids or derivatives can be cyclized to various thienylcyclopenta[*b*:*c'*] or [*b*:*b'*] dithiophenes <84PS(20)121>.



7.21.9.2.2 Compounds with two or more heteroatoms in either heterocyclic ring

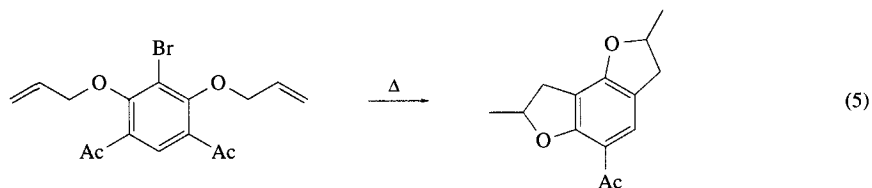
Little information on these systems has been reported.

7.21.9.3 Synthesis of Compounds with a Central Six-membered Ring

7.21.9.3.1 Compounds with one heteroatom in each heterocyclic ring

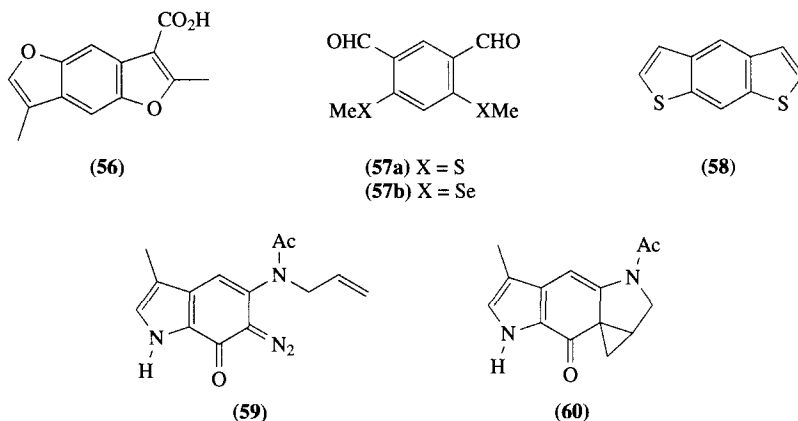
(i) *Synthesis of the heterocyclic ring by formation of one bond*

(a) A C—C bond. The Claisen rearrangement of resorcinol ethers gave benzo[1,2-*b*:3,4-*b'*]difurans <88JCS(P1)623, 91JCS(P1)2089, 92IJC(B)143>, sometimes with loss of ring substituents (Equation (5)).

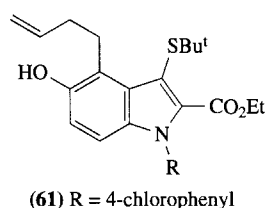


The synthesis of the benzo[1,2-*b*:4,5-*b'*]difuran (**56**) is a variation of a common approach involving base-catalyzed cyclizations <87CA(106)176085>. Other variations formed 2-nitrobenzodifurans by cyclization of *o*-nitromethoxy aldehydes <87CA(107)211476>. The acidity of the *S*-methyl protons in the bismethylthio dialdehyde (**57a**) allowed base-catalyzed cyclization to the benzo[2,1-*b*:3,4-*b'*]dithiophene (**58**) <91BSB1>.

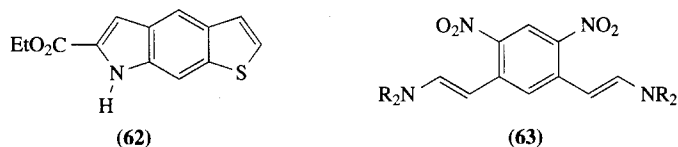
The acid-catalyzed cyclization of appropriate aryloxyketones formed benzo[1,2-*b*:5,4-*b'*]difuran and benzo[1,2-*b*:4,5-*b'*]difuran <63BSF1003>. Another variation involved the cyclization of an aryl thioacetal to a benzo[1,2-*b*:4,5-*b'*]dithiophene <86CB3198>. In investigations of the synthesis of a unit of the CC-1065 skeleton (see Section 7.21.12), a carbene derived from the azo-compound (**59**) constructed the cyclopropano-fused benzodipyrrole (**60**) by simultaneous formation of the heterocyclic ring and the cyclopropane ring <83TL4773>.



(b) *A C—O bond.* The anhydride formed from carbazole-2,3-dicarboxylic acid is a furobenzopyrrole derivative <84CPB902>. Also, a furobenzopyrrole is formed in small quantities by the acid-catalyzed cyclization of the phenol (**61**) <92TL4713>.

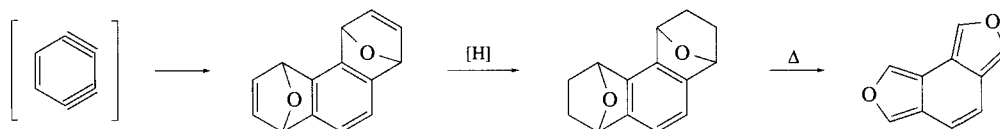


(c) *A C—N bond.* Nitrene approaches to pyrrole rings are fairly common. Thus, an internal reaction of a nitrene, from pyrolysis of an azide, formed the thienobenzo[1,2-*b*:4-*b'*]pyrrole (**62**) <89JCS(P1)603>. A nitrene approach has also been used in two approaches to the phosphodiesterase inhibitors PDE-I and PDE-II, both of which are benzo[2,1-*b*:3,4-*b'*]dipyrroles, and of related compounds <84JOC2240, 85CC1775> (see Section 7.21.12). Reduction of dinitrodienamines, e.g. (**63**) afforded benzo[1,2-*b*:4,5-*b'*]dipyrroles. Related reactions form benzo[1,2-*b*:5,4-*b'*]dipyrroles <87CC1176>, and the internal cyclization of a diamino-1,4-benzoquinone, or the corresponding quinol gave benzo[1,2-*b*:4,5-*b'*]dipyrroles <73JCS(P1)832>.



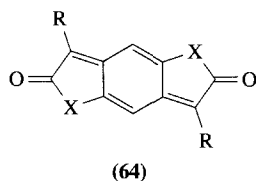
(ii) Synthesis of the heterocyclic ring by formation of two bonds

(a) *Two C—C bonds.* Various dehydrobenzenes, formed from polyhalobenzenes or other sources, reacted with furan to form multicyclic adducts containing benzodifuran and benzotrifuran moieties <80TL3831, 92T6827>. Hydrogenation of the isolated double bonds and elimination of alkenes formed fully conjugated multicyclic [*c:c'*] fused benzodifurans (Scheme 1). The radical cyclization of some cyclohexene-3,6-diyl ethers gave benzodifuran derivatives <92JA3115>.



Scheme 1

(b) *A C—C and a C—O bond.* Benzodifuran analogues of psoralen have been synthesized by reaction of benzofuran analogues of salicylaldehyde with α -haloketones-, nitriles-, esters etc. <77EJM31>, and various heterocycles of the type (64; X = O) were formed by reaction of 5-hydroxybenzofurans etc. with 2-ketoacids and aldehydes, or hydroxymandelic acid and chloroacetic acid. Thiophene and pyrrole analogues could also be made. These compounds are useful as dyes <85EUP146269, 90EUP363034>.



(c) *A C—C and a C—N bond.* The 5-aminoindole sulfonium ylide (65) provided an intermediate which cyclized via a [2,3] sigmatropic rearrangement to a benzo[1,2-*b*:4,3-*b'*]dipyrrole <86TL2735>. An extension of the Gassman method for oxindoles was used in an approach to CC-1065 <81JA5621> (see Section 7.21.12). In an approach to U-71,184, an antitumor agent modelled on CC-1065, the heterocyclic ring was constructed using a sulfur ylide <86TL4103>. Benzo[1,2-*b*:3,4-*b'*]dipyrroles and benzo[1,2-*b*:4,3-*b'*]dipyrroles were formed by Fischer-type indolizations of the appropriate phenylhydrazones <87GEP350825> and double indolizations of cycloalkanedionebisphenylhydrazones afforded benzo-, cyclohepta-, etc. [*b:b'*]diindoles <89JOC824, 89JOC1720, 91T7739>. Other related approaches formed benzo[1,2-*b*:3,4-*b'*]dipyrrole, benzo[1,2-*b*:5,4-*b'*]dipyrrole and benzo[1,2-*b*:4,3-*b'*]dipyrrole <80KGS849, 81KGS268>. The method has also been used as an approach to CC-1065 <79ABC555, 79ABC559>. Other recognizable indole-forming reactions are those of aminobenzofurans with α -haloketones to form furobenzopyrroles <90MIP902735>, and aminobenzothiophenes to thieno[1,2-*b*:4,5-*b'*]benzopyrroles by syntheses akin to isatin-forming reactions <82EUP65393>.

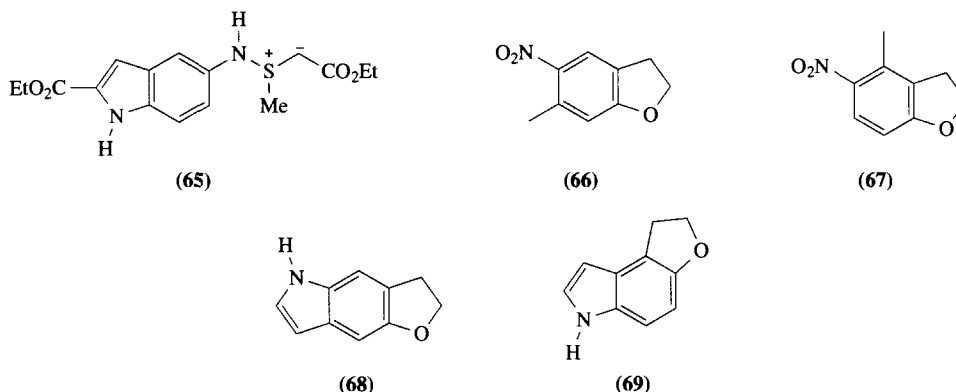
Benzoquinones reacted with four equivalents of isonitriles to form benzo[*c:c'*]dipyrroles <84LA1003>, and variations of the Nenitzescu reaction, i.e. of quinones with enamines, have been useful synthetic approaches to benzo[1,2-*b*:4,5-*b'*]dipyrroles <71T5031, 73T921>.

Heating the nitromethylbenzofurans (66) and (67) with DMF and its diethylacetal gave the furobenzopyrroles (68) and (69) respectively <92T1039>.

(d) *Two C—N bonds.* Condensation of 1-methylpyrrole-2,3-dicarbaldehyde with 1,4-diphenylbutane-1,4-dione gave 1-methyl-5,6-dibenzoylindole which could be cyclized to a [1,2-*b*:4,5-*c'*]benzodipyrrole <78JCR(S)39>.

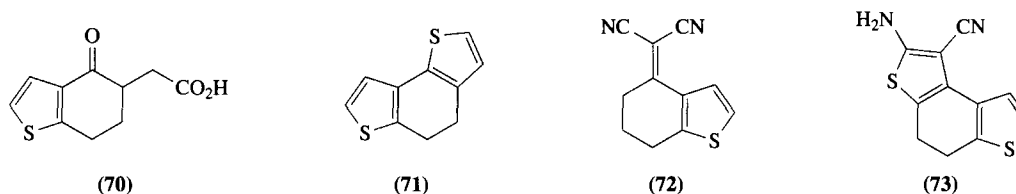
Various [*c:c'*] fused benzo-, di-, and tripyrroles are formed by the reaction of poly(halomethyl) benzenes with amines. The dihydrocompounds formed were further dehydrogenated to fully conjugated derivatives <88ZN(B)125>. 4,6-Diacetylresorcinols reacted with hydrazine in 2-methoxyethanol to form [1,2-*c*:5,4-*c'*]benzodipyrroles <88JMC2034>.

(e) *Two C—O bonds.* Some benzo[*c:c'*] difurans were made by acid cyclization of appropriate diketones <74BSF2105> or polyhalomethylbenzenes with hydroxide ion <88ZN(B)125>. Various [*c:c'*] fused benzo-, di-, and trifurans were formed by the reaction of polychalomethyl)benzenes with base, and further dehydrogenated to fully conjugated derivatives <88ZN(B)125>.



(f) *Two C—S bonds.* The dihydro benzo[1,2-*b*:3,4-*b'*]dithiophene (71) was formed from the 4-ketoacid (70) by treatment with Lawesson's reagent <86M621>, and heating the benzothiophene (72) with sulfur gave a 2-amino-3-cyanodihydrobenzo[1,2-*b*:4,3-*b'*]dithiophene (73) <84IJC(B)918>. Various [*c*:*c'*] fused benzo- di- and trithiophenes were formed by the reaction of poly(halomethyl) benzenes with sulfide ions. The dihydrocompounds formed were further dehydrogenated to fully conjugated derivatives <88ZN(B)125>.

1,4-Diethylbenzene reacted with hydrogen sulfide in the presence of a Cr_2O_3 catalyst to give the isomeric benzo[2,1-*b*:3,4-*b'*]- and benzo[1,2-*b*:3,4-*b'*]dithiophenes <88IZV2857>. Heavily aryl-substituted benzo[1,2-*c*:3,4-*c'*]dithiophenes were formed by thionation of 5,6-dibenzoylbenzo[*c*]thiophenes <75ACR139, 85JAP(K)60254037>.



(g) *Two N—S bonds.* Benzobis-2,1,3-thiadiazole systems were prepared by reaction of trimethylsilyl azide and benzene-1,2,4,5-tetrasulfonyl chloride <86SM233, 86SM239>.

(iii) Synthesis of the carbocyclic ring by formation of one bond

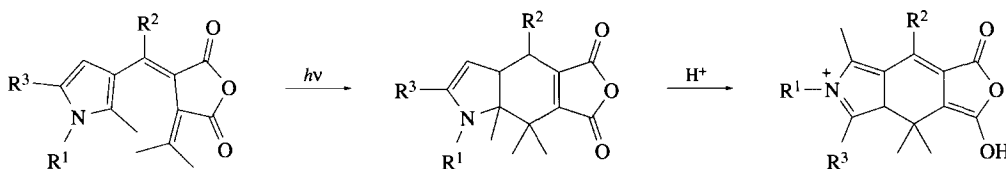
The photolysis of heterocyclic analogues of stilbene is a very versatile method in heterocyclic synthesis, originally applied to many benzo[*b*:*b'*]dithiophenes, thienobenzofurans, and benzo-difurans <67JOC3093>, and subsequently applied to dithienobenzopyrroles and benzotrithiophenes <87JOC2213>, benzodipyrroles, various furobenzopyrroles, thienobenzopyrroles <85TL2423, 86CC826, 86JA2110, 87JOC19>, benzo[2,1-*b*:3,4-*b'*]dithiophene <77CS57>, and benzodiselenophenes <90JOC2592>. It has also provided an approach to CC-1065 (see Section 7.21.12) <87H(25)701> and to tritiated benzodithiophenes <83JCS(P2)813>. However, the approach failed for the preparation of benzo[2,1-*b*:3,4-*b'*]dithiophenes and this is accounted for by the instability of the necessary intermediate radicals <75RTC239>. Appropriately substituted compounds equilibrate photochemically between dicyclic and tricyclic forms <90JOC2592> (e.g. Equation (1) and related reactions).

Electron impact mass spectrometry of 2,2'-dibromo-3,3'-dithienyl gave a radical cation of benzo[2,1-*b*:3,4-*b'*]dithiophene <90JHC1867>.

Another common approach is acid-catalyzed linking, internally and externally, of furans, pyrroles, and thiophenes by means of carbonyl compounds. Thus, benzo[1,2-*b*:5,4-*b'*]benzodithiophenes can also be constructed by cyclization of 2-(3-thienylmethyl)-thiophene-3-carbaldehydes using HBr <83MAC627, 86CB3198>. Benzo[1,2-*b*:4,3-*b'*]dipyrroles, studied as synthetic approaches to CC-1065 (see Section 7.21.12) resulted from the acid-catalyzed cyclization of 3,3'-dipyrrolyl-2-acetyl chlorides or 2-acetaldehydes which are themselves available by elaboration of 3,3'-dipyrroles <83CC26, 87JA2706>. A hydroxybenzo[2,1-*b*:3,4-*b'*]dithiophene was formed by the cyclization of 2,2'-dithienyl-3-acetic acid <87KFZ1320>, and the corresponding [1,2-*c*:4,5-*b'*] system by cyclization of 4-(2-thienylmethyl)thiophene-3-carboxylic acid <71JOC4004>. Some furobenzopyrroles were formed by

the acid- or light-catalyzed cyclization of 3-(3-pyrrolylbutadienedioic)anhydrides (Scheme 2) <91JCS(P1)3259>. Related reactions under acid or light-catalyzed conditions formed furo[1,2-*c*:4,5-*b'*]benzothiophenes, furo[1,2-*c*:5,4-*b'*]benzothiophenes and furobenzopyrroles <85JCS(P1)957, 91CPH311, 91JCS(P1)3259>.

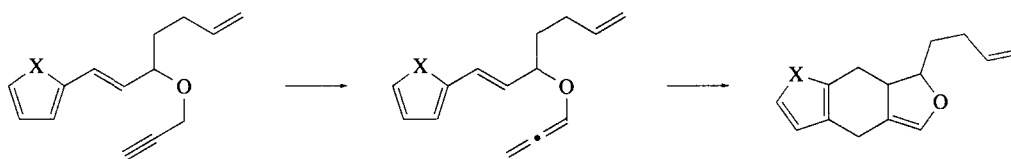
In an approach to CC-1065 (Section 7.21.12), Sundberg used the internal cyclization of a 3-ketoenolate anion with a stabilized carbocation to construct the carbocyclic ring <85JOC425>.



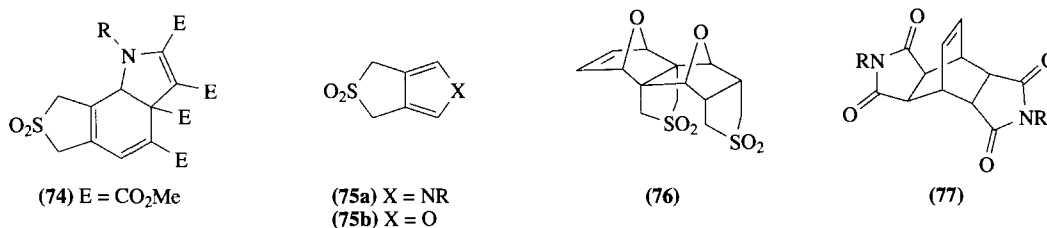
Scheme 2

(iv) *Synthesis of the carbocyclic ring by formation of two bonds*

Pericyclic methods involving [4 + 2] cycloadditions have been widely used. Thus, the addition of dienes containing pyrrole or thiophene moieties to maleic anhydride or maleimide formed various furo[1,2-*c*:4,5-*c'*]benzothiophenes, thieno[1,2-*c*:4,5-*c'*]benzopyrroles, thieno[1,2-*b*:4,5-*c'*]benzopyrroles and thieno[1,2-*b*:4,5-*c'*]benzopyrroles <87TL6085, 90TL1491, 91CC1287, 92KGS173>. Also, 2-vinylindoles react with maleic anhydride to form furo[3,4-*c*]indoles via [4 + 2] cycloadditions <83IJC(B)1004>. Benzodifurans and furobenzopyrroles were also produced by the intramolecular cycloaddition of allenyl ethers, as intermediates in the rearrangement of alkynes, on 2-vinylfurans or 2-vinyl pyrroles respectively (Scheme 3) <84JA6735, 88JOC860>. Under basic conditions an isomeric product results. The thieno[1,2-*c*:3,4-*b'*]benzopyrrole (**74**) was found to be a product of the reaction of a thienopyrrole (**75a**) with DMAD <92CC1100>. The reaction of the related thienofuran (**75b**) led to the multi-ring compound (**76**) which can be regarded as a benzodithiophene <91CC204>. The photolysis of a maleimide with disubstituted benzenes led to the bridged benzo[*c*:*c'*]dipyrrole (**77**), among other products <86JMC2164>.

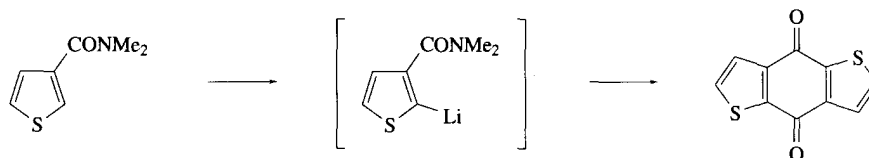


Scheme 3

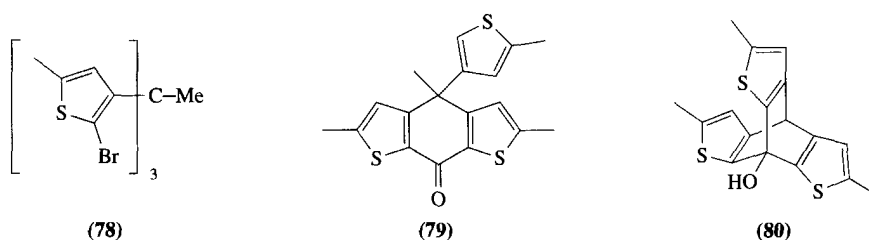


Treatment of thiophene-3-carboxamides with butyllithium gave 2-lithio derivatives, which cross-coupled to form the benzo[1,2-*b*:4,5-*b'*]dithiophene (Scheme 4) <76JOC3668>. Lithium exchange of 1,1,1-tris(2-bromo-5-methylthienyl)ethane (**78**) and reaction with diethyl carbonate gave the

benzo[1,2-*b*:5,4-*b'*]dithiophene (**79**), along with the heterotriptycene (**80**), which rearranged to compound (**79**) either on heating or on treatment with acid or base <91CC751>.

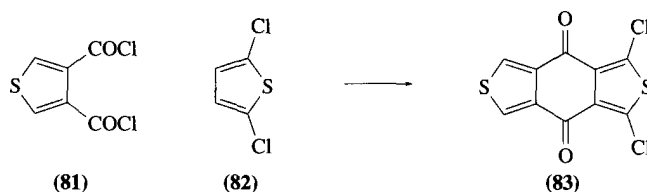


Scheme 4



Acid-catalyzed cyclization methods have been extensively used. Some methods involved the coupling of 2,2'- and 3,3'-dithienylmethanes by acetic acid in ppa, or by DMF in phosphoryl chloride <70CC1094>. The reaction of oxalyl chloride with a 3,3'-bipyrryl, formed by an isonitrile method, was used in an approach to benzo[1,2-*b*:4,3-*b'*]dipyrroles <85TL2985, 87JA2711>. Other acid-catalyzed cyclization approaches involve the 2,2'- and 3,3'-linking of 3,3'- and 2,2'-dipyrlylmethanes respectively to form benzo[1,2-*b*:5,4-*b'*]dipyrroles <71AP(304)288>, and the reaction of the acid chloride (**81**) with thiophene or 2,5-dichlorothiophene (**82**) to give benzo[1,2-*b*:4,5-*c'*]dithiophenes (e.g. (**83**)) (Scheme 5) <72JOC1712>.

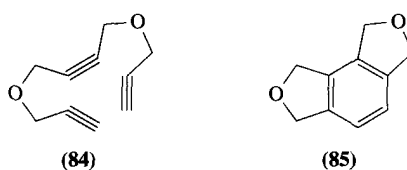
A simple method, but with limited yield, is the pyrolysis of pyrrole-2,3-dicarboxylic anhydride to form benzo[1,2-*b*:4,5-*b'*]- and [1,2-*b*:5,4-*b'*]dipyrrole systems <70TL4631>.



Scheme 5

(v) *Synthesis of the carbocyclic ring by formation of three bonds*

Benzo[1,2-*c*:3,4-*c'*]difurans (**85**) can be formed by the rhodium-catalyzed intramolecular [2 + 2 + 2]cycloaddition of some triynyl ethers (**84**) <88JCS(P1)1357>

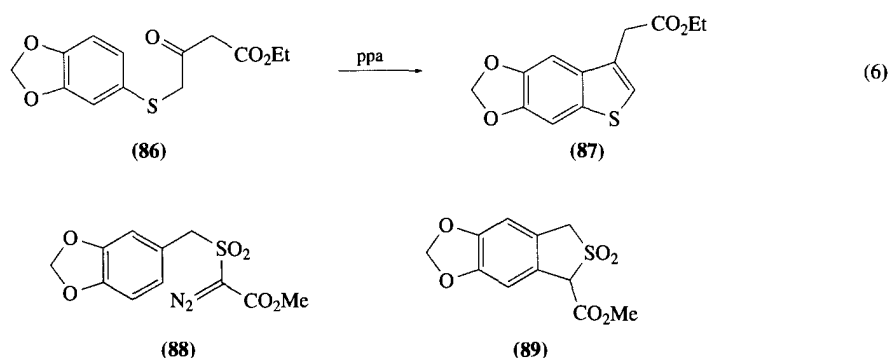


7.21.9.3.2 Compounds with two heteroatoms in one heterocyclic ring and one in the other

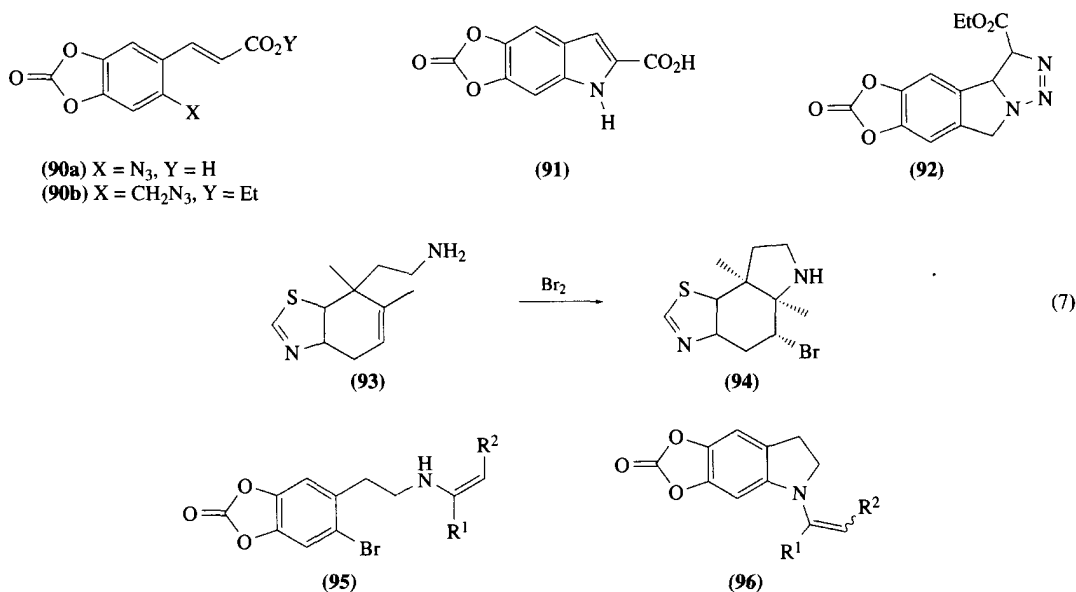
The reaction of 1-aryl-3,4-diacyl-4-(2-furyl)butan-1-ones with acid or with phosphorus pentasulfide led to [2,1-*b*:3,4-*c'*]benzodifurans and thieno[1,2-*c*:3,4-*b'*]benzofurans, by simultaneous cyclization of heterocyclic and carbocyclic rings <74BSF2105>.

(i) Synthesis of the heterocyclic ring by formation of one bond

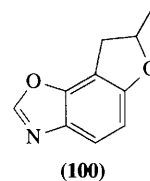
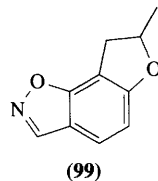
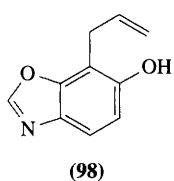
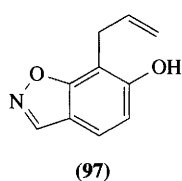
(a) *A C—C bond.* Thienobenzo-1,3-dioxoles (**87**) were made by cyclization of 2-oxoalkyl aryl sulfides (**86**) with polyphosphoric acid <83JHC461> (Equation (6)). Treatment of the diazocompound (**88**) with rhodium acetate gave the thieno[*c*:*d'*]benzo-1,3-dioxole (**89**) by cyclization of a carbene or carbenoid <86TL5679>.



(b) *A C—N bond.* Thermolysis of the azide (**90a**) gave a nitrene which cyclized to the dioxolo[1,2-*d*:5,4-*b'*]benzopyrrole (**91**). Interestingly, a benzyl azide (**90b**) reacted in a dipolar fashion to form a triazole (**92**) with a benzodioxolo moiety <84JHC1183, 86JOC1120>. The pyrrolobenzothiazole (**94**) can be formed by reaction of the aminoalkene (**93**) with bromine (Equation (7)) <83CPB1518>. The photolysis of the 2-bromophenethylamine (**95**) gave the dioxolobenzopyrrole (**96**) <83TL5567>.

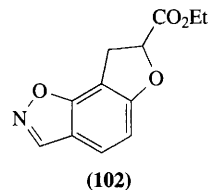
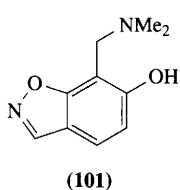


(c) *A C—O bond.* The *o*-allylphenols (**97**) and (**98**), available by Claisen rearrangements, cyclized to the furans (**99**) and (**100**) by treatment with MCPBA <91CPB1760>.

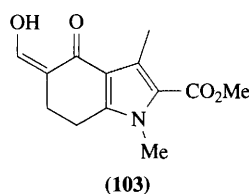


(ii) *Synthesis of the heterocyclic ring by formation of two bonds*

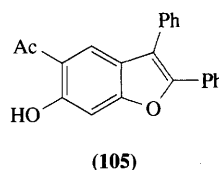
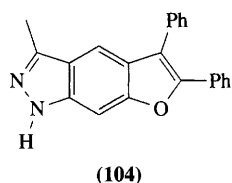
(a) *A C—C bond and a C—N bond.* Treatment of the Mannich base (101) with the 2-ethoxy-2-oxoethyltrimethylsulfonium ion in base gave the furobenzisoxazole (102) <91CPB1760>.



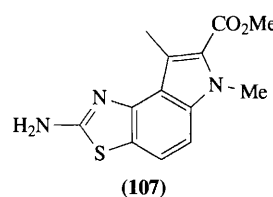
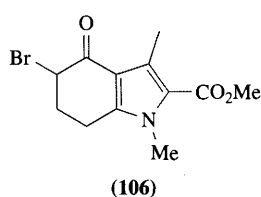
(b) *A C—O bond and a C—N bond.* Reaction of the hydroxymethyleneketones (103) with hydroxylamine gave pyrrolobenzisoxazoles <82IJC(B)853> and related reactions produced benzo-pyrrolooxazoles <83IJC(B)437>. Various hydroxycarbazoles reacted with amines under oxidative conditions to form pyrrolobenzoxazoles. These reactions are related to peroxidase-catalyzed reactions of the hydroxycarbazoles with amino acids <85TL4933, 86CC371>.



(c) *Two C—N bonds.* Examples of the furobenzopyrazole system (104) were made by reaction of hydrazine with 5-acetyl-2,3-diphenyl-6-hydroxybenzofuran (105), a variant of benzopyrazole synthesis <87MI 721-01>, and thienobenzopyrazoles are formed from fused hydroxymethenecyclohexanones <84IJC(B)918>.



(d) *A C—N bond and a C—S bond.* The 2-bromoketone (106) reacted with thiourea to form, after dehydrogenation, the pyrrolobenzothiazole (107) <82IJC(B)853>.



(e) *Two C—S bonds.* Related to simpler benzo[*b*]thiophene syntheses, the thionation of some dibenzoylpyrazoles and dibenzoyl-2,1-benzisothiazoles gave thienobenzopyrazoles and thienobenzisothiazoles respectively <75ACR139, 86CB3158>.

(iii) *Synthesis of the carbocyclic ring*

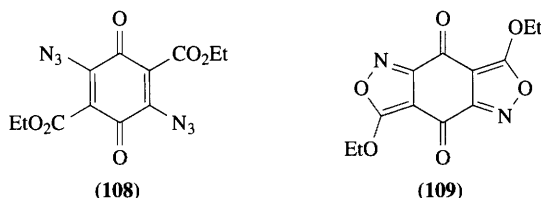
No syntheses of this type have been reported.

7.21.9.3.3 Compounds with two heteroatoms in each heterocyclic ring

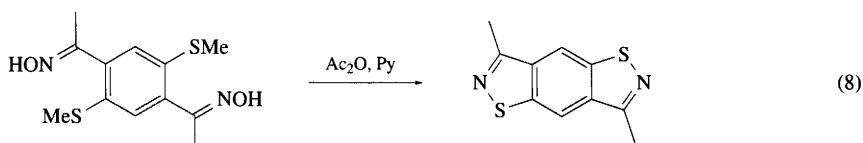
(i) *Synthesis of the heterocyclic ring by formation of one bond*

(a) *A C—S bond.* In variations of the Hugerschoff synthesis of benzothiazoles, the oxidation by iron(III) or bromine of bithioacylaminobenzenes caused ring closure to benzo[*d*:*d'*]bisthiazoles <86JAP(K)61268688, 86JMS(142)459, 92JMC350>.

(b) *An O—N bond.* Reaction of dichlorobenzoquinone dicarboxylic ester with azide ion gave the azide (108), which thermolyzed to form the benzobisoxazole (109) <78CB3346>.

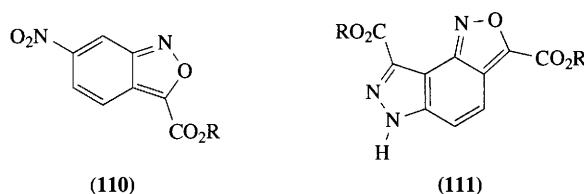


(c) *A S—N bond.* Treatment of the oximes of various bisalkylthiodiacetylbenzenes with acetic anhydride in pyridine afforded four dimethylbenzo[*d*:*d'*]diisothiazoles (e.g. Equation (8) for the [1,2-*d*:4,5-*d'*] system) <91JHC445>. A dialdehyde likewise affords one of the unsubstituted systems <78S58>. These are variations of 2,1-benzisothiazole syntheses.



(ii) *Synthesis of the heterocyclic ring by formation of two bonds*

(a) *A C—C bond and a C—N bond.* The 6-nitro-2,1-benzisoxazole (110) reacted with excess diazoacetic ester to form the isoxazolobenzopyrazole (111), with displacement of a nitro group <82S677>.

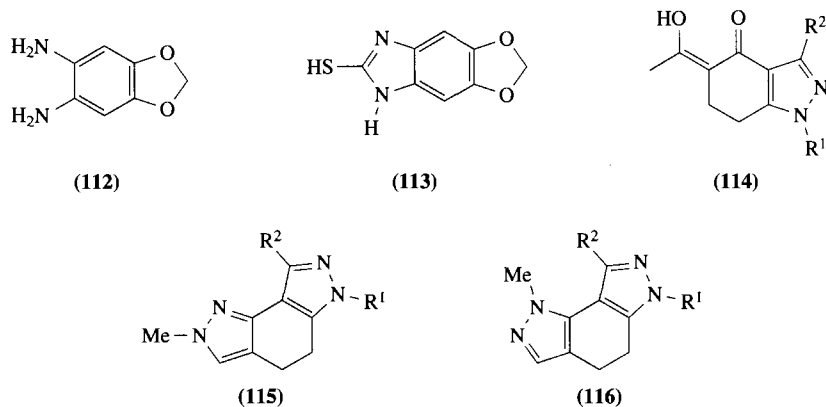


(b) *A C—C bond and a C—O bond.* 1,4-Quinones and cyclohexa-1,4-dienes reacted in a dipolar fashion with nitrile oxides to form benzodiisoxazoles <83BCJ3457, 85CB4203>.

(c) *A C—C bond and a C—S bond.* With a “nitrile sulfide” a 1,4-benzoquinone formed a benzo[1,2-*d*:4,5-*d'*]diisothiazole <80CC1194> in a manner analogous to the sequence described in Section 7.21.9.3.3(ii)(b).

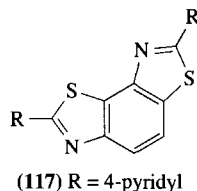
(d) *Two C—N bonds.* The benzo-1,3-dioxole derivative (112), an aromatic 1,2-diamine, reacted

with potassium ethylxanthate to produce the 1,3-dioxolobenzimidazolethiol (**113**) <82BEP890024> and polybenzimidazoles formed from benzene-1,2,4,5-tetraamines and 1,4-benzenedicarbaldehyde or 1,4-benzenedicarboxylic acid <83MM128>. Some polybenzobisthiazoles, bisoxazoles, and diimidazoles were obtained by related syntheses <82CA(97)6890>. A number of angularly fused benzo-dipyrzoles have been obtained by reaction of hydroxymethylenebenzopyrazole ketones with hydrazines <91H(32)41>. Thus, reaction of methylhydrazine with the enol (**114**) gave the isomeric systems (**115**) and (**116**).



(e) A C—N bond and a C—O bond. Some benzobisoxazoles were made by reaction of dihydroxybenzenediamines with benzene-1,4-dicarboxylic acid <82CA(97)6890>. Also, 2,5-diaminobenzoquinones reacted with aromatic acids to give benzobisoxazoles <90JAP(K)02221281>.

(f) A C—N bond and a C—S bond. Some benzobisthiazoles were formed by reaction of dithiolbenzenediamines with benzene-1,4-dicarboxylic acid <82CA(97)6890, 90USP4937321>, and aromatic diamines react with 4-picoline and sulfur to form benzobisthiazoles, e.g. a benzene-1,3-diamine gave the benzobisthiazole (**117**) <82CA(96)52220>.

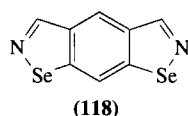


(g) Two C—O bonds. Polyhydroxy-benzenes and 1,4-benzoquinones reacted with phosgene to form benzo[*d*:*d'*]bis-1,3-dioxoles <84T4897>.

(h) Two C—S bonds. Benzene-1,2,4,5-tetrathiols reacted with aldehydes, ketones, or carbon disulfide to form benzo[*d*:*d'*]bis-1,3-dithioles. With benzenehexathiol, benzo[*d*:*d'*:*d''*]tris-1,3-dithioles are obtained <82PS(13)309, 87SUL135, 90S1149>. These types are also obtained by reaction of polyhalonitrobenzenes and 2,2'-bismethylthioethene-1,1-dithiolate <86C200, 90JOC5347>.

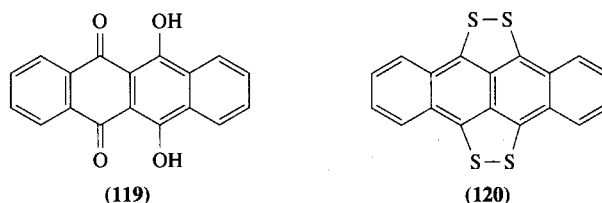
(i) A C—S bond and a N—S bond. The reaction of appropriately substituted methylaminoisothiazoles with *N*-sulfinylmethane-sulfonamide (NSMSA) gives a series of symmetrical and unsymmetrical benzo[*c*:*c'*]diisothiazole systems. The benzo[1,2-*c*:4,3-*c'*] system is also formed from 1,4-diamino-2,3-dimethylbenzene and NSMSA by simultaneous formation of both heterocyclic rings. <80JHC533, 80JHC537>. A similar approach by reaction of three 1,2-benzisothiazoles containing appropriately situated methyl and amino groups with NSMSA provided three benzo[*c*:*d'*]diisothiazoles <91JHC347, 94UP 721-01>.

(j) A C—N bond and a Se—N bond. The reaction of the bismethylselenobenzenedial (**57b**) with ammonia gave the benzo[*d*:*d'*]diisosenazole (**118**) <91BSB1>.



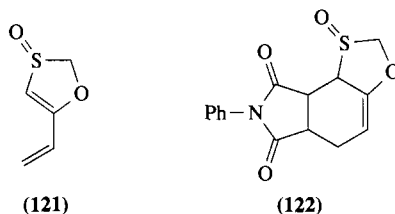
(k) Two P—N bonds. Benzo[1,2-*c*:4,5-*c'*]bis-2,1,3-phosphazoles were formed from 1,2,4,5-tetraaminobenzenes and trisdiethylaminophosphine <91IC2342>.

(a) *Two C—S bonds and one S—S bond.* The compound (**120**), which has a benzobis-1,2-dithiole moiety, may be made by various sulfurization or thionation procedures from the dihydroxy naphthacenedione (**119**), or from tetrachloronaphthacene $\langle 90\text{CA}(112)178743 \rangle$. 1,8,9,10-Tetrachlorophenanthrenes reacted with sodium polysulfide in DMF to form phenanthro[1,10-*cd*:8,9-*c'**d'*]bis-1,2-dithioles $\langle 92\text{CC}278 \rangle$. Other benzobis-1,2-dithiole derivatives, based on naphthalene rings, have been reported $\langle 76\text{JA}252 \rangle$, but no simple benzobis-1,2-dithioles appear to have been described.



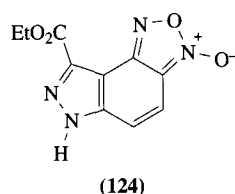
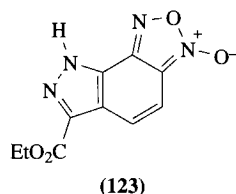
No syntheses of this type have been reported.

A diene with a 1,3-thioxole moiety (**121**) reacted with *N*-phenylmaleimide to form a 1,3-thioxolo-[1,2-*d*:3,4-*c'*]benzopyrrole (**122**) <88JA4625>.



No preparations of this type have been reported.

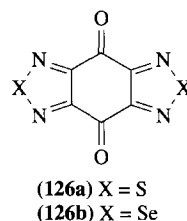
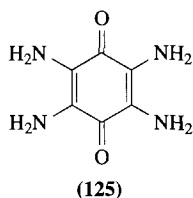
(a) *A C—C bond and a C—N bond.* 4-Nitro- and 5-nitrobenzoxazoles reacted with ethyl diazoacetate to form the angular pyrazolobenzoxadiazoles (**123**) and (**124**) respectively (<83CC990>: these reactions are related to the synthesis of the isoxazolobenzopyrazoles (**111**) (see Section 7.21.9.3.3(ii)(a)).



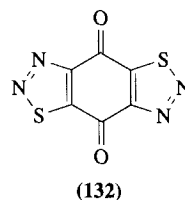
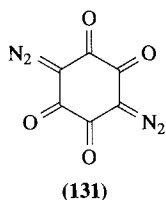
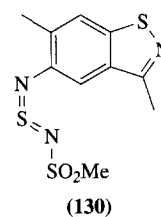
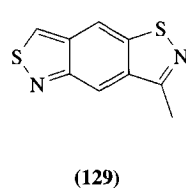
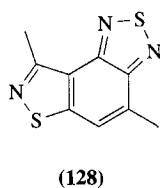
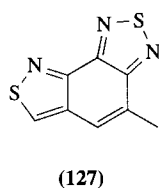
(b) *Two C—N bonds.* Benzobis- and benzotris-thiadiazoles can be made by reaction of halocatechols and haloresorcinols with tetrasulfur tetranitride $\langle 89\text{BCJ3127} \rangle$. This gives better yields than syntheses from phenyl ethers.

(c) *A C—S bond and a C—N bond.* Angular isothiazolobenzothiadiazoles were formed from a benzothiadiazole with adjacent methyl and amino substituents in a process related to other 2,1-benzisothiazole syntheses $\langle 80\text{JHC533}, 91\text{JHC347} \rangle$, by reaction with *N*-sulfinylmethanesulfonamide $\langle 80\text{JHC537} \rangle$.

(d) *Two N—S bonds.* The tetraaminobenzoquinones (**125**) reacted with thionyl chloride or selenium oxychloride to form benzo[*d*:*d'*]bisthiadiazoles and benzo[*d*:*d'*]bisselenadiazoles (**126a**) and (**126b**) $\langle 82\text{CB2898} \rangle$, and an isothiazolobenzothiadiazole was made similarly from a diamino-2,1-benzisothiazole $\langle 80\text{JHC537} \rangle$.



(e) *A C—S bond and a S—N bond.* Reaction of 1,3-dimethyl-4,6-diaminobenzene with *N*-sulfinylmethanesulfonamide gave 8-methylisothiazolobenzothiadiazole (**127**), rather than the expected benzodiisothiazole $\langle 80\text{JHC537} \rangle$. In a related reaction, 3,6-dimethyl-5-amino-1,2-benzisothiazole gave, in addition to traces of a benzo[*c*:*d'*]diisothiazole (**129**), an isothiazolobenzothiadiazole (**128**). A pericyclic reaction of the intermediate (**130**) may be involved. Thionation with Lawesson's reagent of the 3,6-bisdiazocyclohexane-1,2,4,5-tetraone (**131**) gave the linear benzo-bisthiadiazole (**132**) $\langle 91\text{CB2613} \rangle$.

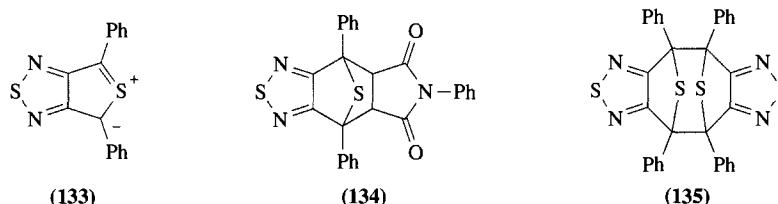


(iii) Synthesis of the heterocyclic ring by formation of three bonds

(a) *Two C—S bonds and a S—S bond.* Benzobis-1,2,3-trithioles are formed from 1,2,4,5-tetrabromobenzenes and sulfur in liquid ammonia $\langle 91\text{PS}(51)431 \rangle$.

(iv) *Synthesis of the carbocyclic ring*

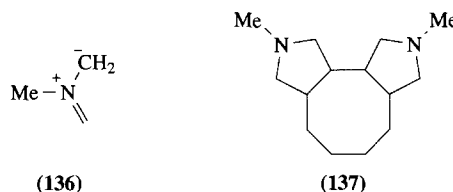
Reaction of the thieno[*c:c'*]thiadiazole (133) with *N*-phenylmaleimide gave the pyrrolobenzo-thiadiazole (134) <75ACR139>. The thieno[*c:c'*]thiadiazole (133) equilibrates photochemically with the cyclooctabisthiadiazole dimer (135).

7.21.9.4 *Synthesis of Compounds with a Central Seven- or Larger Membered Ring*7.21.9.4.1 *Compounds with one heteroatom in each heterocyclic ring*(i) *Synthesis of the heterocyclic ring by formation of one bond*

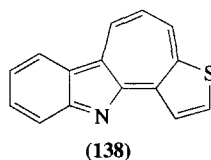
No syntheses of this type have been reported.

(ii) *Synthesis of the heterocyclic ring by formation of two bonds*

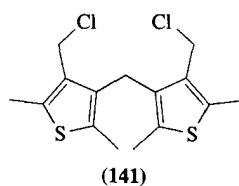
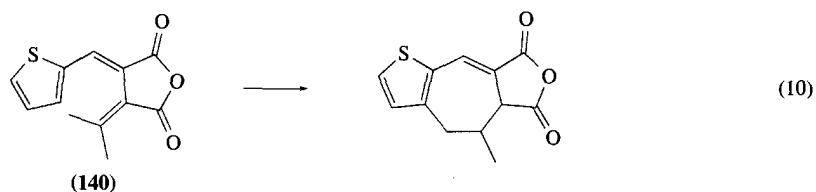
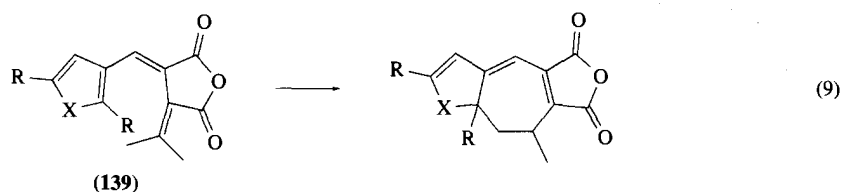
(a) *Two C—C bonds.* The nitrogen ylide (136) reacted with cycloocta-1,3-diene to form a cycloocta[*c:c'*]dipyrrole (137) <85CJC725>.



(b) *A C—C bond and a C—N bond.* Cyclohepta- and cyclooctadithiophenes were formed by double indolization of the phenylhydrazones of cycloheptane- and cyclooctanediones <89JOC1720> and a cycloheptathiophene ketone was similarly used to form a thienocyclohepta-indole (138) <84JHC1585>.

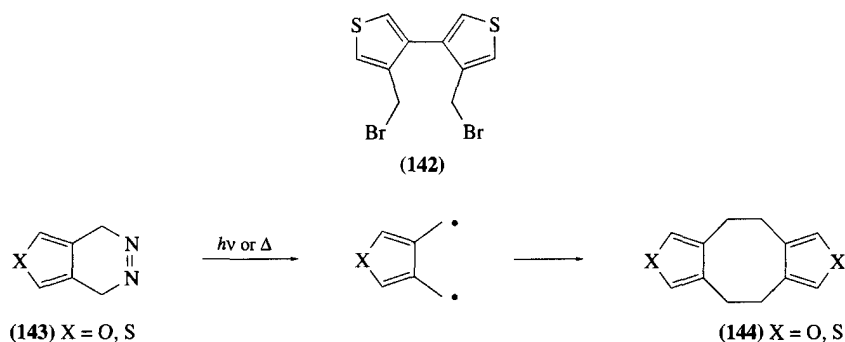
(iii) *Synthesis of the carbocyclic ring by formation of one bond*

Cycloheptadifurans and thienocycloheptadifurans have been made from the 3-furyl and 3-thienyl derivatives (139a,b) by cyclization in pyridine (Equation (9)) or from the 2-thienyl derivative (140) by a mechanism involving a 1,5-shift (Equation (10)) <92JCS(P1)725>. Some cycloheptadipyrroles were formed by the effect of light on (*Z,Z*)bilirubin <82JA6867, 89BJ(257)711>. The acid-catalyzed cyclization of a 3-(2,2'-dithienyl)-3-propanoic acid gave a cyclohepta[2,1-*b*:3,4-*b'*]dithiophene <92IJC(B)449> and some cycloheptadithiophenes were constructed by a Wittig-type coupling of the bischloromethyl-3,3'-dithienylmethane (141) <81JCS(P1)2904>.



(iv) *Synthesis of the carbocyclic ring by formation of two bonds*

The 3,3'-bisbromomethyldithiophene (**142**) formed a cycloheptadithiophene via malonate couplings $\langle 82CS53 \rangle$. Thermolysis or photolysis of the thienodiazoles or furodiazoles (**143**) formed bi-radicals which dimerized in a head-to-head fashion to tetrahydrocycloocta[*c:c'*]dithiophenes or -difurans (**144**) (Scheme 6). $\langle 89JA3659 \rangle$. Also, the dimerization of 2, 3-bismethylene furans, thiophenes, and pyrroles proceeded in a head-to-head fashion to form cycloocta [1,2-*b*:5,6-*b'*]difurans, dithiophenes, and dipyrroles $\langle 81JA6691, 88TL117, 91JOC6948, 92CC549 \rangle$. Another source of cycloocta[1,2-*c*:5,6-*c'*] fused difurans, dithiophenes, and dipyrroles was from certain diynes, which cyclized via diallenyls, with further dimerization $\langle 75JA3255 \rangle$. Some derivatives are also available by rearrangement of macrocyclic diynes $\langle 87AG805, 88TL4529 \rangle$.



Scheme 6

(v) *Synthesis of the carbocyclic ring by formation of three bonds*

No methods have been reported.

(vi) *Synthesis of the carbocyclic ring by formation of four bonds*

The cyclodimerization of dipropynylamines using dicobalt octacarbonyl gave a cycloocta[1,2-*c*:5,6-*c'*] dipyrrole as one of the products $\langle 89JOM(363)209 \rangle$.

7.21.9.4.2 Compounds with two heteroatoms in one heterocyclic ring and one in the other

No data has been reported on these systems.

7.21.9.4.3 Compounds with two heteroatoms in each heterocyclic ring*(i) Synthesis of the heterocyclic ring by formation of one bond*

No data is available on this approach.

(ii) Synthesis of the heterocyclic ring by formation of two bonds

(a) Two C—N bonds. Some cycloheptadipyrzoles were formed from hydroxymethylenecycloheptapyrazole ketones and hydrazines <91H(32)41> in a manner analogous to the preparation of the dihydrobenzopyrazoles (**115**) and (**116**).

(iii) Synthesis of the carbocyclic ring

No data is available on this approach.

7.21.9.4.4 Compounds with more than two heteroatoms in either ring

No data is available on these systems.

7.21.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

As seen in Section 7.21.9 many systems are made by elaboration of existing heterocyclic rings, or of fused systems. This section covers those situations where an existing heterocyclic ring is converted to a five-membered heterocyclic ring, or the carbocyclic ring is being constructed from another ring.

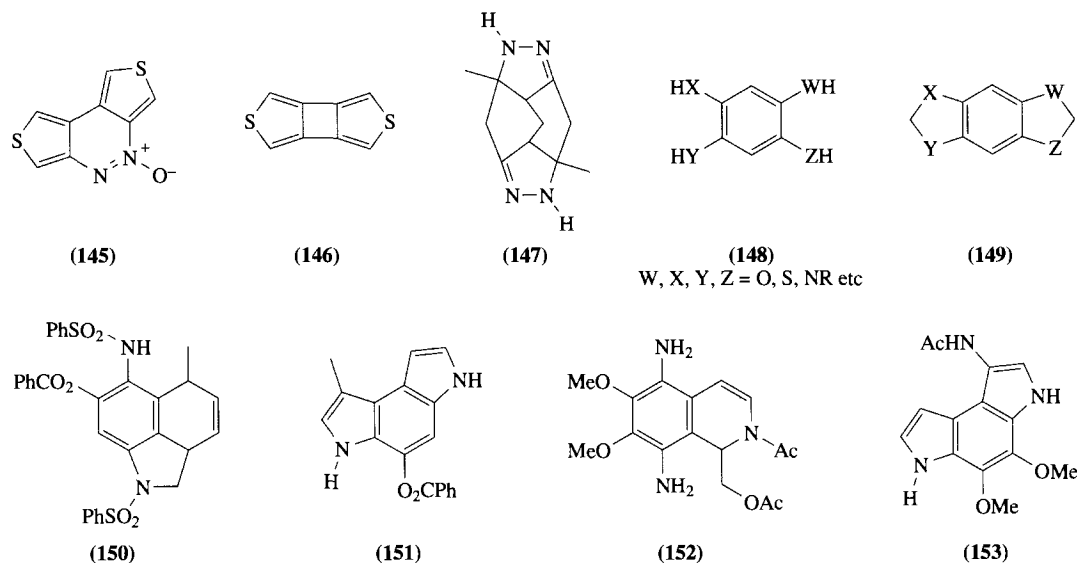
The trivial conversion of cyclic five-membered anhydrides to imides (pyrrole derivatives) is common <82USP4340715, 82USP4358579, 83CA(98)108189, 88JAP(K)63249127, 88JAP(K)632595, 89CA(110)76187, 89JAP(K)0161747, 90CA(112)199247, 90CA(113)6913, 91CA(114)196193, 91JAP(K)03153786, 92JAP(K)0413724>.

The flash vacuum pyrolysis of the dithienodiazene (**145**), obtained by sulfide reduction of 4,4'-dinitro-3,3'-dithienyl, gave cyclobuta[*c:c'*]dithiophene (**146**) <85CC880>. An oxiranocyclopentapyrrole undergoes a palladium(0)-catalyzed insertion of carbon dioxide to form a 1,3-dioxole <88JA6123>.

The aluminum chloride-catalyzed rearrangement of the multiring bisphenylhydrazone (**147**) gave two [1,2-*c:4,5-c'*]benzopyrazoles <82TL4493>. Functionalized benzenes of the type (**148**), available by reduction of many heterocycles, react with carbonyl compounds to construct a variety of benzodiheterocycles of the general type (**149**).

One of the approaches to CC-1065 (see Section 7.21.12) uses the fused benzoindole (**150**). Ozonolysis, followed by acid treatment, afforded the fused benzodipyrrole (**151**) <83CC1198>. In another approach, acid treatment of the enamine (**152**), a dihydroisindole, gave products which recycled to a benzo[1,2-*b:4,3-b'*]dipyrrole (**153**) <87CC1406>.

A Baeyer–Villiger oxidation of an azulenodifuran forms an enol lactone which can be regarded as a cyclohepta[*b:c*]difuran <83JOC732>.



7.21.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

The great diversity of systems in this chapter makes a comparison of synthetic approaches difficult, but many approaches to these systems have involved the use of cycloalkanetetracarboxylic acids and derivatives. Poly(halomethyl)benzenes are reasonably accessible and are precursors of the benzo-fused systems. Most of the best synthetic approaches will have counterparts in the syntheses of simpler heterocycles.

Cyclopenta-fused systems are often accessible by linking diheterocycles with methylene bridges, formed by Bradsher-type reactions.

Many benzo-fused heterocycles are obtained by elaboration of substituted benzenes, especially useful for benzobis-1,3-types. The strategy of photocyclization of 1,2-diheterocyclic substituted ethenes is a versatile approach to angular fused systems, and, while it has some limitations, it may yet be further exploited for systems with more than one heteroatom per heterocyclic ring. Otherwise a linking of diheterocycles by a two-carbon bridge is necessary. For compounds with indole moieties the Fischer approach is often successful.

Synthetic approaches to the benzodipyrrole units in the antitumour agent CC-1065 (**155**) and the protein kinase C inhibitor staurosporine (**170**) are discussed briefly in Section 7.21.12.

7.21.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Many variations of carbocyclic tetracarboxylic acid anhydrides or imides exist, especially for polymer applications <84CA(100)156997>. From the patent literature it is obvious that polyimide derivatives of cyclobutane and cyclopentane-1,2,3,4-tetracarboxylic acids, and of benzene-1,2,4,5-tetracarboxylic acids, have hundreds of applications, ranging from the mechanical to electronic. Some selected references are <84CA(100)156997, 87CA(107)176568, 90CA(112)199247, 91CA(114)133947>. Some derivatives have been proposed for optical recording materials <87JAP(K)60258381>. A benzodipyrrole dication has also been proposed for this application <85JAP(K)60252345>.

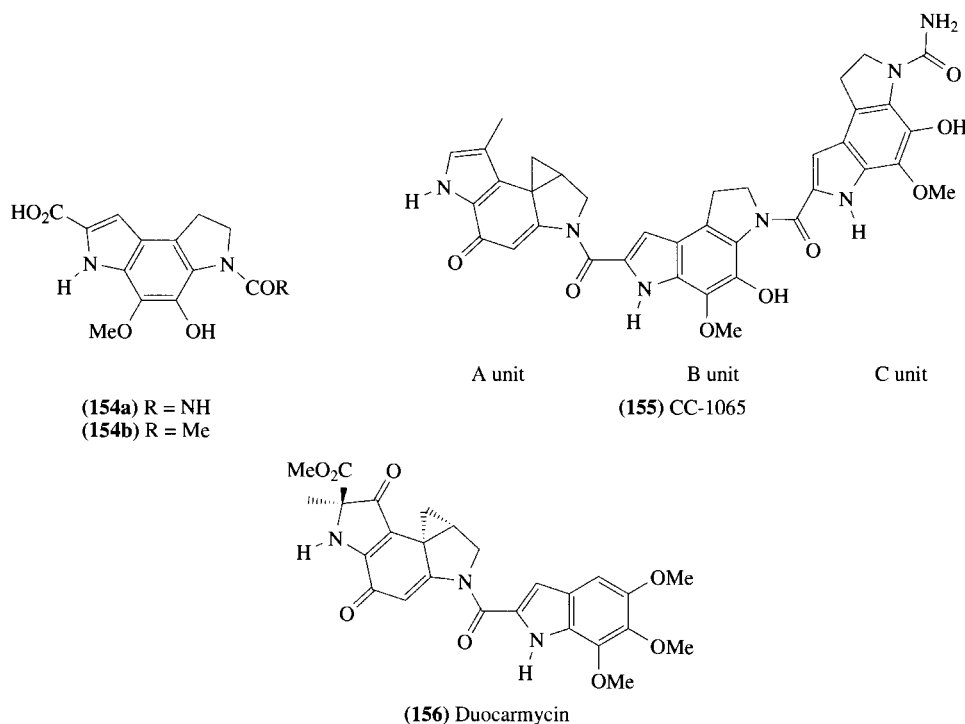
Polymers based on benzobisthiazoles, -oxazoles, and -imidazoles, which form rigid rod-like polymers with high specific strength, have many engineering applications <83CA(98)35048, 83CA(98)35076, 86USP4607095, 90JAP(K)02221281, 91CA(114)164828>.

Many sulfur-containing heterocycles have potential as materials for inducing electrical conductivity, for example materials based on polymeric thiophenes have been examined for possibilities in electrical conductivity <90SM327>, and cyclopenta- and benzobis-1,3-dithiols and benzothiadiazoles

have been examined for electrical conductivity and charge transfer properties <86GEP343947, 87SUL135, 88JAP(K)63241548, 89SM15, 90CC1624, 90T1553, 91CC752, 91CC1268, 92CC278, 92CC1137, 93CC1802, 93SM103>.

A number of compounds with benzodipyrrole moieties have been the subject of much investigation. The phosphodiesterase inhibitors known as PDE-I (**154a**) and PDE-II (**154b**) possess benzodipyrrole skeletons and act in cyclic adenosine-3',5'-monophosphate regulation. The anti-tumor agent CC-1065 (**155**), isolated from *Streptomyces zelensis* <81JAN1119>, possesses three benzodipyrrole units linked by amide bonds. It bonds covalently to N-3 of adenine at the minor groove of DNA. While CC-1065 is too toxic for clinical use, it has sparked much interest in synthetic benzodipyrrole analogues with reduced toxicity <86TL4103>. Duocarmycin (**156**) and pyrimidamycins possess moieties related to the A ring of CC-1065 and also act by DNA alkylation (on the cyclopropane ring) <90JA8961>. Analogues of these with naphthopyrrole units replacing the benzodipyrrole units have been synthesized <92JA9318>.

Some synthetic approaches to the benzodipyrrole units have been referred to above (see Sections 7.21.5.2.7, 7.21.6.1.1, 7.21.9.3.1, 7.21.9.3.1.2, 7.21.10). The choice of strategy is somewhat determined by which ring is desired as the A ring of CC-1065 is dioxygenated, whereas the B, and C rings are monooxygenated. A number of these approaches have been reviewed <87H(25)701>. The approaches may be roughly divided into heterocyclic ring synthesis and carbocyclic ring synthesis.

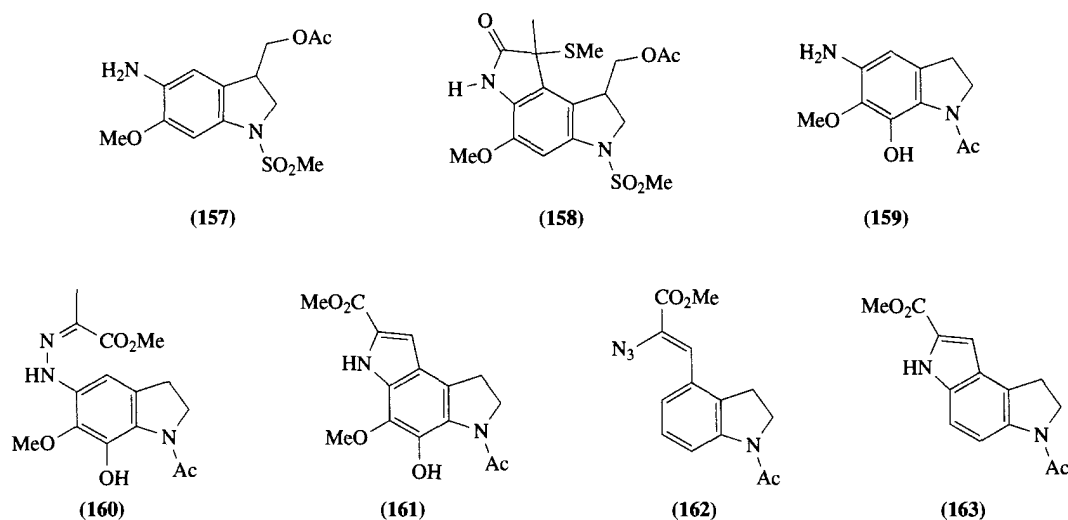


(a) *Heterocyclic ring synthesis approaches.* In an approach to the A ring, Wierenga used a functionalized dihydroindole (**157**) on which another dihydropyrrole ring was constructed, using a modified Gassman reaction, forming compound (**158**) <81JA5621>. This was converted to the fully aromatic pyrrole and final construction of the cyclopropane ring in compound (**39**) was achieved by Hunig's base (see Section 7.21.6.1.2). Another approach to the A unit of CC-1065 used the fused naphthopyrrole (**150**). Ozonolysis, followed by acid-catalyzed cyclization formed the fused benzodipyrrole (**151**). The cyclopropane moiety was constructed by an approach similar to that of Wierenga <85JOC284>.

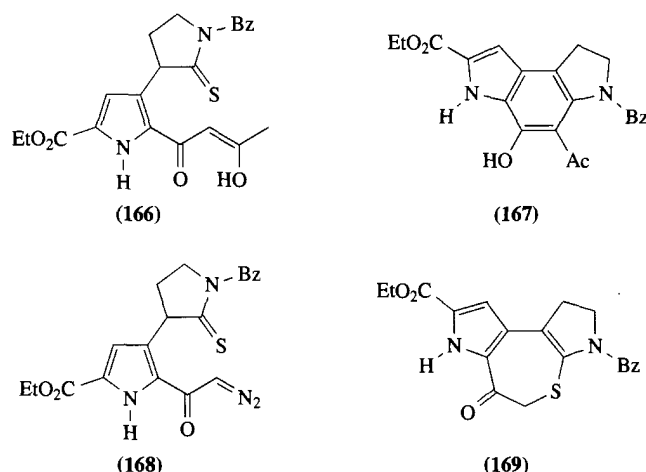
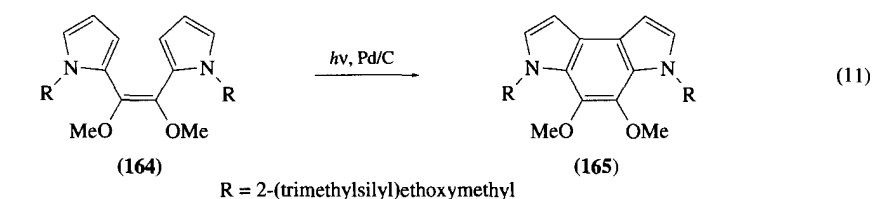
The pyrrole ring may also be approached via Fischer-type indolizations. Thus the amine (**159**) was elaborated to the pyruvate hydrazone (**160**) which by Fischer procedures gave the benzodipyrrole (**161**) <79ABC555, 79ABC559>.

Pyrrole ring syntheses employing nitrene strategies are also feasible. Thus thermolysis of the azide (**162**) formed the benzodipyrrole (**163**) <84JOC2240>. Nitrene approaches have also been applied to syntheses of PDE-I and PDE-II <85CC1775>.

(b) *Carbocyclic ring synthesis.* Cava and co-workers used a photocyclization-dehydrogenation strategy on dipyrrolethene. Thus compounds of the type (**164**) gave dioxygenated benzodipyrroles

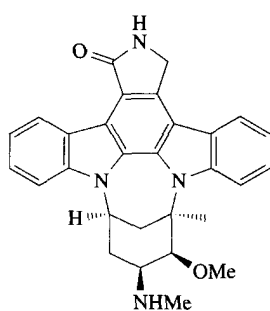


(165) (Equation (11)). The overall yield of the benzodipyrrole from starting pyrrole was 20% <87H(25)701>. Magnus and co-workers used cyclizations of dipyrrolyl-acetic acids and -acetaldehydes, or reaction of 3,3-dipyrrolys with oxalyl chloride to construct mono- or dioxygenated carbocyclic rings <83CC26, 85TL2985, 87JA2706>. Another approach to the system employed the thiolactam (166) which by reaction with iodomethane and mild base formed the benzodipyrrole (167). Alternatively, the diazoketone (168) cyclized to the ketone (169) by treatment with boron trifluoride. Sulfur extrusion gave the required benzodipyrrole system <85JOC425>. However, this approach eventually proved unsuitable for further extension to CC-1065 or PDE units.

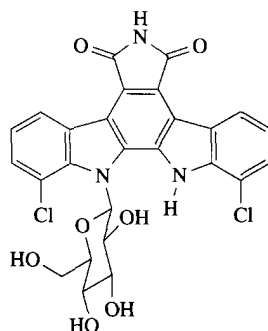


A number of compounds, for example staurosporine (170), rebeccamycin (171), and SE 2370, possessing indolo[2,3-*a*]carbazole skeletons can also be regarded as substituted benzodipyrroles. These are potent inhibitors of protein kinase C. <87CA(106)213608, 90CC1667, 92AP(325)353>. Other effects of various members of this family are specific inhibition of NGF-induced biochemical effects. For example, inhibition of tyrosine phosphorylation of p140^{prototrk} by K-252a (172a) and K-252b (172b) and of topoisomerase inhibition by stabilization of enzyme-cleaved DNA covalent intermediates

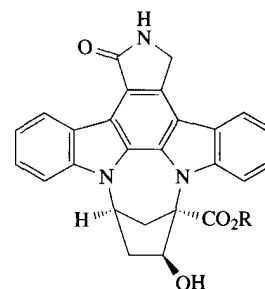
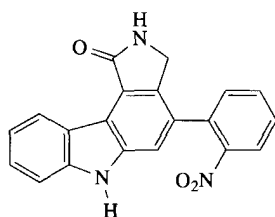
<92B12069, 92JBC(267)13>. Approaches to the construction of these have involved ring closures of nitro compounds to carbazole units by trivalent phosphorus compounds, for example the conversion of compound (173) to compound (174) by triethyl phosphite <90CC1667>. A related approach was used in the simultaneous construction of both pyrrole rings <90JCS(P1)2475>. Another interesting method is a double Fischer indolization of hydrazones of the type (175) <89JOC824>. This method has also been applied to the syntheses of tjipanazoles which are new agents with moderate antifungal activity and which have been isolated from the blue-green algae *Tolypothrix tjipanasensis*. These have [2,1-*b*:3,4-*b'*]benzodipyrrole structures related to the indolo[2,3-*a*]carbazoles (i.e. staurosporin (170)) but are usually lacking the pyrrolidone ring <91T7739>.



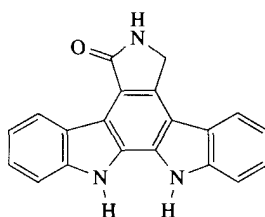
(170) Staurosporine



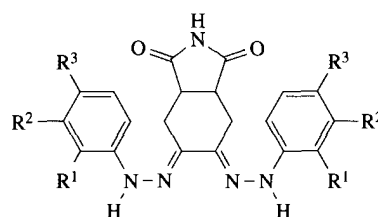
(171) Rebeccamycin

(172a) R = Me
(172b) R = H

(173)



(174)



(175)

Other compounds with pharmaceutical or medical applications are thienocyclobutapyrroles for psychotropic and anxiolytic agents <88JMC1382, 91USP5053508>, a benzodithiophene active against gram-positive bacteria <87KFZ1320>, a benzobisfuran and a benzobisthiazole as antiarrhythmic agents <83CA(98)198073, 92JMC350>, fused pyrrolobenzothiazoles and related compounds as anti-inflammatories <86EUP173520, 92JMC350>, and a thienocycloheptapyrrole for analgesic activity <81EUP35853>.

Some benzodipyrroles, furans, and thiophenes with quinonoid structures have been patented as dyes <90EUP363034>, and some thienobenzothiazoles have potential in cyanine dyes for photographic uses <84URP1082786>.

7.22

Tricyclic Systems: Central Carbocyclic Ring with Fused Five- and Six-membered Rings

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7.22.1 INTRODUCTION

There is no corresponding chapter in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) that relates to the material presented here. Although some 6-4-5, 6-5-5, and 6-7-5 fused compounds have been reported, the great majority of tricyclic ring systems with a central carbocyclic ring and fused five- and six-membered heterocyclic rings are of the 6-6-5 variety. Of these, separate treatment has been reserved for the imidazo[4,5-*g*]-, imidazo[4,5-*f*]-, or imidazo[4,5-*h*]quinazoline-based benzo-separated purines (Section 7.22.12.1), the furocoumarins and furochromones (Section 7.22.12.2), the pyrrolo[3,2-*g*]isoquinoline-based tetracyclic ellipticines (Section 7.22.12.3), and the pyrrolo[2,3-*f*]quinoline quinone (PQQ) and related compounds (Section 7.22.12.4); each is an important class of compounds with special applications. Brief mention is made of two pyrrolo[3,4-*g*]quinoline-based tetracyclic ergolide drugs (Section 7.22.12.5). Although duocarmycins B₁ and C₁ (pyrindamycin B) are pyrrolo[3,2-*f*]quinoline-based members of an important new class of antitumor antibiotics <91JA6645>, these compounds are not covered in depth as the number of investigations on them is limited. Separate sections cover synthetic work related to the benzo-separated purines (Section 7.22.11.1), the furocoumarins and furochromones (Section 7.22.11.2), the ellipticines (Section 7.22.11.3), and PQQ and related compounds (Section 7.22.11.4). Structural formulae, equations, and schemes are presented fully in the synthetic sections, but only when there is a particularly strong reason to do so in the nonsynthetic ones.

7.22.2 THEORETICAL METHODS

7.22.2.1 Molecular Orbital Methods

Molecular orbital computational analysis by PM3-CI-UHF semiempirical methods have been used to support the contention that preferable HSOMO-LUMO interactions produce a favored biradical and explain the site selectivity in the sensitized photochemical [2 + 2] cycloadduct formation of 2-pyrones with electron-deficient ethylenes <92BCJ354>. The lowest ionization energies, dipole moment, and dominant electronic configurations of a 5-methylenated version of 7-nitroso-oxazolo[4,5-*g*]cyclopenta[*e*]pyrimidine of unknown origin were calculated by the ADC(3) *ab initio* method <92CPH11>. An extensive semiempirical and *ab initio* investigation into the mechanism of oxidation of methanol by PQQ is cited in Section 7.22.12.4.

7.22.2.2 Molecular Mechanics and Related Methods

An *ab initio* computation of the structure of 5,6-dihydropyrrolo[3,2-*h*]quinoline at the STO-3G level provided data of importance to a Monte Carlo simulation study of the relative binding of guests dimethyl urea and imidazolidinone to a macrocyclic host whose structure contains the above-mentioned quinoline as a hydrogen bond accepting and donating subunit <93JA879>. The x-ray crystal structure of vernolepin, a 6-6-5 saturated tricyclic dilactone, was used to help define the scope and limitations of a computer program written to conduct a systematic conformational analysis of saturated polycyclic ring systems <84T3729>.

7.22.2.3 Other Methods

In a demonstration that a spatial correspondence between apomorphine and certain ergoline alkaloids indicates their dopaminergic activity (DA) is due to binding at the same receptor site, the molecular electrostatic potential (MEP) patterns of heterocycles representative of substructures of the larger fragments were calculated by *ab initio* SCF computations at the HF/STO-3G level <86JMC1418>. Among the potent DA agonists central to this study were an octahydropyrrolo- and pyrazolo[3,4-*g*]quinoline, both tricyclic ergoline partial structures synthesized by Eli Lilly chemists.

7.22.3 EXPERIMENTAL STRUCTURAL METHODS

7.22.3.1 X-ray Methods

Of the x-ray crystal structure determinations made of 6-4-5, 6-5-5, 6-6-5, and 6-7-5 fused heterocycles, many are of furocoumarin/furochromone, ellipticine, and PQQ derivatives because of their importance to biomedical investigations. Mention is made of these in their respective sections (7.22.12.2–7.22.12.4). A bibliography which lists the remaining structures, arranged according to central ring size and ring system formula, is presented in Table 1.

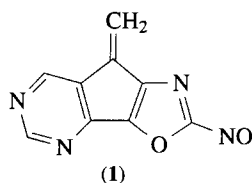
Table 1 Bibliography of x-ray crystal structure determinations.

System	Formula	Heterocyclic base unit	Ref.
6—4—5	C ₃ O—C ₄ —C ₄ N	3-Oxa-11-azatricyclo[6.3.0. ^{1,8} 0 ^{2,7}]undecane	90CPB370
6—5—5	C ₃ O—C ₅ —C ₄ O	5,9-Dioxatricyclo[6.4.0.0 ^{2,6}]dodecane	90JCS(P1)751
6—6—5	C ₃ O—C ₆ —C ₄ N	Pyrrolo[3,4- <i>f</i>]benz[<i>b</i>]pyran, decahydro-	90JOC3555, 93JOC4979
	C ₃ N—C ₆ —C ₄ N	Pyrrolo[3,2- <i>h</i>]isoquinoline, octahydro-	84JOC5109
		Pyrrolo[2,3- <i>g</i>]quinoline, dihydro-	91AX(C)561
	C ₃ N—C ₆ —C ₃ N ₂	Pyrazolo[3,4- <i>g</i>]quinoline, octahydro-	83JMC1112
	C ₃ N—C ₆ —C ₃ NO	Oxazolo[5,4- <i>g</i>]isoquinoline, tetrahydro-	92AX(C)1243
	C ₃ N—C ₆ —C ₃ NS	Thiazolo[4,5- <i>f</i>]quinoline, hexahydro-	91JMC2736
	C ₄ N ₂ —C ₆ —C ₂ N ₂ S	1,2,5-Thiadiazolo[3,4- <i>g</i>]quinoxaline, dihydro-	92H(33)337
	C ₃ N—C ₆ —C ₂ N ₂ S	1,2,3-Thiadiazolo[5,4- <i>h</i>]isoquinoline, tetrahydro-	89JMC1566
	C ₃ O—C ₇ —C ₄ O	2,9-Dioxatricyclo[9.3.0. ^{1,6} 0 ^{7,12}]tetradecane	90AX(C)875
6—7—5			

In addition to focused crystallographic structural studies, x-ray methods have been applied to problems of developing models for the topography of enzymes' active sites, or inhibitors of the same. For example, the x-ray crystallographically derived structural parameters of three 7-alkylated 2,4-diaminopyrrolo[3,2-*f*]quinazolines were among 62 of these heterocycles employed in the 3D QSAR development of a distance geometry model for the inhibition of dihydrofolate reductases <84JMC901>. Finally, in an application of an iterative protein crystal structure analysis approach to enzyme inhibitor design, a set of novel imidazolo[4,5-*g*]tetrahydroquinoline inhibitors of thymidylate synthetase was developed in a systematic fashion by using newly generated enzyme-inhibitor complex data as feedback for structural modification <92JMC847>.

7.22.3.2 PE Spectroscopy

The 5-methylidenated version of 7-nitrosooxazolo[4,5-*g*]cyclopenta[*e*]pyrimidine (**1**) was the only tricyclic ring structure among 36 heterocycles examined by *ab initio* computational analysis for their lowest ionization energies related to experimentally determined molecular photoelectron spectroscopic (PES) data <92CPH11>. It is not clear if this compound's preparation has been reported, nor whether its PE spectrum has ever been obtained.



7.22.3.3 IR Spectroscopy

The assignment of lactone ring size (six instead of five) in an *f*-fused benzofuran tricycle was confirmed by an IR absorption frequency for the lactone carbonyl group present at 1740 cm⁻¹, instead of at 1760 cm⁻¹ where it is present in a known 5-6-5 analogue <85JCS(P1)747>. The absence of a C=S IR stretching frequency at 1250 cm⁻¹ in (pyrano[2,3-*g*]benzothiazol-2-yl)benzamides distinguished them from the isomeric thiol-substituted pyrimidyl[5,4-*f*]-fused flavones <94BCJ2326>. The IR spectrum of 1,4-benzodioxano[6,7-*c*]furoxan was found to exhibit characteristic bands in the 1580–1620 cm⁻¹ region <88JHC803>.

7.22.3.4 UV/Visible and Fluorescence Spectroscopy

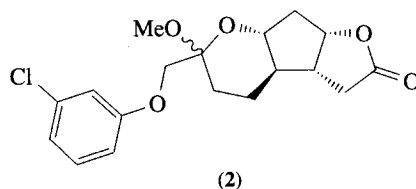
9-(Phenylsulfonyl)furo[2,3-*g*]quinoline and its parent unsubstituted heterocycle were found to have very similar absorption maxima; hence, the sulfone group does not provide an additional conjugative effect <83JOC774>. In addition, furo[2,3-*g*]quinoline and its isomeric furo[3,2-*g*] counterpart were found to exhibit UV absorption maxima that are almost identical. An absorption maximum at 435 nm consistent with the presence of a 2*H*-1,4-benzothiazine chromophore was one of the key pieces of data that enabled the structure determination of compounds based upon the new 1,2-dihydro-3*H*,8*H*-pyrrolo[2,3-*h*][1,4]benzothiazine skeleton <87T5357>. The UV spectrum of 1,4-benzodioxano[6,7-*c*]furoxan was found to exhibit four characteristic band maxima in the 350–480 nm region <88JHC803>.

Many of the fully aromatic 6-6-5 tricyclics show good fluorescence properties, and in some instances this has been utilized in biochemical applications. The reader is directed to the literature cited in Section 7.22.12.1 (benzo-separated purines) for examples of how the sensitivity of the fluorescence properties of tricyclic fluorophores to environmental conditions can be utilized to analyze the binding parameters associated with biomacromolecules. Of particular interest in this regard is a method known as *fluorescence-polarization titration* <83B2347>.

7.22.3.5 Mass Spectrometry

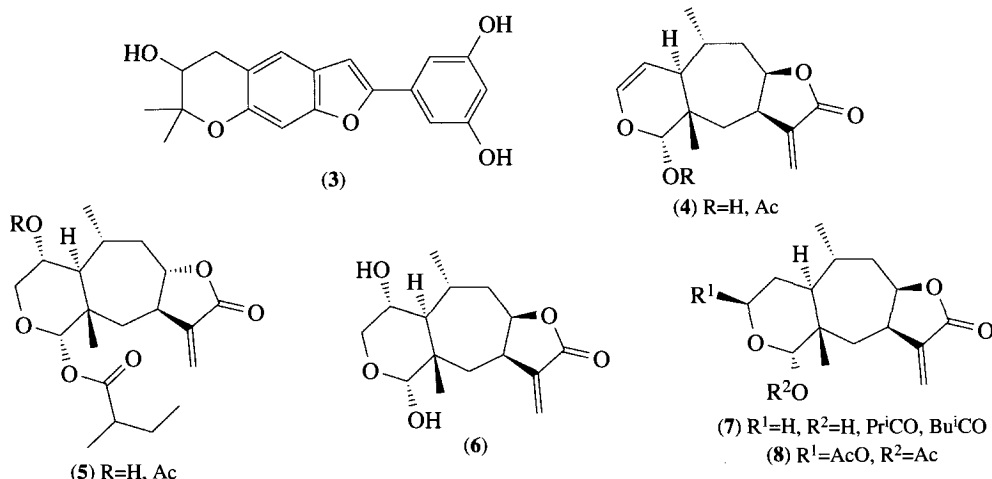
The use of mass spectrometry for structure identification is of particular importance to studies in which the quantity of analyte is limited. For example, certain carcinogenic monoamino, dialkylated imidazo[4,5-*f*]quinoxalines and imidazo[4,5-*f*]quinolines present in a few ppb in heated food of

muscle origin have been identified in this way (92MI 722-01, 92MI 722-02). When the quantity of material is more substantial, however, complex fragmentation patterns such as the positive ion generated from saturated tricyclic acetal lactone (2) can be elucidated (90JPR122).

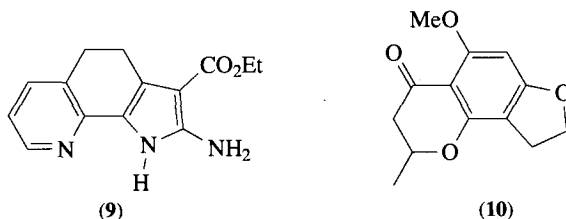


7.22.3.6 NMR Spectroscopy

Often used in concert with mass spectrometry, NMR spectroscopy remains an invaluable structural diagnostic tool of particular importance to tricyclic natural products chemistry. For example, the tricyclic phenolic compound moracin P (3) was one of eight previously known compounds identified together with two new isoprenoid-substituted flavanones in isolates of the root bark of mulberry trees (89H(29)807). In a series of studies of 6-7-5 tricyclic natural products, 1D and 2D ^1H and ^{13}C NMR spectroscopy were employed extensively in the structure determination of sesquiterpene lactones (4)–(8) found among the aerial natural products of toxic plants (85P1378, 90P551, 90P3875).

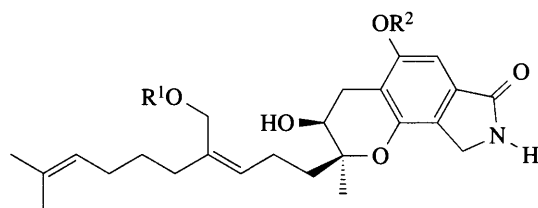


In another example of the utility of NMR to structure determination, ^{13}C — ^{13}C chemical shift-correlated NMR spectroscopy has been used to establish the regioisomeric identity of a disubstituted dihydropyrrolo[2,3-*h*]quinoline (9) (91JA9687). The structure of one (LL-D253γ) of the two minor cometabolites of an antibiotic chromone has been revised to that of (10) with the help of ^1H -coupled ^{13}C NMR spectral analyses of related chromones that revealed diagnostic ^1H — ^{13}C long-range couplings (92JCS(P1)2271).



The stachybotrins A and B (11) and (12), two new aromatic alkaloids with antibacterial and antifungal activity, were isolated from an aquatic isolate of a new species of the genus *Stachybotrys*

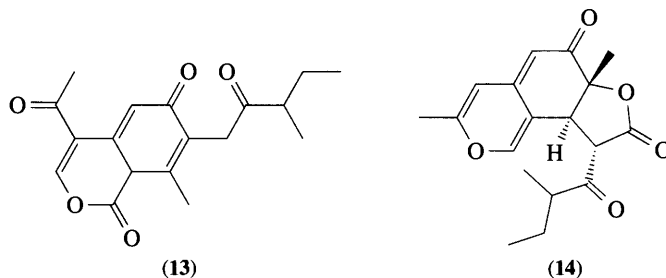
<92JOC6700>. Their structures were determined primarily by analysis of high field 2D (HMBC, HMQC, COSY, and NOESY) NMR data.



(11) $R^1=OH$, $R^2=H$

(12) $R^1=R^2=H$

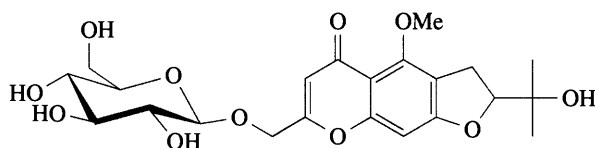
A correction of structure from (13) to the azaphilone structure (14) for monochaetin, a metabolite elaborated by the fungus *Monochaetia compta*, was made possible by examination of the long-range $^1H-^{13}C$ connectivity pattern as determined by the heteronuclear selective population inversion (SPI) NMR technique <86JCS(P1)1975>.



(13)

(14)

One of six chromenone glycosides isolated from the tubers of *Eranthis hyemalis* and structurally identified by a combination of FAB-MS and 2D (COSY, COLOC) NMR techniques was compound (15), a β -D-glucopyranoside of 7-(hydroxymethyl)-2,3-dihydro-2-(1-hydroxy-1-methylethyl)-4-methoxy-5H-furo[3,2-g][1]benzopyran-5-one <91HCA611>.



(15)

Some unusual substituent-derived chemical shift effects have been noted in certain tricyclic systems. Upon formation of 9-(phenylsulfonyl)furo[2,3-g]quinolines by furan ring annelation <83JOC774>, an unusually strong deshielding (to ca. 9.7–9.75 ppm) of the former C-4 proton of the quinoline (the C-8 one in the furoquinoline numbering system) was noted. The assumption was that the formation of the third ring of the tricyclic system forced the sulfone substituent into a conformation which causes deshielding of the (former) C-4 proton. Together with UV spectroscopic data, a close examination of the ^1D ^1H and $^1H^{13}C$ NMR spectral characteristics was sufficient to permit the structure determination of compounds based upon the new 1,2-dihydro-3H,8H-pyrrolo[2,3-h][1,4]benzothiazine skeleton <87T5357>.

7.22.4 THERMODYNAMIC ASPECTS

7.22.4.1 Solubilities and Chromatographic Behavior

Both analytical LC and quantitative TLC have been used successfully in the separation of all the regioisomers ([2,3-g] vs. [2,3-h]) and stereoisomers (*trans*-fused vs. *cis*-fused) of octahydro, pyrrolo-fused isoquinolines <84JOC5109>.

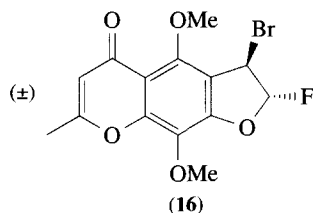
7.22.4.2 Tautomerism

In a study reporting the resolution and x-ray crystal structure-determined absolute configuration of *trans*-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1*H*(or 2*H*)-pyrazolo[3,4-*g*]quinoline, an ergoline-related dopamine agonist, it was noted that in the solid state, the pyrazole ring is protonated on the 1-nitrogen rather than on the 2-position <83JMC1112>. It was suggested that solutions contain a mixture of the 1 and 2 protonated tautomers. The rapid degenerate equilibrium between 1,4-benzodioxano[6,7-*c*]furoxan *N*-oxide forms has been probed by variable temperature ¹H NMR, and a ΔG^* of 13.1 kcal mol⁻¹ for this process was calculated <88JHC803>.

7.22.5 REACTIVITIES OF FULLY CONJUGATED RINGS

7.22.5.1 Electrophilic Attack at Carbon

As expected, the 1-position of 8,9-dihydropyrano[3,2-*e*]indoles is susceptible to acylation under conditions (POCl₃/DMF, oxalyl chloride) known to be effective at the 3-position of indoles <92JMC3625>. The electrophilic introduction of fluorine into the furan ring of the furochromone nucleus of khellin has been accomplished <87TL4003> in excellent yield (82–84%) by the action of either BrF (HF/dibromantin/THF/CH₂Cl₂/4 °C) or poly HF/NBS/CH₂Cl₂/0 °C to afford *trans*-3-bromo-2-fluoro-2,3-dihydrokhellin (**16**). These methods nicely circumvent the problem of oxidative demethylation known to be associated with treatment of benzofurans with CF₃OF in freon at –78 °C. Transformation of compound (**16**) into other 2,3-disubstituted-2,3-dihydrokhellins and into the 2-fluoro and 3-fluoro versions of khellin itself was accomplished.



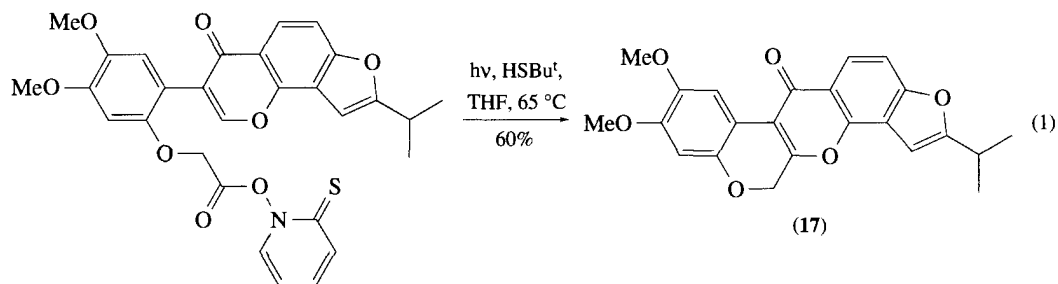
The substitution pattern of TfOH-mediated electrophilic aminomethylation of psoralens (furocoumarins) by *N*-(hydroxymethyl)phthalimide has been elucidated <85JHC73>. Multiple phthalimidoylated adducts were obtained when a B-ring hydroxy or methoxy activating group was present, and these resisted simple cleavage with NH₂NH₂. However, this two-step procedure to aminomethyl group introduction worked well when the psoralens contained only methyl substituents.

7.22.5.2 Nucleophilic Attack at Carbon

Nitrogen nucleophiles in the form of aryl amines readily displace a chloro substituent at the 9-position of the 1*H*-pyrazolo[3,4-*f*]quinoline <92JMC4595> and 1*H*-imidazo[4,5-*f*]quinoline ring systems <92BCJ579, 92JMC4595>. Similarly, aryl hydrazines readily displace the chloro group of 8-(ethoxycarbonyl)-substituted 9-chloropyrazolo[4,3-*f*]-, [3,4-*f*]-, and imidazo[4,5-*f*]quinolines, but this is then followed by spontaneous cyclization to give the pyrazolones <90JMC2640>. 4,9-Dibromo-1,2,5-thiadiazolo[3,4-*g*]quinoxaline has been found unreactive towards nucleophilic displacement by *t*-butylmalononitrile or malononitrile anion in the presence of palladium(II) catalyst <92H(33)337>.

7.22.5.3 Reactions With Radicals and Electron-deficient Species

In the potentially biomimetic transformation shown in Equation (1), a photogenerated aryl(methylene)oxyl radical generated by fragmentation of a thioxopyridyl ester undergoes 6-*endo* cyclization onto the 5-position of an isoflavone, and the radical cycloadduct formed apparently abstracts a pyridinethio moiety and undergoes a thermal elimination of pyridine-2 thiol to give the pentacycle (**17**) <89CC1613>. Without the unsaturation such as that introduced in this last step, the central rings of compounds like (**17**) are known to be susceptible to ring opening upon treatment with primary amines <86H(24)1109>.



Treatment of 5-hydroxy- or 5-methoxy-1*H*-pyrrolo[2,3-*f*]quinolines with can in aqueous acetonitrile solution is effective at generating the *o*-quinone derivatives <87JOC1942>. The furan ring of khellin, a furochromone, has been fragmented in 73% yield to a chromone hydroxy carbaldehyde by catalytic osmylation (OsO₄, NaIO₄, THF, 50 °C), and in the same yield to a chromone hydroxy ester by oxypalladation (PdCl₂, CuCl, 30 psi O₂, MeOH, 70 °C, 20 h) <84TL2953>.

7.22.5.4 Reductions

TCNQ derivatives fused with 1,2,5-thiadiazolo and pyrazino units (4,9-bis(dicyanomethylene)-1,2,5-thiadiazolo[3,4-*g*]quinoxalines) undergo reversible four-stage one-electron reductions, as determined by cyclic voltammetry <92H(33)337>).

7.22.6 REACTIVITIES OF NONCONJUGATED RINGS

7.22.6.1 Isomers of Aromatic Compounds in Equilibrium with a Fully Conjugated Derivative

Oxazolo[4,5-*h*]quinolin-2(3*H*)-ones could be acylated effectively at the N-3 position with reagents such as AcCl, ethyl chloroformate, *trans*-cinnamoyl chloride, and dimethyl carbamoyl chloride <85JMC1255>.

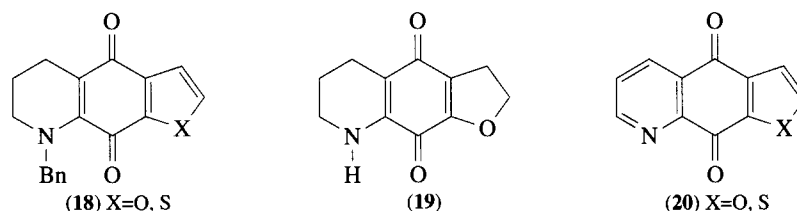
7.22.6.2 Dihydro Derivatives

Most of the reports on the reactivity of dihydro derivatives of the tricyclics are concerned with the ease of oxidation to fully aromatic ring systems. Certain 6,7-dihydropyrano[2,3-*e*]indazol-2(7*H*)-ones have been found to be very resistant to full aromatization upon treatment with DDQ in refluxing benzene, providing the pyrano[2,3-*e*]indazol-2(7*H*)-ones in only two instances after extended (12 d) reaction time <84JHC361>. On the other hand, methyl 1,2-dihydro-3*H*,8*H*-pyrrolo[2,3-*h*][1,4]benzothiazine-2-carboxylates not bearing a 2-alkyl substituent were found to be quite reactive towards a presumed autoxidative decomposition to red orange oligomeric materials <87T5357>. Yet a third reactivity has been found for certain 4,5-dihydrothiazolo[4,5-*f*]quinolines, which in 8-cyano-7-oxo-4,5,6,7-tetrahydro form was found to require aeration in refluxing EtOH (2 h) in the presence of DBU to afford the 4,5-unsaturated derivative (77%) <89H(29)1517>.

7.22.6.3 Tetrahydro and Higher Derivatives

The furan ring of the *N*-benzyl furan-fused tetrahydroquinolinequinone (18; X = O) suffers reduction under debenzyl conditions (H₂, Pd/C) affording compound (19) (89%) <91JOC6379>. The thiophene derivative (18; X = S) gives a similar overreduction product, but in low yield only,

even when one equivalent of palladium is used. The *N*-benzyltetrahydropyridine rings of both systems (**18**), however, are easily oxidized with three equivalents of DDQ in benzene to give the quinolinequinones (**20**) (35–37%).



7.22.7 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.22.7.1 Alkyl Groups

Decarboxylation of 5,7-dimethyl-8-oxo-6-aza-8*H*-indeno[2,1-*b*]thiophene-4-carboxylic acid could be effected by heating an admixture of it and copper powder (87H(26)1535). Direct sublimation *in vacuo* afforded the desired product (58%). 9-Chloro-2- and 3-methyltriazolo[4,5-*f*]quinoline-7-carboxylic acids are decarboxylated under similar conditions (93H(36)259). The cyano group of 8-cyano-7-oxo-4,5,6,7-tetrahydrothiazolo[4,5-*f*]quinolines can be converted into an amino group by conc. HCl mediated hydrolysis to the amide, followed by Hofmann rearrangement (89H(29)1517).

7.22.7.2 Sulfur Groups

Reductive desulfurization of 9-(phenylsulfonyl)furo[2,3-*g*]quinoline and its 2-methyl derivative can be effected by treatment with LAH in THF solution at reflux, but proceeded poorly with aluminum amalgam, the reagent of choice for the reductive cleavage of vinyl sulfones (83JOC774). Raney nickel was used to remove a thiomethyl substituent from the central ring of a furochromone direct precursor to visnagin (89JOC4481).

7.22.8 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

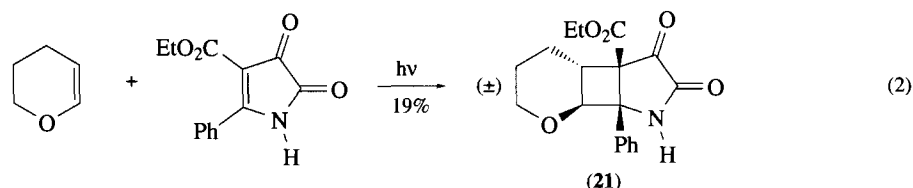
Although reactions at ring heteroatoms have been conducted and reported on members of this class of heterocycles, in general the outcome of these is not reflective of a unique characteristic of the tricyclic framework.

7.22.9 RING SYNTHESSES

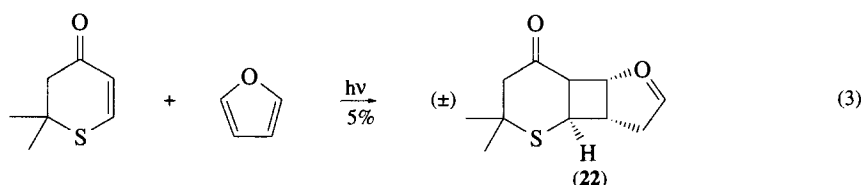
7.22.9.1 Synthesis of Compounds with a Central Four-membered Ring

7.22.9.1.1 With one heteroatom in each heterocyclic ring

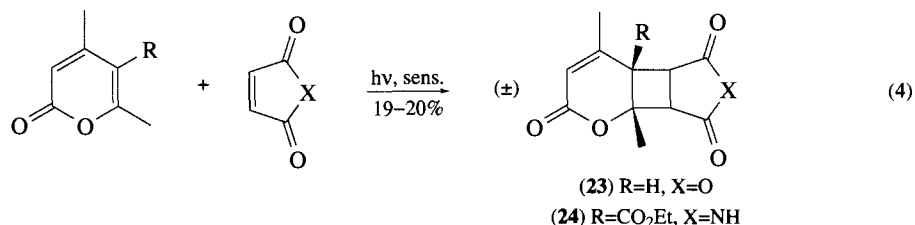
4-Ethoxycarbonyl-5-phenyl-1*H*-pyrrole-2,3-dione (a dioxopyrroline) undergoes head-to-tail regiochemical photocycloaddition with dihydropyran to give the *cis-syn-trans* adduct (**21**) in 19% yield (Equation (2)) (90CPB370). The structure and stereochemistry of this product, which arises via a [$\pi 2s + \pi 2a$] process in an *endo* encounter complex, was determined by x-ray analysis.



Dihydro-4*H*-thiophene-4-one, upon irradiation in neat furan, affords the tricyclic photoproduct (**22**) isolated in 5% yield after chromatographic separation (Equation (3)) <92HCA1925>. This product is also formed (by GC) when 1 : 1 furan/MeCN or furan/MeOH is employed as solvent. Excitation of the dihydrothiophenone is thought to be followed by an intersystem crossing, producing a triplet that reacts with furan to give a triplet 1,4-biradical intermediate as a mixture of diastereomers. Intersystem crossing from this mixture then provides the singlet biradical diastereomer from which the product is derived.

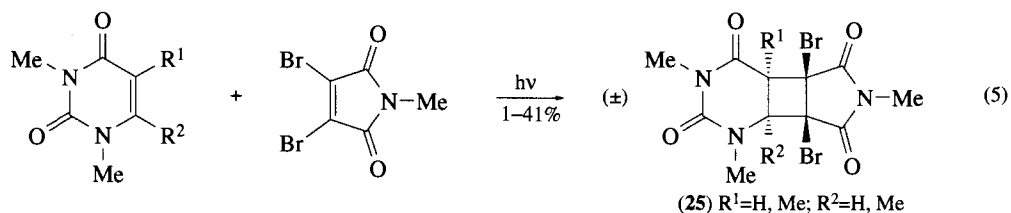


As shown in Equation (4), the sensitized irradiation of a mixture of 4,6-dimethyl-2-pyrone and maleic anhydride, or of 4,6-dimethyl-5-ethoxycarbonyl-2-pyrone and maleimide, gives the mixed photoadducts (**23**) and (**24**) in ca. 20% yields <90BCJ3456, 92BCJ354>. As with many other [2 + 2] cyclocondensation reactions involving heterocycles, these are thought to proceed via biradical intermediates.



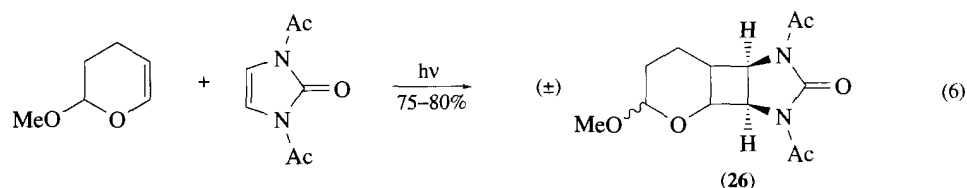
7.22.9.1.2 With two heteroatoms in one heterocyclic ring and one in the other

Sensitized UV irradiation of 1,3-dimethyluracil with 1-methyl-3,4-dibromomaleimide in acetone solution gives the *cis-anti-cis*-[2 + 2] cycloadduct (**25**) (41%) (Equation (5)) <83AG(E)161>. The presence of methyl substituents at the C-5, C-6, or both of these loci resulted in a severe reduction of yield (1–8%). With 1,3,5-trimethyluracil as starting material, a small amount of the *cis-syn-cis*-[2 + 2] cycloadduct (3%) was obtained along with the *cis-anti-cis*-isomer. For the latter, a diamagnetic shifting of the C—Me group by the imide C=O moiety was noted in its ¹H NMR spectrum.



Photochemical cyclocondensation of 1,3-diacetylimidazolin-2-one with 3,4-dihydro-2-methoxy-2*H*-pyran in acetone solution gives a mixture of four stereoisomeric [2 + 2] cycloaddition products

(**26**) in 75–80% combined yield. A single isomer can be obtained by recrystallization (Equation (6)) <83CJC1158>. The mixture of photoadducts was further elaborated, in nine steps, to ($\pm$)-biotin.

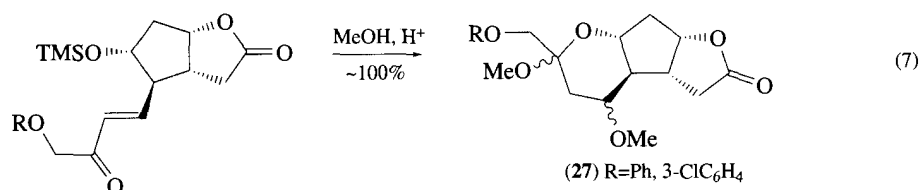


7.22.9.2 Synthesis of Compounds with a Central Five-membered Ring

7.22.9.2.1 With one heteroatom in each heterocyclic ring

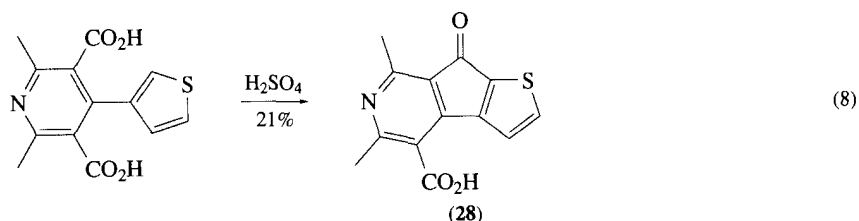
(i) By synthesis of a heterocyclic ring

Acid-catalyzed removal of a TMS protecting group from a bicyclic lactone in methanol solution proceeded with intramolecular acetylation after conjugate addition of methanol to an α,β -unsaturated ketone side chain. By this route the 6-5-5 tricyclic acetal (**27**) is obtained in excellent yield (Equation (7)) <90JCS(P1)751>. Hemiacetal derivatives of the acetals were also prepared, and were found to exist in equilibrium with their open hydroxy-ketone forms by ^1H NMR.



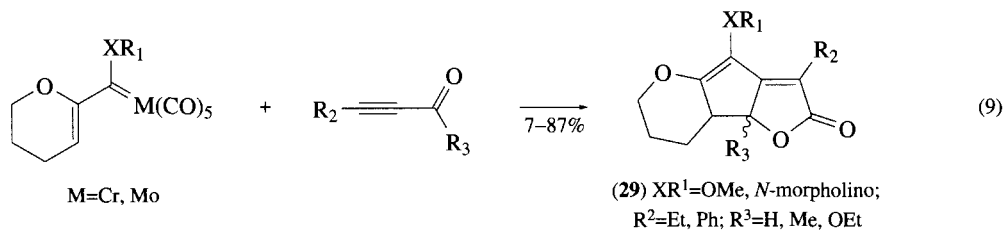
(ii) By synthesis of the carbocyclic ring

Cyclization of a 4-(3-thienyl)-3,5-pyridinedicarboxylic acids in hot H_2SO_4 was shown to be a viable route to the substituted 8-oxo-6-aza-8*H*-indeno[2,1-*b*]thiophenes (e.g. (**28**)) (Equation (8)) <87H(26)1535>. In the case of the dimethylated carboxylic acid shown, the neutral tricyclic heterocycle (**28**) is obtained in 21% yield.



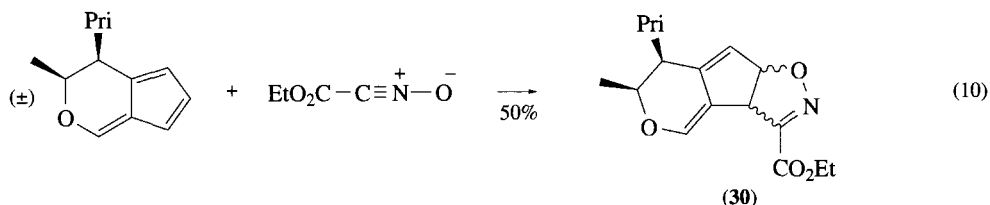
(iii) By synthesis of two contiguous rings

Chromium- and molybdenum-based carbene complexes condense with ketoalkynes along a CO insertion pathway to afford tricyclic pyran-containing lactone products (**29**) in variable yield (Equation (9)) <90JA1645, 91JA5459>.

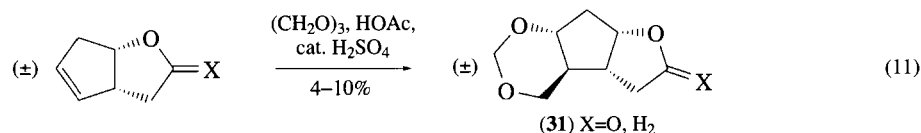


7.22.9.2.2 With two heteroatoms in one heterocyclic ring and one in the other

As shown in Equation (10), the 1,3-dipolar cycloaddition of *in situ* generated carboethoxy-formonitrile oxide to a dihydropyran has been used to construct the terminal isoxazoline ring of the tricyclic heterocycle (30) <86T1407>. The [$\pi 4s + \pi 2s$] pericyclic product is obtained as a 70/30 inseparable mixture of diastereomers in 50% yield.

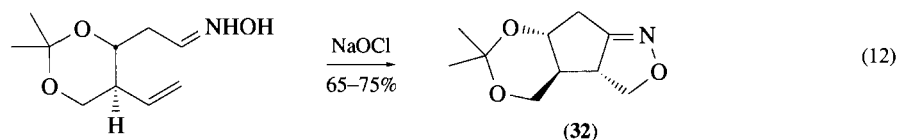


In an early step in an enantioselective total synthesis of certain prostaglandins <88T4989, 92T10345>, application of the Prins reaction conditions to an unsaturated bicyclic lactone or ether (Equation (11)) afforded tricyclic heterocycles (31) containing cyclopentane-fused tetrahydrofuran and 1,3-dioxane units in 4–10% yield. The major products in each case were bicyclic diacetate derivatives of the starting material.



7.22.9.2.3 With two heteroatoms in each heterocyclic ring

An intramolecular nitrile oxide cycloaddition reaction of a 1,3-dioxolane monocyclic precursor provided the construction of the two five-membered rings of the isoxazoline (32), a precursor to prostaglandin F_{2α} (Equation (12)) <84JOC2301>.



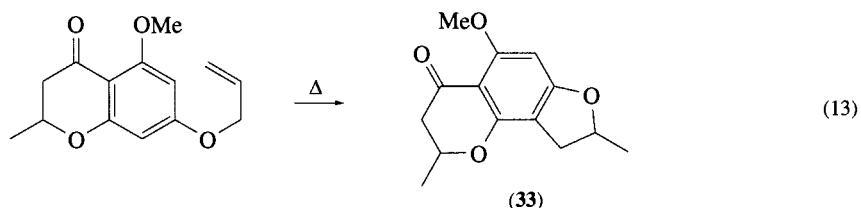
7.22.9.3 Synthesis of Compounds with a Central Six-membered Ring

7.22.9.3.1 With one heteroatom in each heterocyclic ring

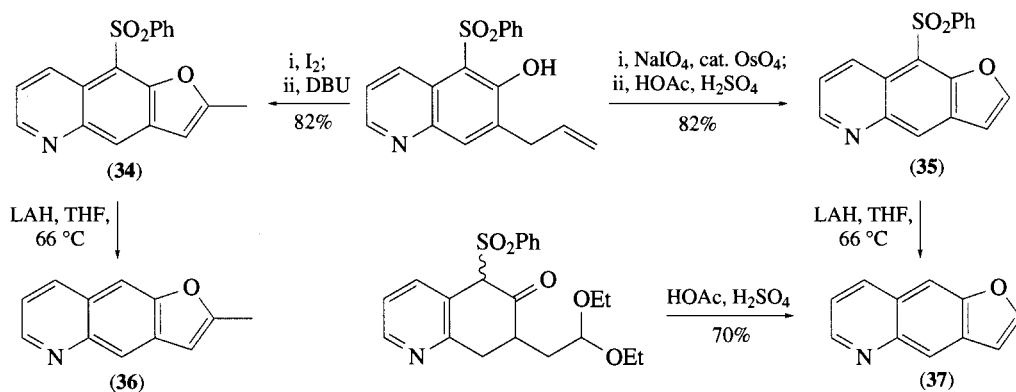
(i) By synthesis of a heterocyclic ring

(a) By formation of one bond. A minor by-product in the pyrolysis (Equation (13)) of 7-allyloxy-5-methoxychromone has been assigned the structure of the dihydrofuran-fused 5-methoxychromone

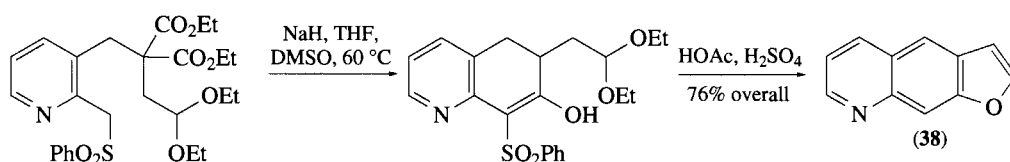
(33) on the basis of its ^1H NMR spectrum <92JCS(P1)2271>. The major product (68%) is the C-8 allyl-bearing 7-hydroxy-5-methoxychromone.



In a report describing new syntheses of substituted quinolines, furo[2,3-*g*]quinolines (34) and (35) were prepared in high yield from the same 7-allylquinolinol (Scheme 1) <83JOC774>. Reductive desulfonylation of these tricyclics with LAH gave 2-methylfuro[2,3-*g*]quinoline (36) and the unsubstituted parent heterocycle (37), respectively. The latter could also be prepared in good yield by a simultaneous desulfurization-aromatization route from 5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline. The versatility of this second route is demonstrated by the synthesis of the isomeric furo[3,2-*g*]quinoline (38) shown in Scheme 2.

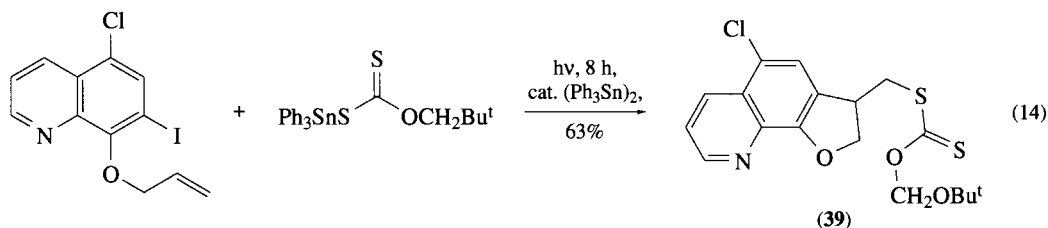


Scheme 1

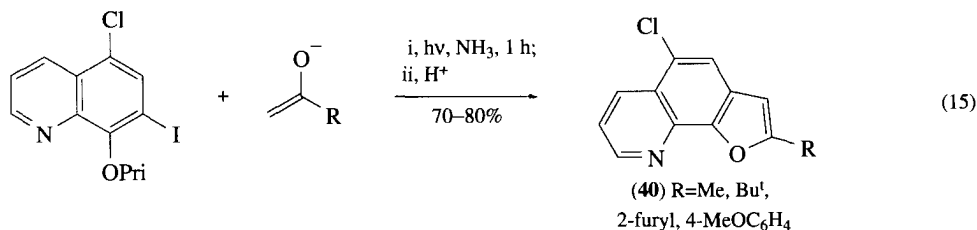


Scheme 2

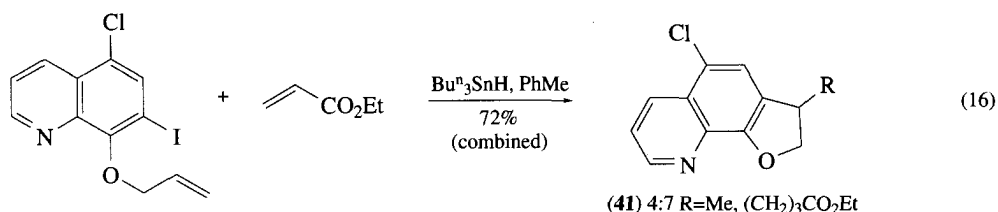
In an application of a novel radical chain reaction based on *O*-alkyl tin dithiocarbonates, the disubstituted dihydrofuro[3,2-*h*]quinoline (39) was prepared in good yield from an 8-allyloxy-7-iodoquinoline precursor (Equation (14)) <92JA7909>.



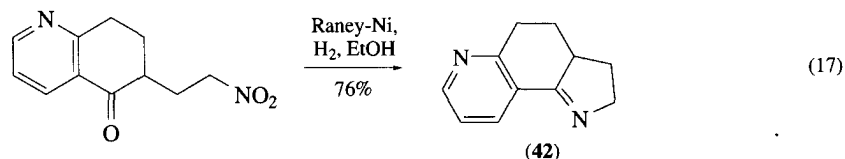
A convenient access to fully unsaturated furo[3,2-*h*]quinolines (40) via $S_{\text{RN}}1$ reactions between 5-chloro-7-iodo-8-isopropoxyquinoline and ketone enolates is shown in Equation (15) and affords these compounds in very good yield <87H(26)1863>.



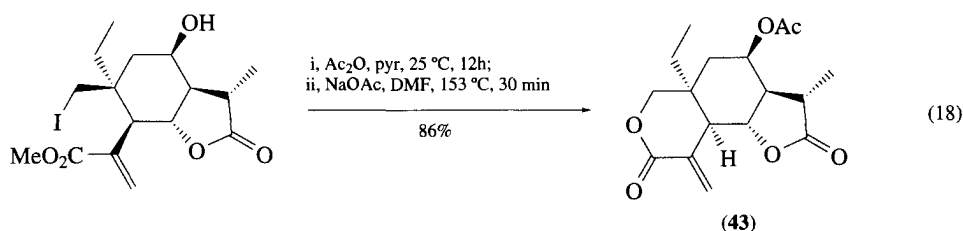
As shown in Equation (16), reaction of an allyl *o*-iodoaryl ether with tributyltin hydride in the presence of the activated alkene ethyl acrylate gives a mixture of 2-substituted dihydrofuro[3,2-*h*]quinolines (**41**) <89H(28)373>.



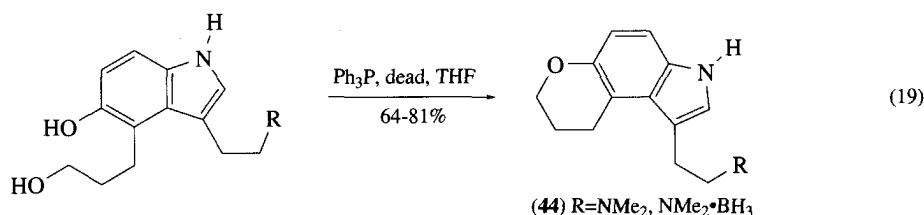
The reduction of a nitroketone with H₂ and Raney nickel in EtOH directly provided the bridged myosmine (**42**) (76%), presumably via an intermediate amino ketone which undergoes an intramolecular Schiff base cyclization (Equation (17)) <83JOC492>.



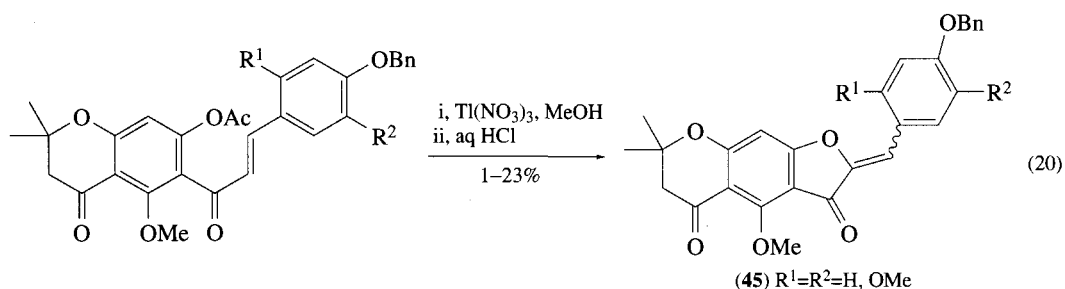
In one of the last transformations in a multistep synthesis of 1,2-dihydro-8-*epi*-vernolepin (**43**), nucleophilic intramolecular substitution at an iodomethyl group was promoted by heating an ester precursor with an equivalent of NaOAc in DMF (Equation (18)) <95TL311>. Molecular mechanics analysis of the precursor produced a minimum energy conformer that showed the hydroxyl substituent too distant from the iodomethyl group to have interfered with this high yield transformation.



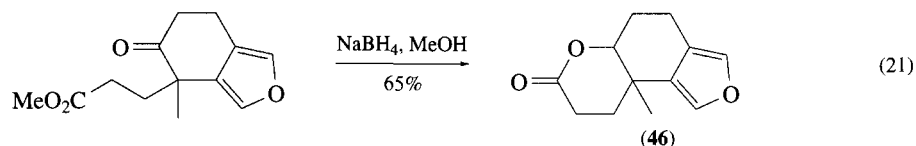
As shown in Equation (19), 1-(2-dimethylaminoethyl)-8,9-dihydropyrano[3,2-*e*]indoles (**44**), rotationally restricted phenolic analogues of the neurotransmitter serotonin, were prepared in good yield from 5-hydroxyindoles in a cyclization reaction using an intramolecular variant of the Mitsunobu reaction <91TL3345, 92T1039>. The borane complex could be dissociated with CsF and Na₂CO₃ in refluxing EtOH.



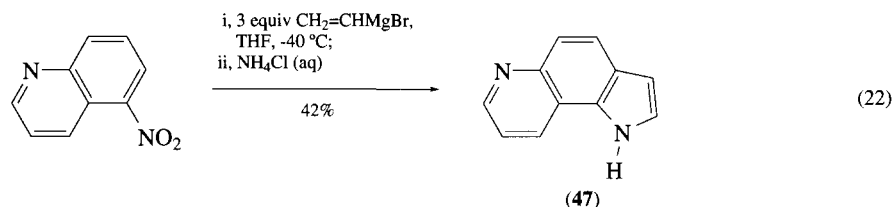
In a TTN-mediated oxidative rearrangement route to certain linear pyranoisoflavones, the aurones (2-alkylidene-6,7-dihydro-4-methoxy-7,7-dimethyl-5*H*-furo[3,2-*g*]benzopyran-3(2*H*),5-diones) (**45**; $R^1 = R^2 = \text{H, OMe}$) were obtained in low yields (Equation (20)) <89BCJ826, 92H(34)505>. A signal at δ 6.45 ppm in the ^1H NMR spectrum due to the benzylidene proton was noted as being characteristic of the aurone system.



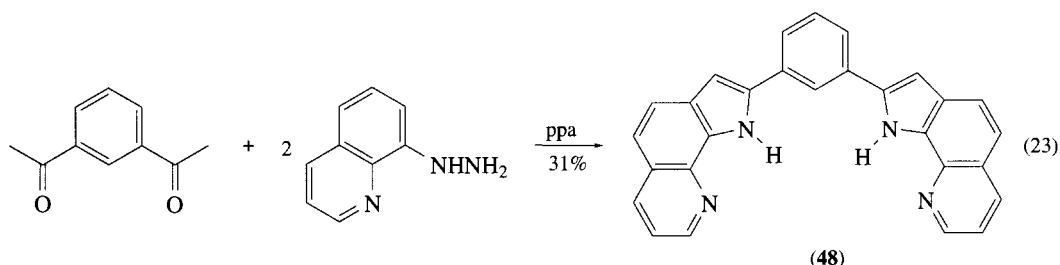
The lactone (**46**) was obtained in 65% yield via reduction of a ketoester with sodium borohydride in MeOH and subsequent acidic workup (Equation (21)) <90H(30)223>.



(b) *By formation of two bonds.* A study of the reaction of 2-substituted nitroarenes with vinyl Grignard reagents was undertaken to develop a new approach to the synthesis of 7-substituted indoles <89TL2129>. One of the findings was that treatment of 5-nitroquinoline with three equivalents of vinylmagnesium bromide affords, upon workup, pyrrolo[2,3-*f*]quinoline (**47**) in moderate yield (Equation (22)).

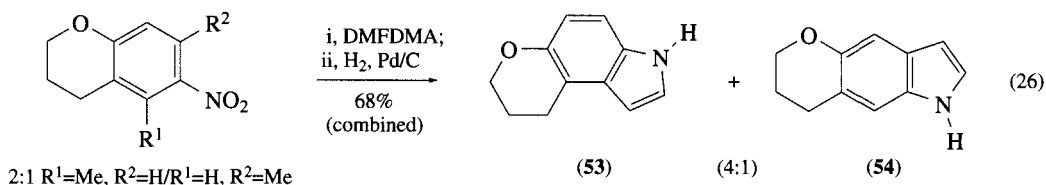


As shown in Equation (23), the condensation of *m*-diacetylbenzene with two equivalents of 8-hydrazinoquinoline gives the bis(pyrido[3,2-*g*]indole) (**48**) in a Fischer synthesis upon cyclization of the intermediate bis(quinolinylhydrazone) with ppa <93JA872>.

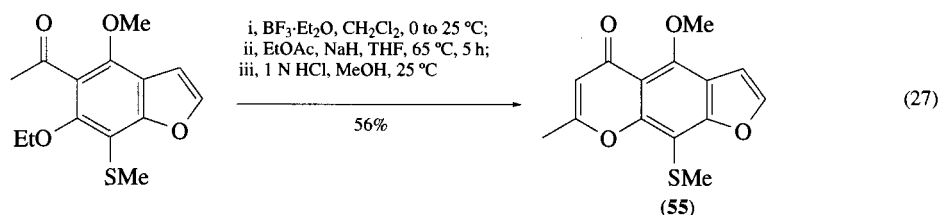


The improved synthesis of an antipsychotic pyrrolo[2,3-*g*]isoquinoline from an areca alkaloid shown in Scheme 3 <84JOC5109> began with a condensation of arecolone with dimethyl or diethyl malonate to give diketone (**49**). This diketone could be isolated and characterized as either the hydrochloride salt or the free base but was more conveniently subjected in crude form to Knorr



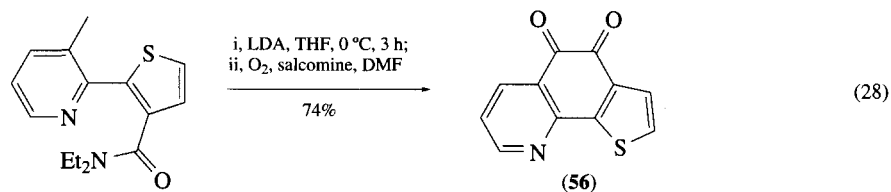


Synthesis of furochromone (**55**) was accomplished in 56% overall yield from a 5-acetyl-6-ethoxybenzofuran via $BF_3 \cdot Et_2O$ -mediated deethylation (70%) followed directly by a Claisen-type condensation of the resultant hydroxyketone and EtOAc (Equation (27)) <89JOC4481>.

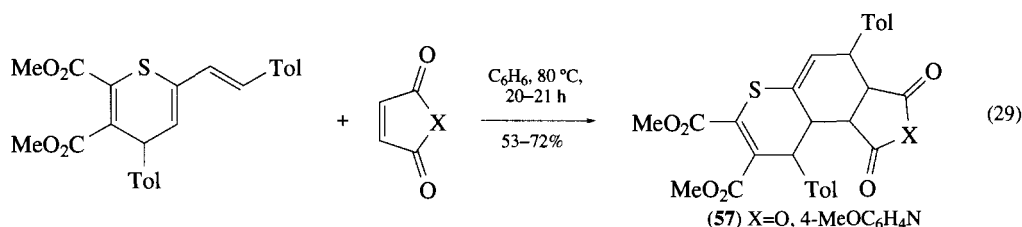


(ii) *By synthesis of the carbocyclic ring*

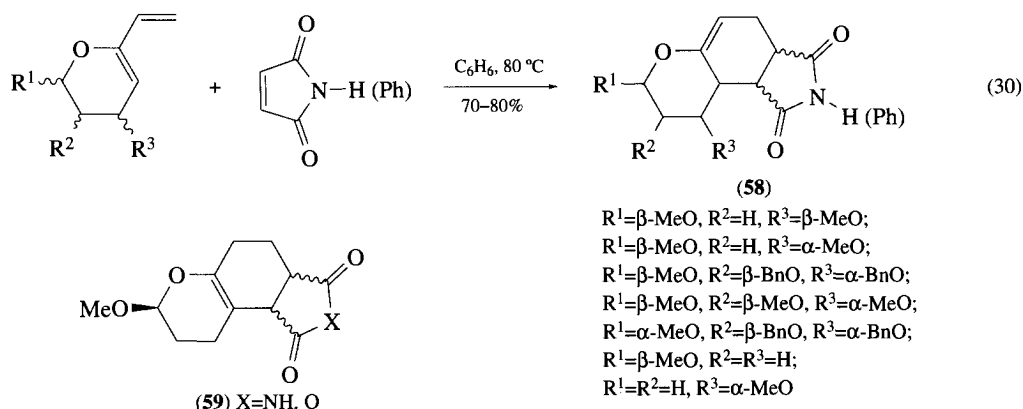
(a) *By formation of one bond.* An LDA-mediated cyclization of a heterobiaryl precursor was followed by oxidation (Equation (28)) to prepare the pyrido- and thieno-fused *ortho*-naphthoquinone (**56**) in 74% yield <93TL2437>.



(b) *By formation of two bonds.* In a study of diene-transmissive Diels–Alder reactions <90BCJ284>, cycloaddition of a substituted 1,4-dihydrothiane and maleic anhydride or *N*-(*p*-methoxyphenyl)maleimide gave 4-oxa-10-thia- and 10-thia-4-aza- versions of the substituted tricyclo [7.4.0.0^{2,6}]trideca-8,11-diene-3,5-diones (**57**) in good yield (Equation (29)). The starting material is itself a Diels–Alder adduct of an $\alpha,\beta:\alpha',\beta'$ -unsaturated thioketone and DMAD.

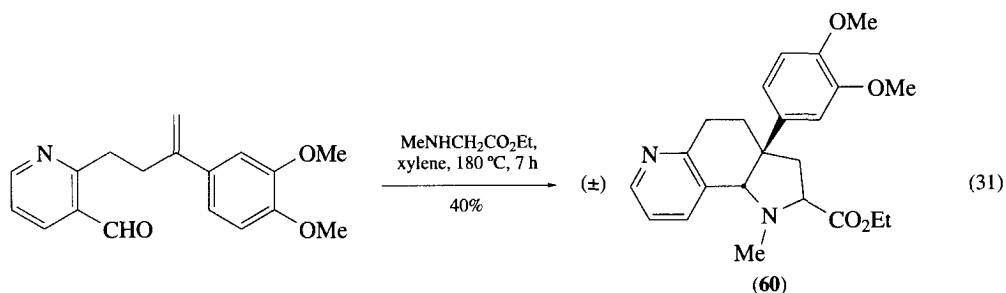


In another study of Diels–Alder reactions, but with dienopyranosides <90JOC3555>, condensations of these carbohydrate-derived dienes with maleimide or its *N*-phenyl derivative gave annelated pyranosides (**58**) in a highly stereoselective manner, giving single products in some cases (Equation (30)). Double bond migration products (**59**) were also obtained, but these were discovered to have been generated by the presence of a trace of acid. Conducting the condensations in the presence of Et_3N or $(Pr^i)_2NEt$ prevented this migration.

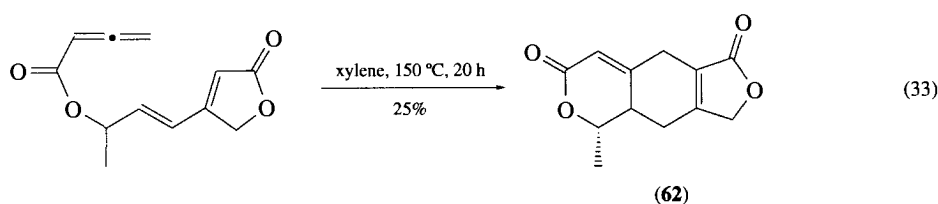
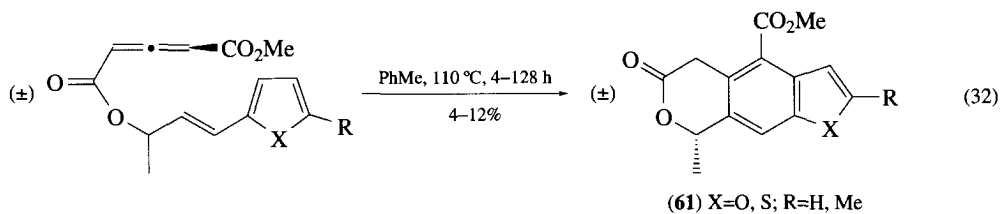


(iii) Synthesis of two contiguous rings

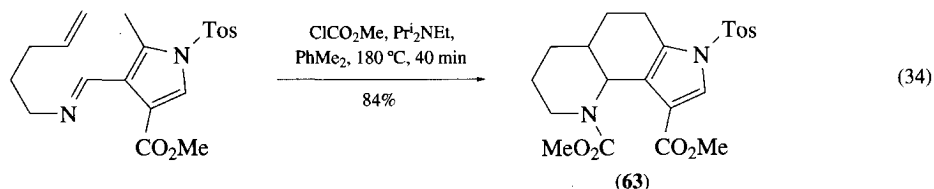
Heating the 1,1-disubstituted alkene with excess sarcosine ethyl ester in xylene with molecular sieves in a sealed tube at 180 °C (7 h) afforded (**60**) (40%) (Equation (31)) <84JA7175>. This product was then processed in two steps to ($\pm$)-*Sceletium* alkaloid A₄.



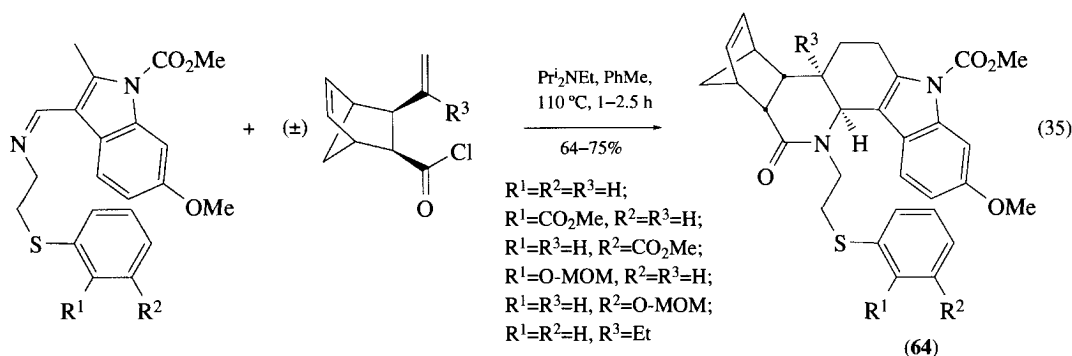
Although obtained only in low yields upon troublesome chromatography of product mixtures that contained much polymeric material, the tricyclic benzofuran and benzothiophene lactones (**61**) were shown to be isolable products from attempted Diels–Alder reactions on the allene ester precursors shown in Equation (32) <85JCS(P1)747>. Although it was noted in the case of the two thiophenes that the tricyclics appeared to be forming from a precursor (presumably a dihydro form) on the chromatographic column, it was not possible to convert the crude suspected cycloaddition adducts directly into the aromatics by dehydrogenation with DDQ. Complex mixtures were obtained instead. It is possible that the actual dienophiles in these Diels–Alder reactions are alkynes. In a related study, the bis-lactone (**62**) was also obtained (Equation (33)) <86H(24)881>.



The generation of a pyrrole-2,3-quinodimethane was demonstrated by trapping it in intramolecular Diels–Alder fashion, as shown in Equation (34) <92CC1401>. Diastereomerically pure octahydropyrrolo[2,3-*h*]quinoline (**63**) was obtained (84%) when its imine precursor was subjected to conditions that effected both carboxylation at the imino nitrogen (by ClCO_2Me) and deprotonation at the methyl group (by Pr_2NEt) to give a 2,3-dimethylene-2,3-dihydropyrrole intermediate which cyclized directly.

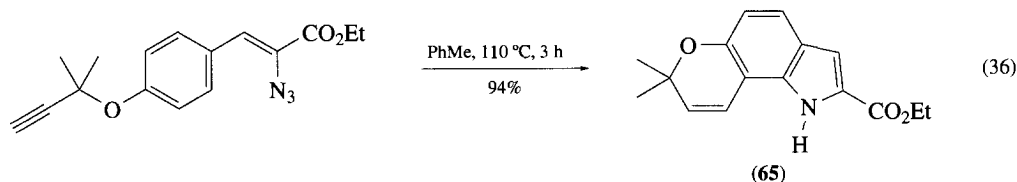


In a similar heterocyclic quinodimethane ring construction strategy, the hexacyclic adducts (**64**) were isolated in good yield upon condensation of appropriately functionalized indole imines with ($\pm$)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid chloride (Equation (35)) <88JA2242>. In a demonstration of the utility of this new method for indole alkaloid synthesis, further transformations conducted on compound (**64**; $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Et}$) were shown to lead to (–)-16-methoxytabersonine.



(iv) Synthesis of both heterocyclic rings

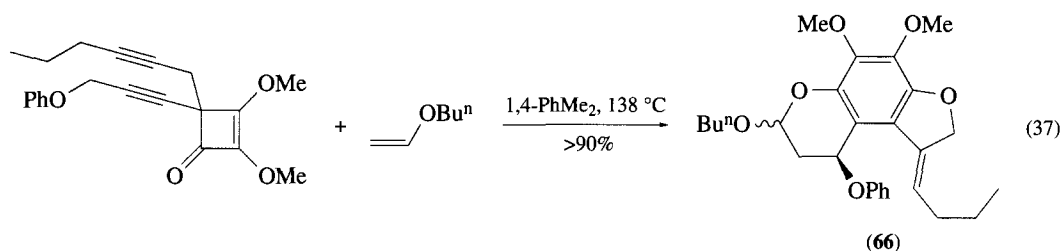
Based on the fact that the thermal rearrangement of 1,1-dimethylprop-2-ynyl aryl ethers is known to afford chromenes, it was expected and then found that the pyrano[2,3-*g*]indole (**65**) forms by sequential indolization and regioselective rearrangement via thermolysis of the appropriate azido ester precursor (Equation (36)) <84JCS(P1)1333>. This transformation proceeded in remarkably high yield (94%) simply upon heating the azide for 3 h in toluene at reflux. The intermediate, unrearranged 1,1-dimethylprop-2-ynyloxyindole was not isolated.



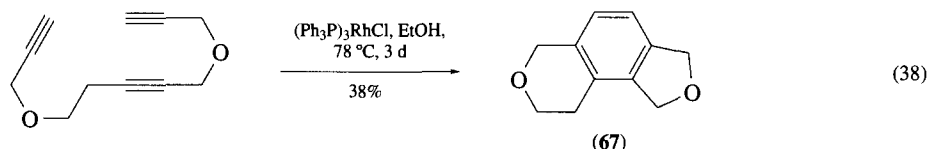
(v) Synthesis of all three rings

In a study of annelation reactions of 4-alkynylcyclobutenones <91JOC6104>, thermolysis of a 4-alkynyl-4-(propargyloxy)cyclobutenone was observed to give a high yield of a quinone methide as evidenced by the formation of a hetero-Diels–Alder product in the presence of butoxyethene as a

trapping agent (Equation (37)). Adduct (66) was isolated in excellent yield as a 2:1 mixture of diastereomers.



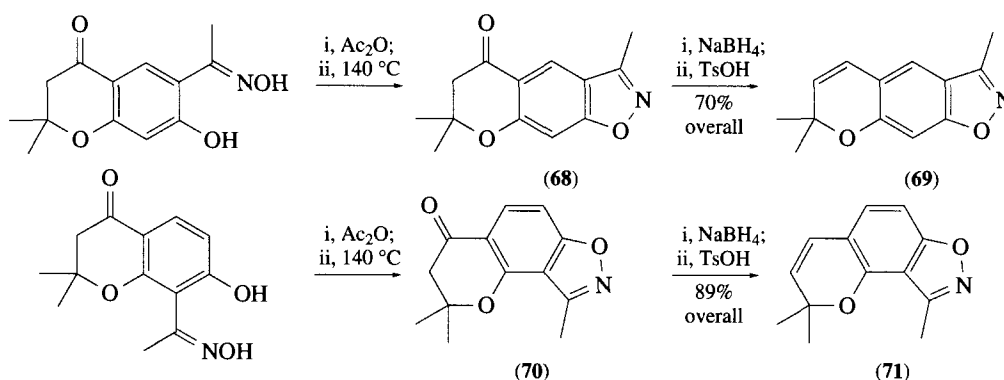
In a study of rhodium-catalyzed [2 + 2 + 2] cycloadditions of alkynes <88JCS(P1)1357>, the intramolecular [2 + 2 + 2] cycloaddition of 4,9-dioxadodeca-1,6,12-triyn catalyzed by Wilkinson's catalyst [(PPh₃)₃RhCl] over a prolonged period of time gave the dihydropyrano- and tetrahydrofuro-fused 6-6-5 tricyclic benzene derivative (67) in moderate yield (Equation (38)). It should be noted that an analogous bis-tetrahydrofuro-fused 5-6-5 tricyclic compound could be prepared (74%) under similar conditions, but after only 3 h at room temperature.



7.22.9.3.2 With two heteroatoms in one heterocyclic ring and one in the other

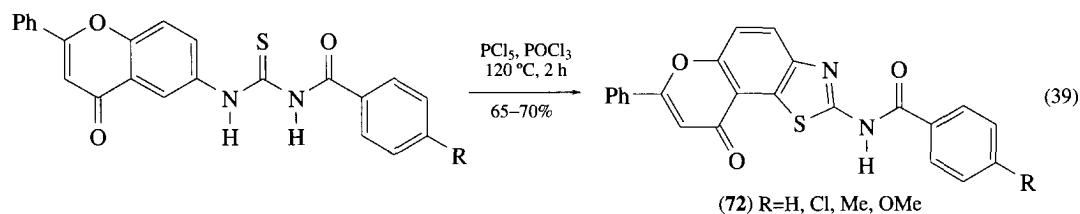
(i) Synthesis of the heterocyclic ring

(a) *By formation of one bond.* As shown in Scheme 4, isoxazoles (68) or (70), prepared from the corresponding *o*-hydroxyketoximes by acetylation followed by thermal cyclization, led to 3,7,7-trimethyl-7*H*-pyrano[3,2-*f*]-1,2-benzisoxazole (69) or 2,2,9-trimethyl-7*H*-pyrano[2,3-*e*]-1,2-benzisoxazole (71) upon sequential reduction with NaBH₄ and dehydration with TsOH <89H(28)711>. The pyrano[1,2]benzisoxazoles (69) and (71) were obtained in excellent overall yield from the ketoximes.

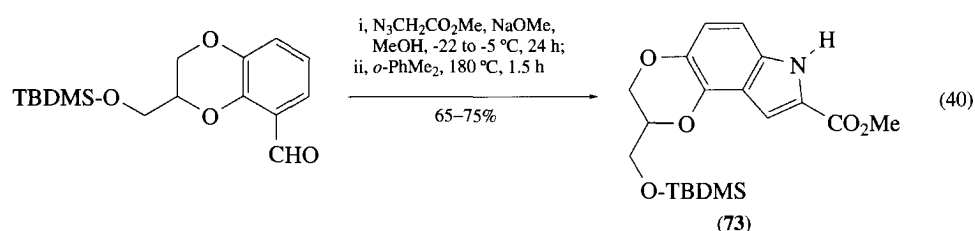


Scheme 4

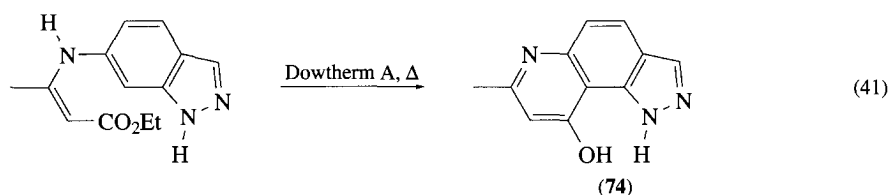
The four (pyrano[2,3-*g*]benzothiazol-2-yl)benzamides (72) shown in Equation (39) were obtained in good yield by heating 6-aminoflavone-derived thiourea precursors in POCl₃ containing PCl₅ <94BCJ2326>.



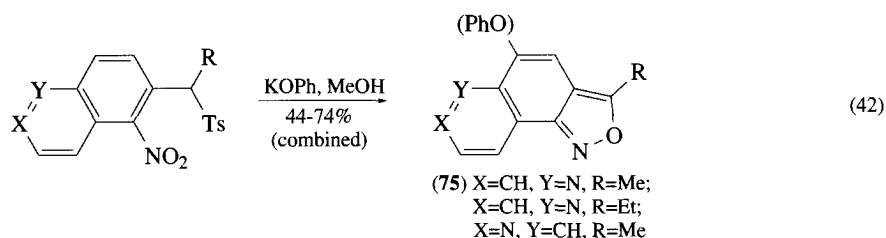
The key steps in the preparation of novel antihypertensive 7*H*-1,4-dioxano[2,3-*e*]indoles are the condensation of a 2,3-dihydro-1,4-benzodioxan-5-carbaldehyde with methyl α -azidoacetate and the thermolytic ring-closure of the resulting vinyl azide to give ester (73), obtained in 65–75% overall yield from the carbaldehyde (Equation (40)) <92JMC3058>. Compound (73) was processed further by removal (TBAF) of the TBDMS group, tosylation (TsCl, pyridine) of the resulting alcohol, and displacement (R^1R^2NH , K_2CO_3 , pyridine) of the tosylate group with amines.



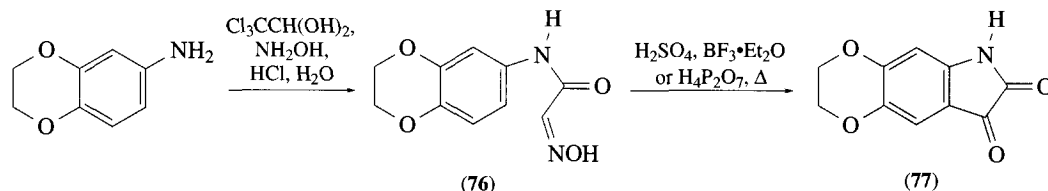
Thermal cyclization was also the route employed to prepare 9-hydroxy-7-methyl-1*H*-pyrazolo[3,4-*f*]quinoline (74) from the 6-aminoindazole/ethyl acetoacetate condensation adduct shown in Equation (41) <92JMC4595>. The hydroxyl substituent of compound (74) was then converted ($POCl_3$, DMF) to a chloro, which in turn was displaced by treatment with aryl amines to give tricyclics with potent *in vivo* immunostimulatory activity like that noted for regioisomeric 1*H*-imidazo[4,5-*f*]quinolines but unlike the inactive pyrazolo[4,3-*f*]quinolines. Although it was noted with some interest that none of the linear tricyclic isomer had been isolated, this finding actually parallels that reported earlier for the similar condensation of 1- and *N*(6)-alkyl and unsubstituted 6-aminoindazoles with diethyl ethoxymethylenemalonate <83JHC1351>.



Isoxazole rings were annelated onto 5-nitroquinoline and isoquinoline-based *o*-nitrobenzyl-*p*-tolylsulfones by treatment with potassium phenoxide, which acted as both base and reductant (Equation (42)) <95H(40)187>. In the cases of quinolines as starting materials, product benzisoxazoles (75) both with and without phenoxy substitution were obtained, but in the case of an isoquinoline starting material no phenoxy-substituted product was generated. The reaction is thought to proceed via a nitrosobenzylsulfone carbanion intermediate, and can be applied to nitronaphthalenes but not to less active nitrobenzenes.

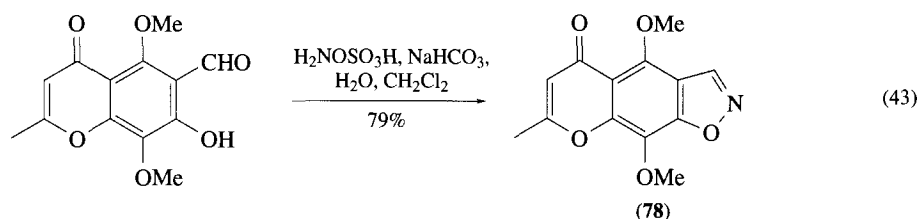


As shown in Scheme 5, isatin (77) was synthesized according to the Sandmeyer procedure whereby the α -oximinoanilide (76) formed by condensation of chloral hydrate, NH_2OH , and the appropriate ethylenedioxy aniline was cyclized by concentrated H_2SO_4 <95JMC906>. This isatin was then used to 2-oxo-1,2-dihydroindol-3-ylidenate a tricyclic ketone to give one of those in a series of camptothecin analogues tested for activity as topoisomerase I inhibitors.

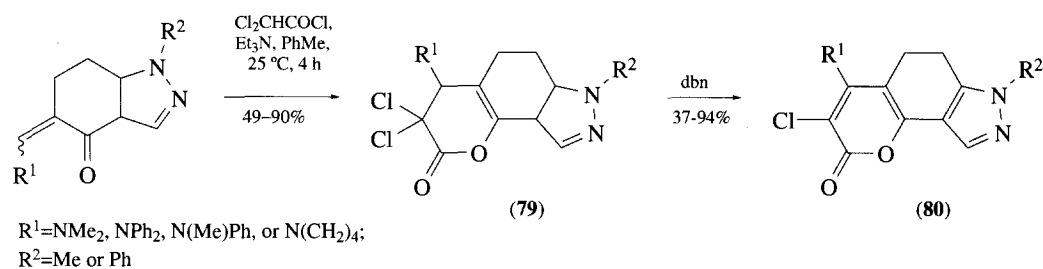


Scheme 5

(b) *By formation of two bonds.* The isoxazole analogue (78) of a 2-acetyl furochromone has been prepared (79%) by slow addition of hydroxylamine *O*-sulfonic acid to a hydroxy carbaldehyde precursor in a two phase system ($\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$) containing two equivalents of sodium bicarbonate (Equation (43)) <84TL2953>.

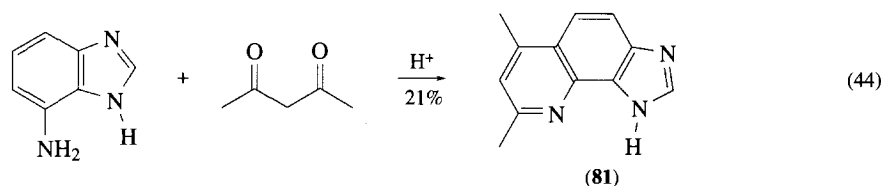


4-Dialkylamino-3,3-dichloro-4,5,6,7-tetrahydropyrano[2,3-*e*]indazol-2(3*H*)-ones (79) were obtained in good yield by the cyclocondensation of 5-(dialkylamino)methylene derivatives of 1,5,6,7-tetrahydro-4*H*-indazol-4-one with dichloroketene prepared *in situ* from Cl_2CHCOCl and Et_3N (Scheme 6) <84JHC361>. Compounds (79) readily underwent dehydrochlorination upon treatment with DBN to give the 6,7-dihydropyrano[2,3-*e*]indazol-2(7*H*)-ones (80), but these proved to be very resistant to full aromatization with DDQ in refluxing PhH, although extended reaction time (12 d) did afford two 3-chloro-4-dimethylaminopyrano[2,3-*e*]indazol-2(7*H*)-ones in 40–76% yield.



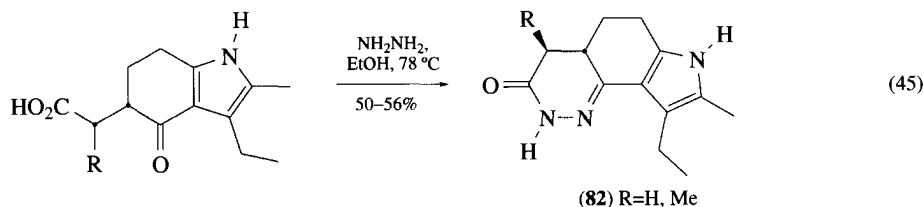
Scheme 6

In an example of the Combes synthesis of quinolines, acid-catalyzed condensation of 4(7)-aminobenzimidazole with excess acetylacetone afforded 5,7-dimethylimidazo[4,5-*h*]quinoline (81), albeit in low yield (Equation (44)) <91T7459>.

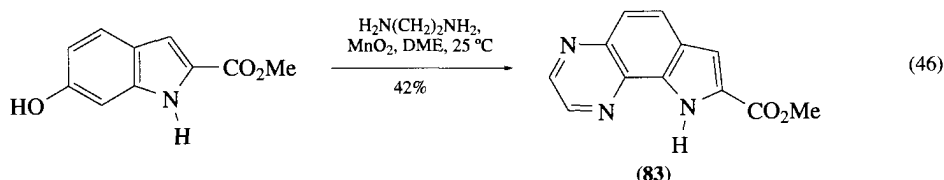


4-Oxo-1*H*-4,5,6,7-tetrahydro-5-indoleacetic acids gave the tetrahydroindolo[4,5-*c*]pyridazin-3(2*H*)-ones (82) upon condensation with hydrazine in ethanol (Equation (45)) <92H(34)1303>. Stereo-

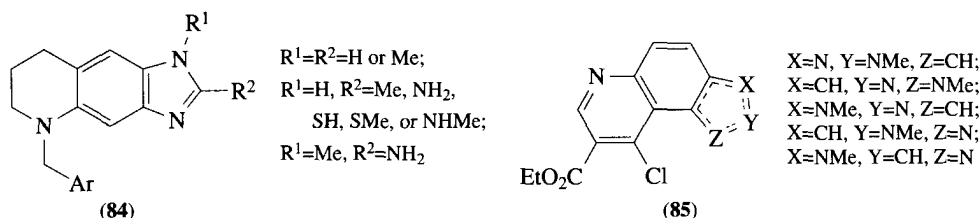
chemical determinations of the products (**82**) were made by comparing the ring ^1H — ^1H coupling constants to those of a *cis*-fused tricyclic lactone derived from one of the tetrahydro-5-indoleacetic acid starting materials.



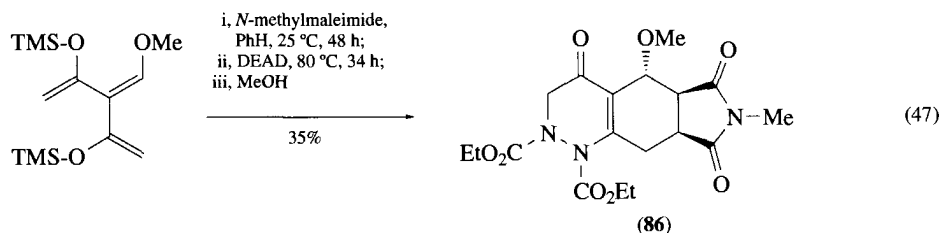
As part of an examination of an oxidative coupling of methyl 6-hydroxyindole-2-carboxylate with primary amines which enabled the development of a facile preparation of 2-substituted methyl pyrrolo[2,3-*e*]benzoxazole-5-carboxylates, the reaction of this indole with 1,2-diaminoethane and excess MnO_2 gave compound (**83**) in an apparent intramolecular interception of a transient intermediate *o*-quinone monoimine (Equation (46)) (88JOC5163).



A series of substituted imidazotetrahydroquinoline thymidylate synthetase inhibitors (**84**) was prepared (92JMC847) according to imidazole ring annelation of 6,7-diamino-1,2,3,4-tetrahydroquinolines by condensation with appropriate electrophilic reagents (e.g., CNBr , HC(OMe)_3 , Im_2CS). In a separate study, a series of aryl[*e*]fused pyrazolo[4,3-*c*]pyridines with potential anxiolytic activity (90JMC2640), substituted pyrazolo[4,3-*f*]-, [3,4-*f*]-, and imidazo[4,5-*f*]quinolines (**85**) were prepared by pyridine ring annelation of aminoindazoles or an aminobenzimidazole via [(arylamino) methylene]malonates by a modified Gould–Jacobs cyclization with the use of POCl_3 at reflux.

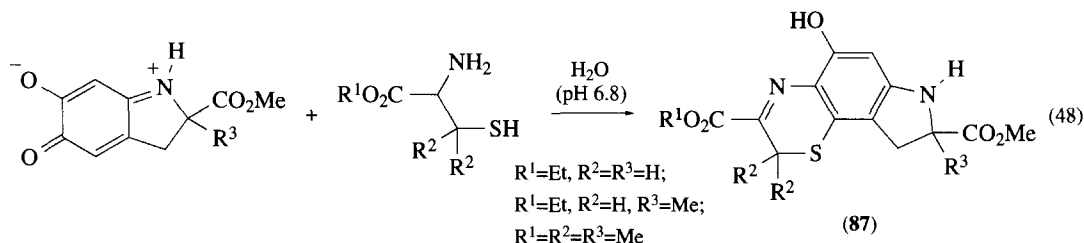


In an example of one of the more promising cross processes of diene-transmissive hetero-Diels–Alder reactions of bis(silyloxy) cross-conjugated trienes (94CL1833), 3-(methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene was first condensed with *N*-methylmaleimide to give an *endo* mono-cycloadduct: this in turn was condensed with DEAD to give the cross bis-adduct (**86**) upon workup with MeOH (Equation (47)). It was established by ^1H NMR that the initially formed ring of the product (**86**) had the *trans* configuration, indicating that the stereochemistry of the initial *endo* monocycloadduct had been inverted during the formation of the second ring.

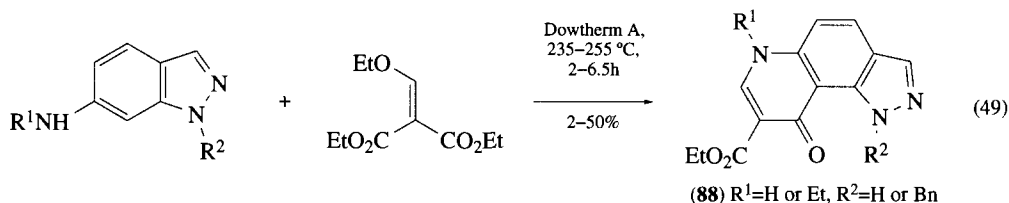


Condensation of dopachrome methyl or ethyl esters with cysteine ethyl ester in pH 6.8 aqueous phosphate buffer led to the 1,2-dihydro-3*H*,8*H*-pyrrolo[2,3-*h*][1,4]benzothiazines (**87**), as shown in

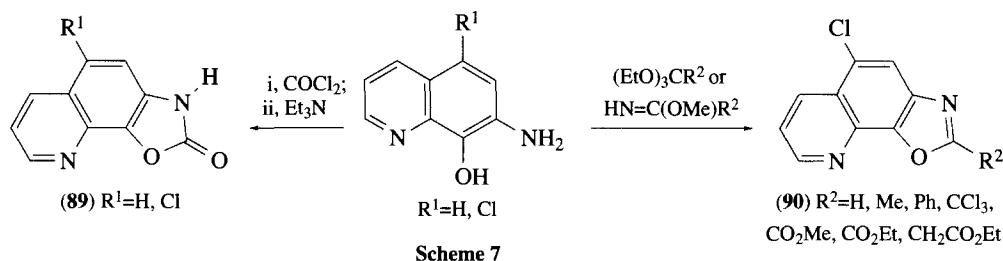
Equation (48) <87T5357>. A mechanism similar to that commonly accepted for the formation of 2*H*-1,4-benzothiazines via condensation of β -aminothiols with simple *o*- and *p*-benzoquinones was suggested. It was noted that the products (**87**; $R^3 = H$) rapidly decompose to oligomeric materials whereas the others are much more stable to this presumed oxidative lability.



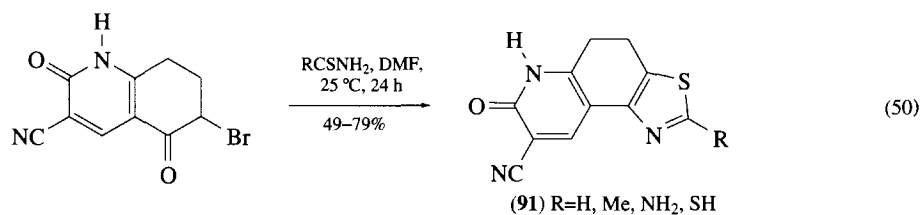
Condensation of 1- and *N*(6)-alkyl and unsubstituted 6-aminoindazoles with diethyl ethoxymethylenemalonate in Dowtherm A at elevated temperature gave the ethyl 6,9-dihydro-9-oxo-pyrazolo[3,4-*f*]quinoline-8-carboxylates (**88**) (Equation (49)) <83JHC1351>. The 6-ethyl-8-carboxylic acid derivative is a potent antibacterial agent.



The oxazolo[4,5-*h*]quinolin-2(3*H*)-ones (**89**) and 2,5-disubstituted oxazolo[4,5-*h*]quinolines (**90**) were prepared as new antiallergic agents by oxazole ring annelation conducted by condensing 7-amino-8-hydroxyquinoline intermediates with phosgene, *o*-ester, or imidate reagents (Scheme 7) <85JMC1255>.

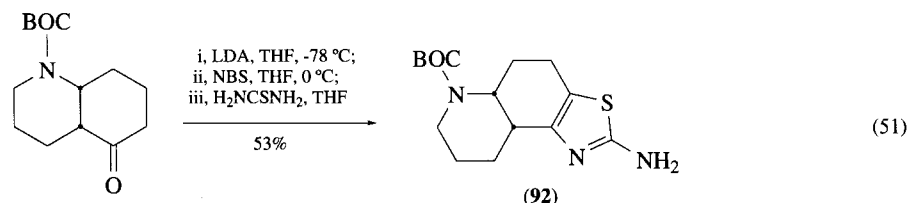


[4,5-*f*]Thiazole ring annelation onto 6-bromo-3-cyano-5-oxo-5,6,7,8-tetrahydro-2(1*H*)-quinolinone was effected by treatment with thioformamide and its derivatives under mild conditions, giving the 8-cyano-7-oxo-4,5,6,7-tetrahydrothiazolo[4,5-*f*]quinolines (**91**) in good yield (Equation (50)) <89H(29)1517>.



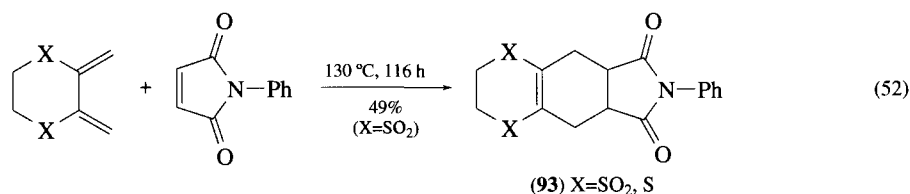
Together with syntheses of 2-amino-8,9-dihydrothiazolo[4,5-*f*]- and [4,5-*f*]isoquinoline and 2-amino-4,5-dihydrothiazolo[5,4-*h*]isoquinoline based upon an α -bromoketone/thiourea condensation similar to that described above, a direct thiazole ring annelation method for an *N*-protected octahydroquinolin-5-one has been developed. This involves the trapping of a kinetic enolate with TMS—Cl followed by regioselective bromination (NBS) and condensation with thio-

urea <89H(29)1517>. This sequence (Equation (51)) gave the *cis*-fused 2-aminooctahydrothiazolo[4,5-*f*]quinoline (**92**) in 53% overall yield. By a similar sequence, a *trans*-octahydroquinolin-5-one gave a *trans*-fused version of compound (**92**), indicating that the starting ketones were fairly stable toward epimerization under the reaction conditions.

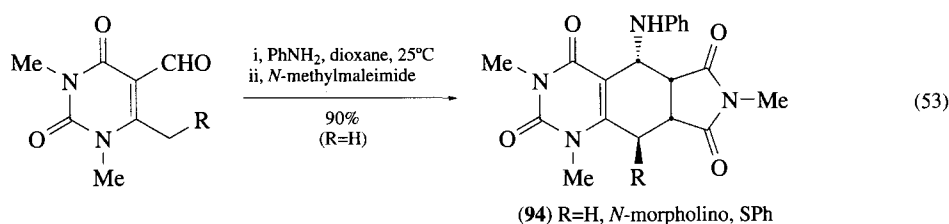


(ii) *By synthesis of the carbocyclic ring*

(a) *By formation of two bonds.* The thermal cycloaddition of *N*-phenylmaleimide to the very reactive 2,3-(ethylenedisulfonyl)-1,3-butadiene or its bishioether analogue gave the tricyclic cycloadducts (**93**) (Equation (52)) <92CB499>.

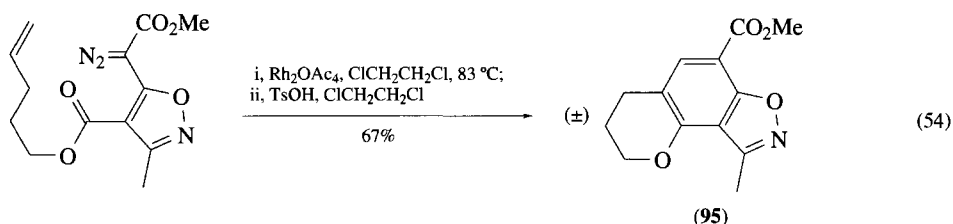


5-Anilino-5a,8a-dihydro-1,3,7-trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8-(3*H*,5*H*,7*H*,9*H*)-tetrone (**94**) were obtained in good yield by the sequential treatment of 5-formyl-1,3,6-trimethyluracil with (i) aniline to form the 6-methylene-5-(phenylamino)methylene derivative, via a [1,5]-hydrogen shift in the aldimine, and (ii) maleimide to achieve the central ring-forming cycloaddition reaction (Equation (53)) <90BCJ2938>.



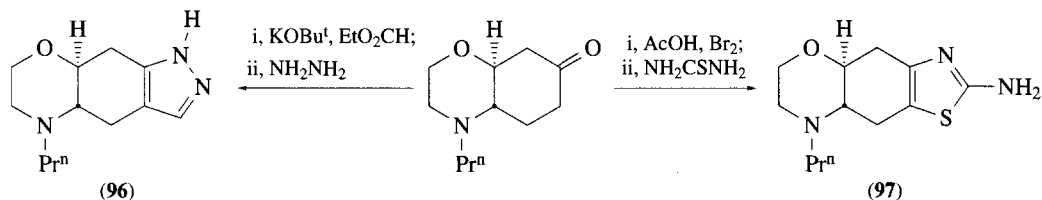
(iii) *By synthesis of two contiguous rings*

The Rh₂OAc₄-catalyzed nitrogen extrusion from the diazoketone shown in Equation (54) leads to isoxazole (**95**) after aromatization of the central ring <89H(29)1003>. The formation of the tricyclic ring system is thought to proceed through a furo[3,4-*d*]isoxazole intermediate that undergoes intramolecular Diels–Alder reaction and then fragmentation.



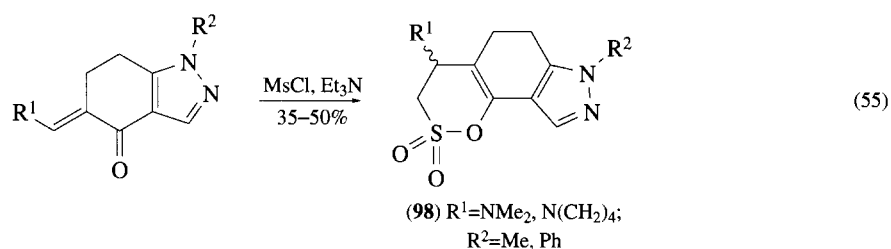
7.22.9.3.3 With two heteroatoms in each heterocyclic ring

As shown in Scheme 8, a common ketone precursor led to the pyrazolo[4,3-*g*]- and thiazolo[5,4-*g*]-fused 1,4-benzoxazines (**96**) and (**97**) (<87JMC580>. For the synthesis of compound (**96**) the ketone was condensed with HCO₂Et and subsequently cyclized with hydrazine. For the synthesis of the thiazole (**97**) α -bromination of the ketone was followed by condensation with thiourea. The linear tricyclic structures (**96**) and (**97**) were supported by ¹H and ¹³C NMR spectroscopic analyses.



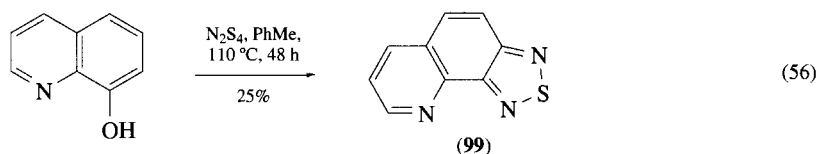
Scheme 8

4-Dialkylamino-4,5,6,7-tetrahydro-3*H*-1,2-oxathiino[6,5-*e*]indazole 2,2-dioxides (**98**) were obtained (35–50%) by the cyclocondensation of 5-(dialkylamino)methylene derivatives of 1,5,6,7-tetrahydro-4*H*-indazol-4-one with sulfene prepared *in situ* from MsCl and Et₃N (Equation (55)) (<84JHC361>).

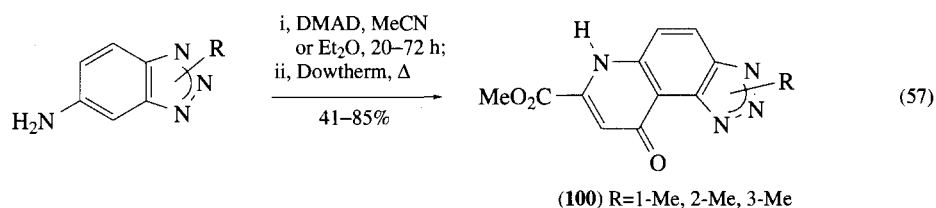


7.22.9.3.4 With more than two heteroatoms in either heterocyclic ring

In an unexpected outcome, 8-quinolinol condensed with tetrasulfur tetranitride in refluxing toluene to give 1,2,5-thiadiazolo[3,4-*h*]quinoline (**99**) (25%) (Equation (56)) (<91BCJ68>).

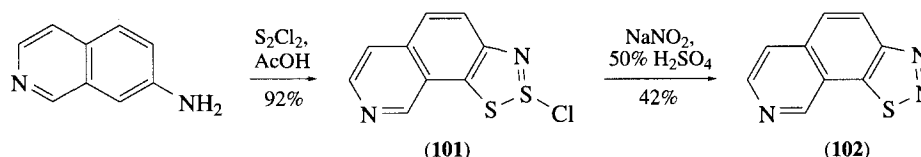


The condensation of aminobenzotriazoles with DMAD gave (*Z*)-conjugate addition adducts which underwent ring closure in boiling Dowtherm to give triazolo[4,5-*f*]quinolinones (**100**) (Equation (57)) (<93H(36)259>. The quinolinone form of the product (**100**) is supported by ¹³C NMR spectroscopic evidence. It was found that ring closure to the tricycle fails in the absence of an *N*-methyl substituent; retro-Michael addition takes place instead.

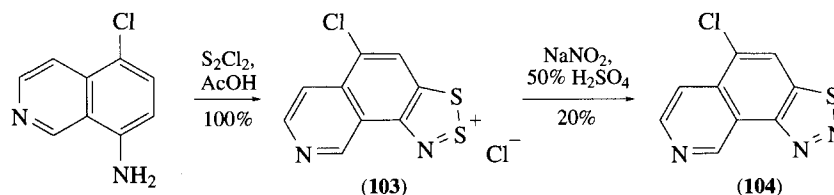


A series of tetrahydrothiadiazoloisoquinolines that could potentially reduce the formation of epinephrine by inhibiting phenylethanolamine-*N*-methyltransferase has been prepared (<89JMC1566>).

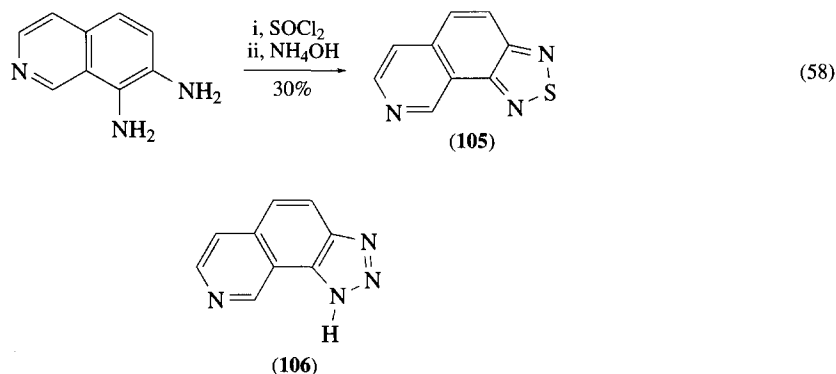
In connection with this study, syntheses of 1,2,3-thiadiazolo[4,5-*h*]isoquinoline (**102**) (Scheme 9), 5-chloro-1,2,3-thiadiazolo[5,4-*h*]isoquinoline (**104**) (Scheme 10), and 1,2,5-thiadiazolo[3,4-*h*]isoquinoline (**105**) (Equation (58)) were developed. 7-Aminoisoquinoline and 8-amino-5-chloroisoquinoline each condensed with sulfur monochloride to give the dithiazoloisoquinolin-2-ium chloride hydrochlorides (**101**) and (**103**), respectively, in excellent yield. Nitrous acid treatment of these intermediates gave compounds (**102**) and (**104**) in moderate yield. Treatment of 7,8-diaminoisoquinoline with SOCl_2 gave the tricyclic product (**105**) directly and treatment with nitrous acid gave 1,2,3-triazolo[4,5-*h*]isoquinoline (**106**).



Scheme 9

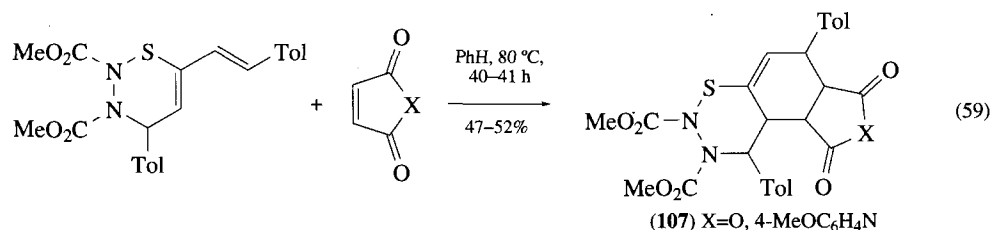


Scheme 10



(58)

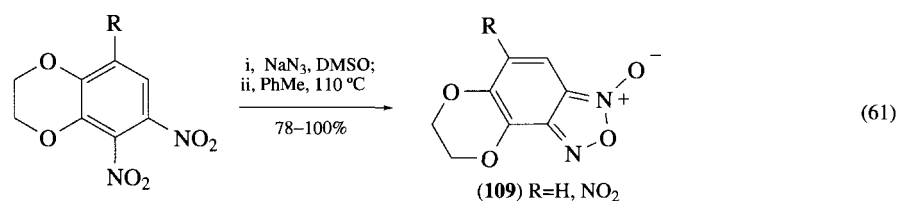
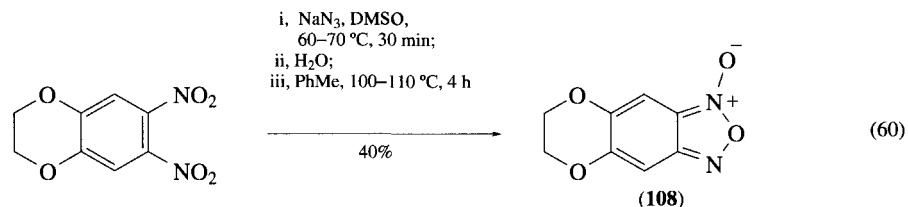
In a study of the diene-transmissive Diels–Alder reactions <90BCJ284>, cycloaddition of a substituted 1,4-dihydrothiadiazine and maleic anhydride or *N*-(*p*-methoxyphenyl)maleimide gave substituted bicyclo[4.4.0]dec-10-enes (**107**) in good yield (Equation (59)) <90BCJ284>. The starting thiadiazine is itself a Diels–Alder adduct of an $\alpha,\beta:\alpha',\beta'$ -unsaturated thioketone and dead.



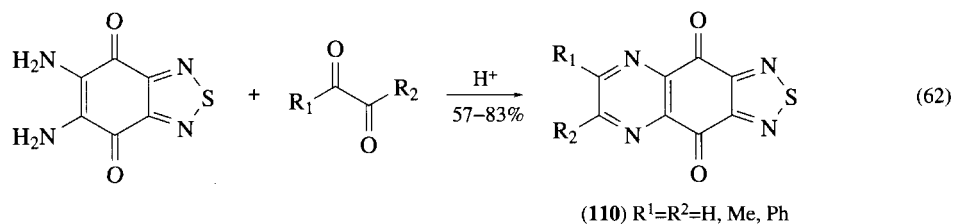
(59)

1,4-Benzodioxano[6,7-*c*]furoxan (**108**) (Equation (60)), which was available previously via NaOCl oxidation of 6-amino-7-nitro-1,4-benzodioxane, has been prepared using a simpler route from 6,7-dinitro-1,4-benzodioxane via azide-for-nitro displacement and pyrolysis of the crude intermediate azide, in spite of a report that pyrolysis of 6-azido-7-nitro-1,4-benzodioxane fails to generate (**108**) in various solvents and at different temperatures <88JHC803>. Di- or trinitro-1,4-benzodioxanes were subjected to a similar nucleophilic displacement with azide ion to afford the bent tricyclic 1,4-

benzodioxano[5,6-*c*]furoxans (**109**) (Equation (61)) <91T7157>. Heating compound (**109**; R = NO₂) in toluene under reflux, or even neat in the solid-state, results in complete and irreversible rearrangement to the linear tricyclic isomer via a Boulton–Katritzky rearrangement.



6,7-Disubstituted and unsubstituted 1,2,5-thiadiazolo[3,4-*g*]quinoxaline-4,9-diones (**110**) have been prepared in good yield by condensation of 5,6-diaminobenzo[*c*][1,2,5]thiadiazole with α -dicarbonyl reagents (Equation (62)) <92H(33)337>. These quinones were then converted into 1,2,5-thiadiazolo-, pyrazino-fused TCNQ analogues by condensation with malononitrile in the presence of TiCl₄ in dry pyridine. The x-ray crystal structure determination of the product derived from compound (**110**; R¹ = R² = H) has been accomplished.

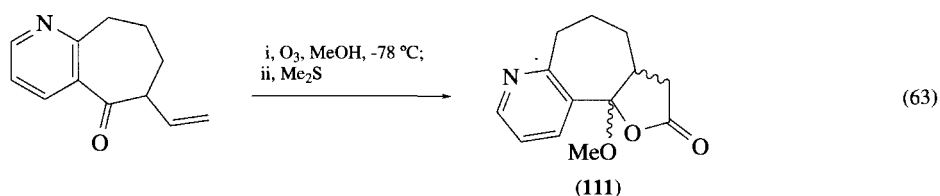


7.22.9.4 Synthesis of Compounds with a Central Seven-membered Ring

7.22.9.4.1 With one heteroatom in each heterocyclic ring

(i) By synthesis of a heterocyclic ring

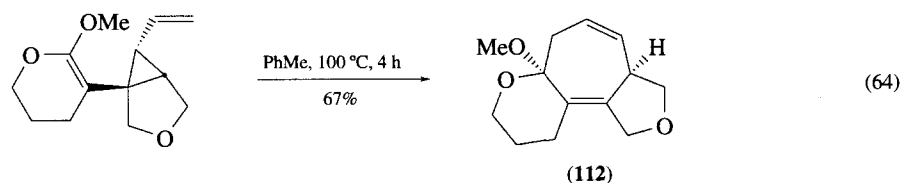
(a) *By formation of one bond.* Ozonolysis of the vinyl substituent on a pyrido[2,3-*b*]cycloheptanone unexpectedly gave, upon reductive workup, the tricyclic ketal lactone (**111**) as a mixture of *cis*- and *trans*-fused isomers (Equation (63)) <94SC273>.



(ii) By synthesis of the carbocyclic ring

(a) *By formation of one bond and fragmentation of another.* As shown in Equation (64), the thermolysis of a divinylcyclopropane precursor induced a [3,3]-sigmatropic rearrangement and

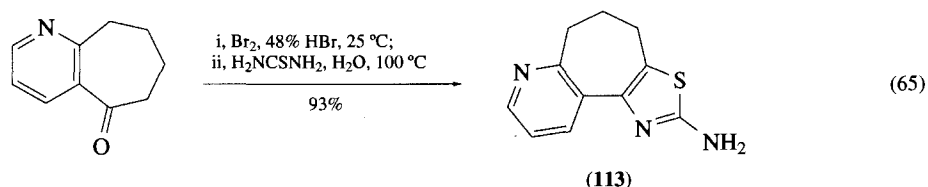
smoothly generated the 6-7-5 tricyclic cycloheptadiene derivative (**112**) <92JOC5559>. It was suggested that this rearrangement occurs via a boat transition state.



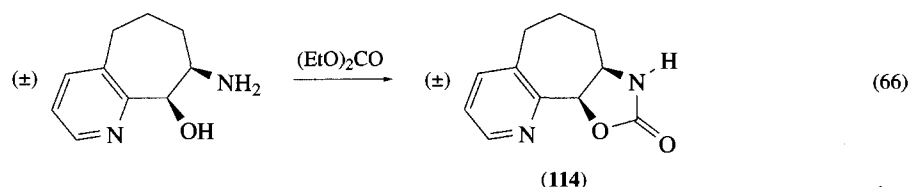
7.22.9.4.2 With two heteroatoms in one heterocyclic ring and one in the other

(i) By synthesis of a heterocyclic ring

(a) By formation of two bonds. Bromination of a pyrido[2,3-*b*]cycloheptanone followed by condensation with thiourea led to the construction (Equation (65)) of the fused thiazole ring of the amine (**113**), isolated in excellent yield <91JMC2736>.

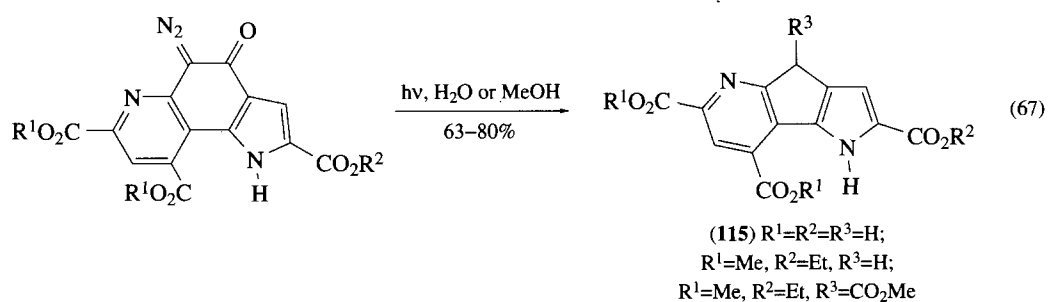


A 6-7 bicyclic, *erythro* diastereomer aminoalcohol precursor derived from 5,6,7,8-tetrahydro-9*H*-cyclohepta[*b*]pyridin-9-one was condensed with diethyl carbonate to afford the 6-7-5 tricyclic *cis*-fused oxazol-2-one (**114**) (Equation (66)) <84JMC20>.

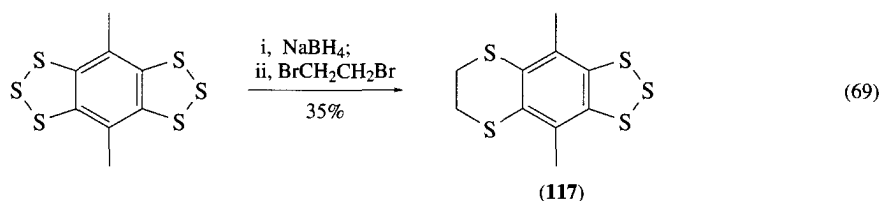
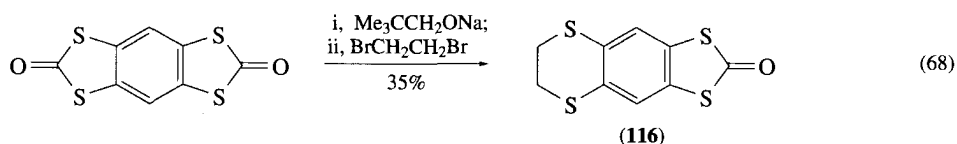


7.22.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

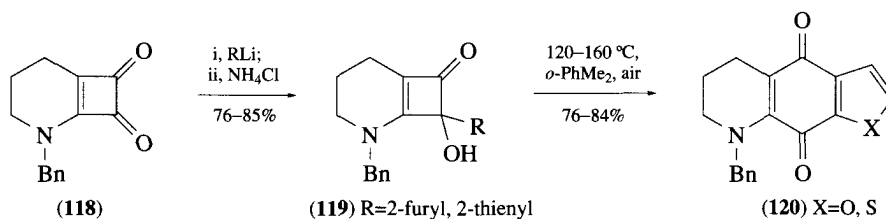
As shown in Equation (67), monotosylhydrazones of PQQ and PQQ-triesters can undergo photogenerated Wolff rearrangements <93HCA1674>. The photogenerated α -diazoketone leads to a carbene-mediated ring contraction to give a ketene that can be trapped with either water or methanol. The latter workup affords 4-methoxycarbonylated versions of 1,4-dihydro-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]pyridin-2,6,8-tricarboxylic acids (**115**), while the former gives 4-unsubstituted ones due to *in situ* decarboxylation at the 4-position.



Ring opening (Equation (68)) of the versatile synthon 1,3,5,7-tetrathia-*s*-indacene-2,6-dione with sodium *t*-amylate followed by 1,2-dibromoethane alkylation gave the tricyclic 1,4-dithiane (**116**) (35%) <87JOC3285>. In a related ring transformative reaction (Equation (69)), reduction of 4,8-dimethylbenzo[1,2-*d*:4,5-*d'*]bis-1,2,3-trithiole with sodium borohydride followed by alkylation with 1,2-dibromoethane afforded the 1,4-dithiane-containing tricyclic monotrithiole (**117**) (35%) <89TL3453>.

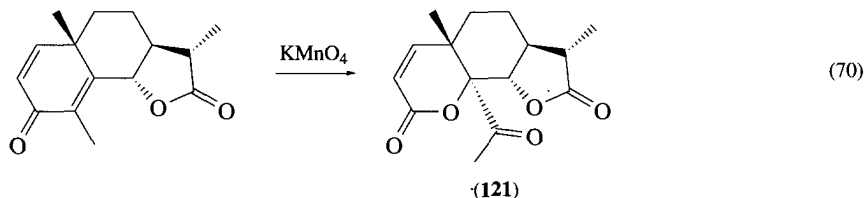


N-Benzyl-1,2,3,4-tetrahydrocyclobuta[*b*]pyridine-5,6-dione (**118**) functions as a synthon of the unstable pyridiocyclobutenedione and undergoes regiospecific introduction of unsaturated nucleophiles at the more reactive carbonyl group to give the 1,2-adducts (**119**) (Scheme 11) <91JOC6379>. These in turn undergo a thermolytic ring expansion in vessels open to air to give the furo- and thieno[3,2-*g*]-fused tetrahydroquinolinequinones (**120**) in good yield. The use of furanyl-3-yl lithium in this sequence gave a furo[2,3-*g*]-fused analogue in 83% yield.



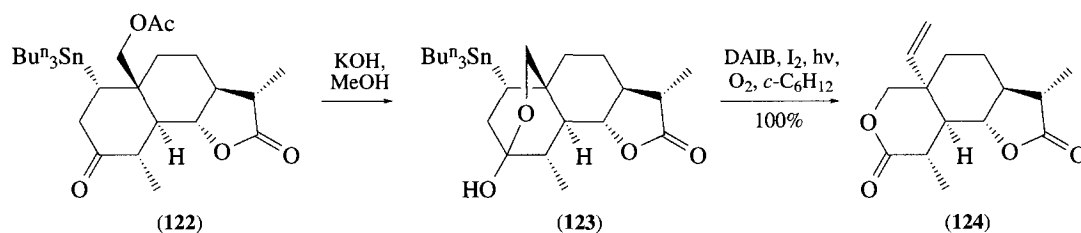
Scheme 11

One product from the oxidation of α -santonin by KMnO_4 (Equation (70)) has been shown to be the ketodilactone (**121**) <94TL8117>. This ring transformation is thought to occur via manganese metalocycle formation at the 4,5-double bond followed by a ring opening/ring closing oxygen atom insertion at the 3,4-single bond.



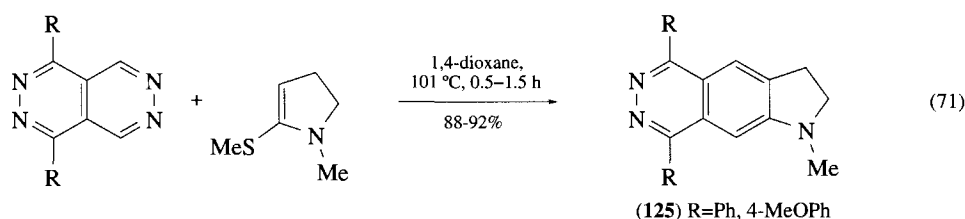
One of the key steps of a short and efficient synthesis of (+)-8-deoxyvernolepin from (–)- α -santonin <94JOC6395> was the 1,4-fragmentation of the γ -hydroxystannane (**123**) to give the δ -valerolactone (**124**) in quantitative yield (Scheme 12). The hemiacetal (**123**), prepared from the ester (**122**) by acetyl group hydrolysis, was irradiated in cyclohexane in the presence of (diacetoxy-iodo)benzene (DAIB) and iodine under a stream of oxygen to suppress a radical I-for- Bu^n_3Sn substitution reaction that had previously caused the yield of product (**124**) to be only 70%. A different total synthesis of (+)-8-deoxyvernolepin from (–)- α -santonin along a route involving a spiro lactone has also been reported <87JCS(P1)2833>.

Cyclocondensation of 1,4-diarylpyridazino[4,5-*d*]pyridazines with a ketene *N,S*-acetal, generated *in situ* by treatment of 2-methylthiol-1-methyl-1-pyrrolinium iodide with DBU, proceeded smoothly



Scheme 12

to give a cycloadduct which underwent spontaneous aromatization to give the 1,4-diaryl-6-methylpyrrolidino[2,3-*g*]phthalazines (**125**) (Equation (71)) <91T3959>.

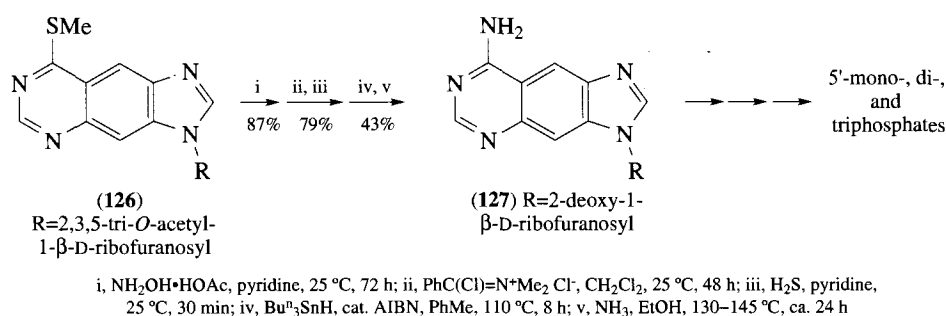


7.22.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

7.22.11.1 Benzo-separated Purines

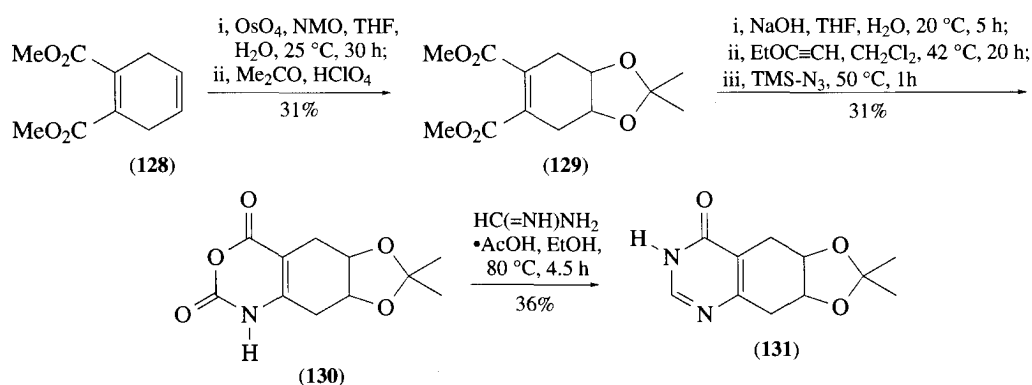
The development of compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or 'stretched-out' purine model was undertaken in the mid-1970s by Leonard and co-workers. Reviews covering the literature through the mid-1980s relate synthetic and other aspects of these compounds <82ACR128, B-84MI 722-01, 84PAC1025, 85MI 722-01, 86T1917>. A general description of these structurally unique purine analogues appears in Section 7.22.12.1, while the highlights of the more recent synthetic developments in this field are summarized here.

The attempt to prepare deoxy-*lin*-benzoadenosine (**127**) directly from *lin*-benzoadenosine was abandoned when efforts to prepare pure 3',5'-di-*O*-benzoyl-*lin*-benzoadenosine gave unstable mixtures. This was attributed to the increased nucleophilicity of the exocyclic amino group of *lin*-benzoadenosine compared to adenosine. In the successful preparation (Scheme 13), treatment of the *lin*-benzoadenosine precursor 8-(methylthio)-3-(tri-*O*-acetyl- β -D-ribofuranosyl)imidazo[4,5-*g*]quinazoline (**126**) with $\text{NH}_2\text{OH} \cdot \text{AcOH}$ afforded a mixture of the 3',5'- and 2',5'-di-*O*-acetyl nucleosides in ca. 4:1 ratio <84B3868>. The mixture was converted to a separable mixture of diacetylthiobenzoyl ribonucleosides, and free-radical reductive deoxygenation of the 2'-thiobenzoyl isomer with Bu^n_3SnH afforded the diacetyl deoxyribonucleoside in good yield. Treatment with ethanolic NH_3 in a pressure vessel at 150°C afforded compound (**127**). The monophosphate was prepared by condensation with pyrophosphoryl chloride in *m*-cresol. The diphosphate was prepared by chemical phosphorylation of the monophosphate via the morpholidate. Pyruvate kinase was used to phosphorylate the diphosphate, affording the triphosphate.



Scheme 13

The use of cycloaddition reactions for the synthesis of partially reduced heterocyclic systems was shown to be an attractive approach to dihydrobenzimidazoles, dihydroquinazolines, and dihydro-*lin*-benzopurines (Scheme 14) <86JOC616>. The dihydroxylation of the Diels–Alder adduct dimethyl 3,6-dihydrophthalate (**128**) with OsO₄ and NMO followed by protection of the diol as the isopropylidene derivative afforded compound (**129**). Saponification, dehydration with ethoxyethyne, and rearrangement with TMS—N₃ effected conversion to the substituted tetrahydroisatoic anhydride (**130**), and subsequent treatment with formamidine acetate yielded compound (**131**). The substituents at the 6,7-positions of compound (**131**) were not amenable, however, for annelation of an imidazole.

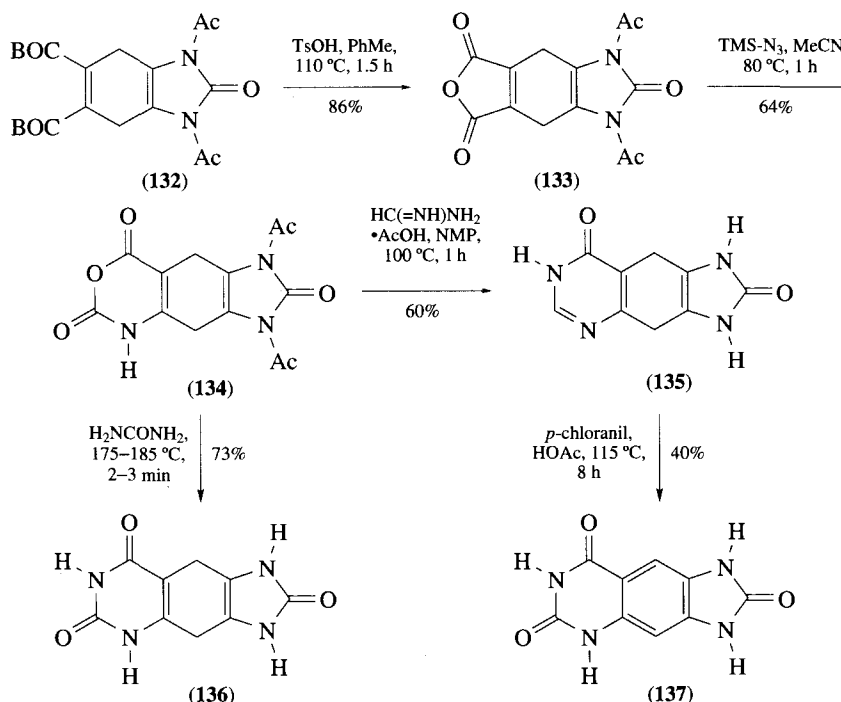


Scheme 14

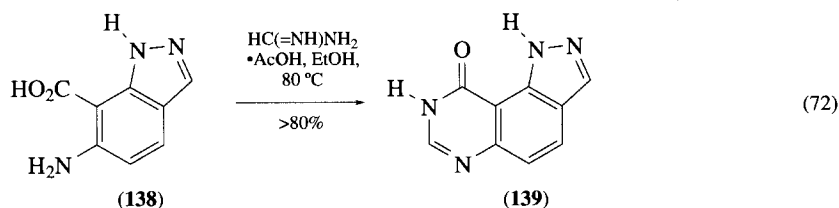
Since the methodology for annelating the pyrimidine ring was already in place, an alternative route of constructing the dihydrobenzimidazole unit prior to addition of the pyrimidine ring was selected (Scheme 15). When the substituted dihydrobenzimidazolinone (**132**) (prepared in 77% overall yield from 1,3-diacetyl-4,5-dimethylimidazolin-2(1*H*)-one via a $4\pi + 2\pi$ cycloaddition route) was heated with a catalytic amount of TsOH in benzene or toluene, two equivalents of isobutylene and one equivalent of H₂O were lost, and anhydride (**133**) deposited in 85% yield when the solution was cooled. A Curtius rearrangement was carried out with an excess of TMS—N₃ in refluxing MeCN to give the substituted dihydroisatoic anhydride (**134**). Conversion to the dihydro-*lin*-benzopurinedione (**135**) was possible if a solution of the precursor (**134**) in NMP was deoxygenated prior to the addition of formamidine acetate and heated at 100 °C (1 h). Compound (**134**) proved to be useful for the synthesis of 4,9-dihydro-*lin*-benzouric acid (**136**): brief reaction with urea in a melt at $180 \pm 5^\circ\text{C}$ gave (**136**) in 73% yield. It was possible to aromatize the central ring of compound (**135**) by heating with *p*-chloranil in glacial AcOH: the product, *lin*-benzouric acid (**137**), had been identified previously as the final enzymatic oxidation product of *lin*-benzohypoxanthine (and *lin*-benzoxanthine) with xanthine oxidase.

The substituted indazole (**138**), an intermediate in the synthesis of *prox*-benzoisallopurinol (**139**), suffered extensive decarboxylation to 6-aminoindazole when heated with formamide at 180 °C in an attempt at direct synthesis. This difficulty was eliminated by heating the acid (**138**) with excess formamidine acetate in EtOH giving compound (**139**), and the extended analogue of isoallopurinol, in >80% yield (Equation (72)). The generality of this reaction with respect to substituted isatoic anhydrides and anthranilic acids was demonstrated by the synthesis of a variety of substituted quinazolin-4(3*H*)-ones <86JOC616>.

A convenient synthesis (Scheme 16) of *lin*-benzopurines through a common intermediate has been developed <87JOC2933>. 5,6-Dimethylbenzimidazole (**140**) was oxidized by KMnO₄ to benzimidazole-5,6-dicarboxylic anhydride (**141**) (48%) and conversion to 1-acetylbenzimidazole-5,6-dicarboxylic anhydride (**142**) (93%) was effected by heating with Ac₂O. The five-membered cyclic anhydride was then enlarged to a six-membered oxazinedione ring by treatment with TMS—N₃. The mixture of 1- and 3-acetylimidazo[4,5-*g*]-7,5-benzoxazine-6,8(5*H*)-diones (**143**) was then used directly as the pivotal intermediate for the synthesis of *lin*-benzohypoxanthine (**144**), *lin*-benzoxanthine (**145**), *lin*-benzoguanine (**146**), and *lin*-benzoadenine (**147**). Formamidine acetate in DMF or Cellosolve was used to convert (**143**) to imidazo[4,5-*g*]quinazolin-8(7*H*)-one (**144**) in 86% overall yield from (**142**). Fusion with urea produced imidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (**145**) in



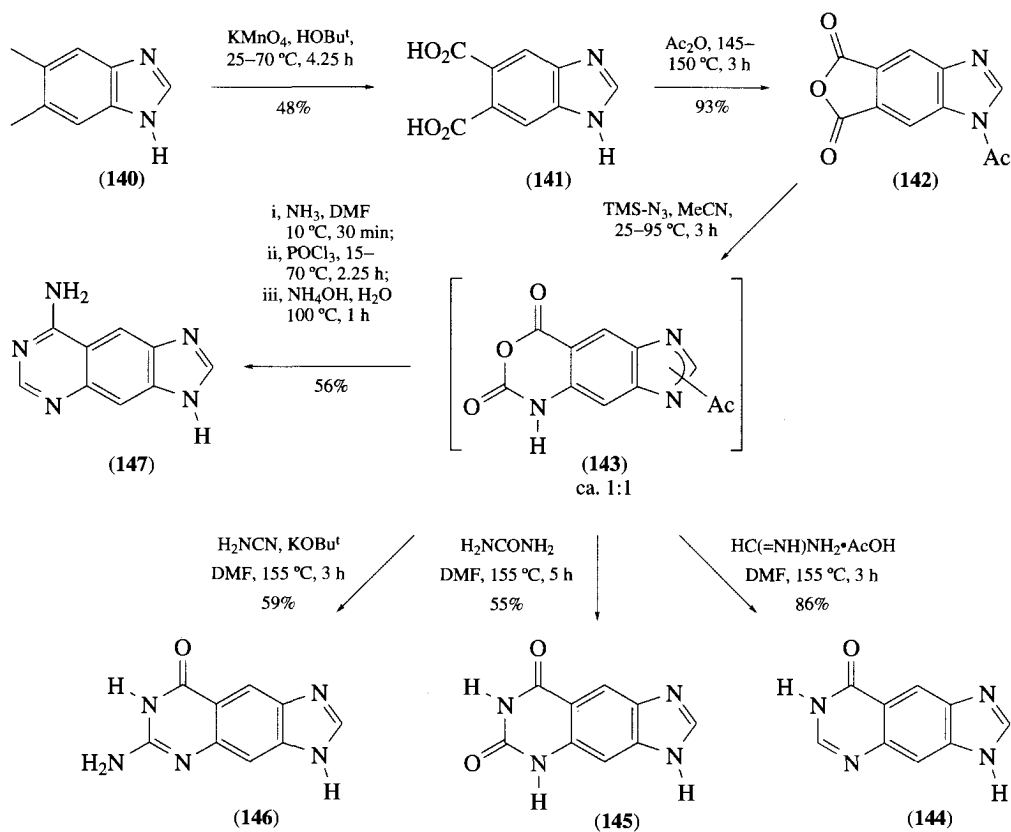
Scheme 15



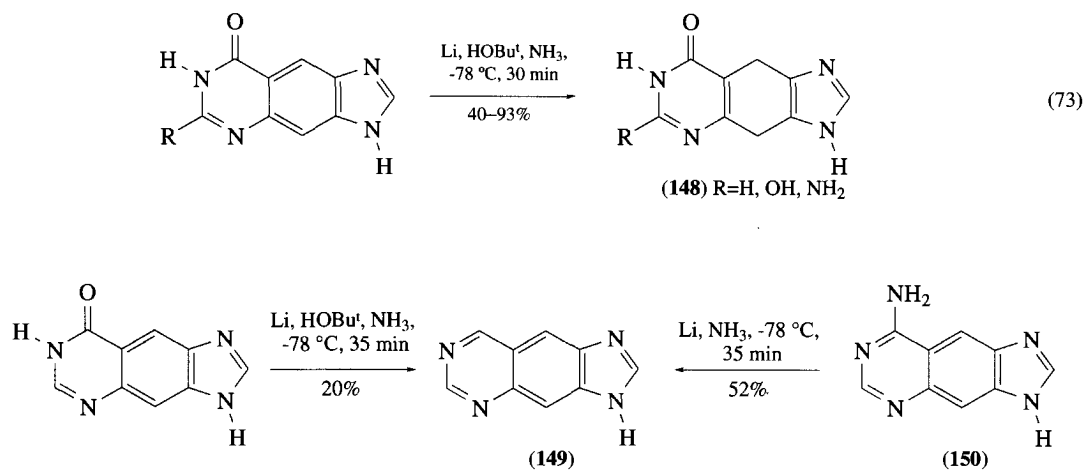
an overall yield of $\geq 55\%$. Upon treatment with cyanamide and KOBu^t in DMF 8-aminoimidazo[4,5-*g*]quinazolin-8(7*H*)-one (**146**) was obtained (59% overall yield). Direct conversion of the intermediate (**143**) to 8-aminoimidazo[4,5-*g*]quinazoline (**147**) (56% overall yield) was accomplished by sequential treatment with: (i) anhydrous NH_3 in anhydrous DMF; (ii) POCl_3 ; and (iii) concentrated NH_4OH .

The selective reduction of the central ring of *lin*-benzopurines by means of excess lithium in liquid NH_3 containing one equivalent of HOBu^t gave the 4,9-dihydro-*lin*-benzopurines (**148**) (Equation (73)) [88JOC3873]. Although *lin*-benzohypoxanthine gave 4,9-dihydro-*lin*-benzohypoxanthine (**148**; $\text{R} = \text{H}$) as the major product (40%), it was accompanied by *lin*-benzopurine (**149**) (20%) (Scheme 17). The reduction of *lin*-benzoadenine (**150**) with excess Li in NH_3 (heterogeneous) at -78°C yielded *lin*-benzopurine (**149**) almost exclusively (by TLC analysis). An attempt to prepare 4,9-dihydro-*lin*-benzoadenine (**154**) by P_2S_5 conversion of 4,9-dihydro-*lin*-benzohypoxanthine (**151**) to 4,9-dihydro-8-thioimidazo[4,5-*g*]quinazoline (**152**), methylation to 4,9-dihydro-8-(methylthio)imidazo[4,5-*g*]quinazoline (**153**), and displacement of the 8-SMe group with NH_3 failed in the last step (Scheme 18). However, it was possible to obtain 4,9-dihydro-*lin*-benzoadenine (**154**) by reduction of compound (**150**) with Li in MeNH_2 and HMPT at -6.5°C (Equation (74)).

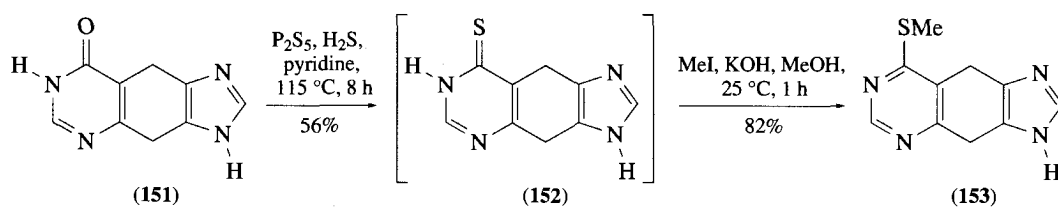
The synthesis of 3,7-dimethylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione and imidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione, the 1-methyl and 1,9-dimethylated versions (**155**) of *lin*-benzoxanthine, respectively, has been achieved using an approach (Equation (75)) based upon an imidazole ring assembly on 7-chloro-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione, effected by treatment with NH_3 or MeNH_2 followed by reductive cyclization in HCO_2H [84JHC791]. In this same investigation, the 9-(formylamino)-*lin*-benzoxanthine derivatives (**156**) were obtained from 7-hydrazino-6-nitroquinazoline-2,4(1*H*,3*H*)-dione precursors.



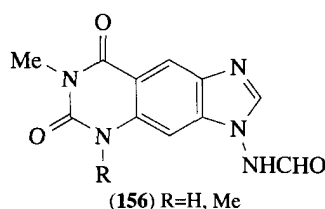
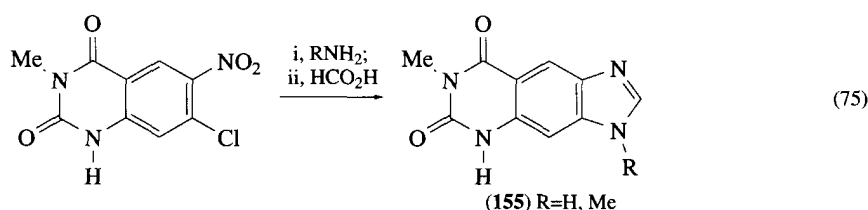
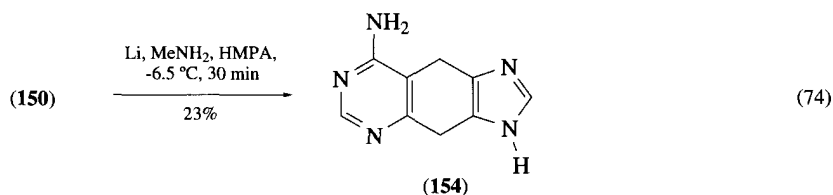
Scheme 16



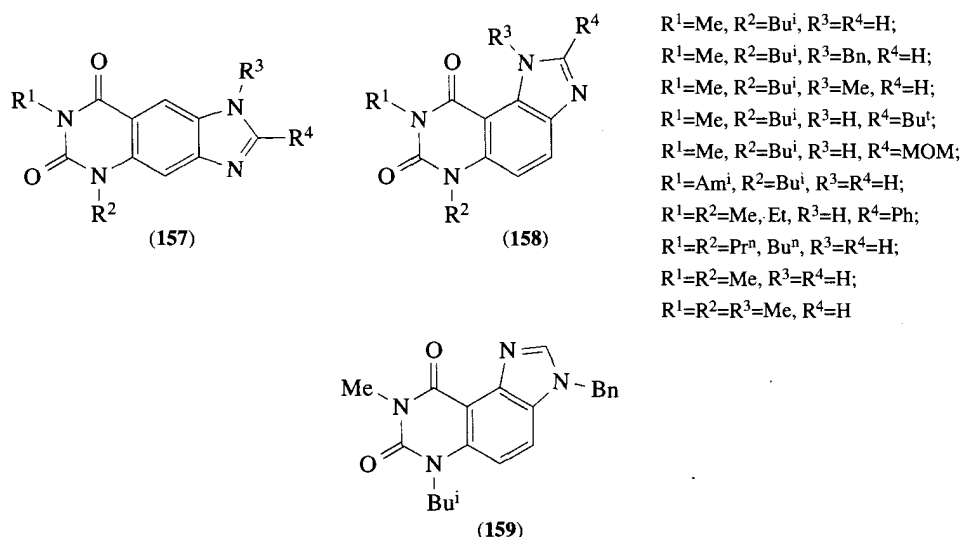
Scheme 17



Scheme 18

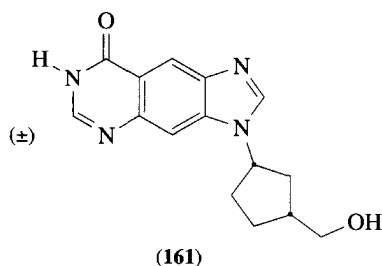
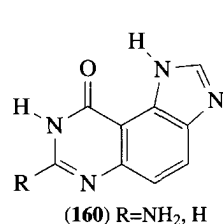


Using the same general approach, a large number of *lin*-(157) and *prox*-(158)–(159) benzo-separated analogues of theophylline, caffeine, isocaffeine, and the potent cyclic nucleotide phosphodiesterase (PDE) inhibitor 3-isobutyl-1-methylxanthine (IBMX), among others, were prepared as potential PDE inhibitors or as potential A₁ or A₂ adenosine receptor antagonists <86JMC972, 89JMC2247>. For the most part, their syntheses utilized 7- or 5-chloro-6-nitroquinazoline-2,4(1*H*,3*H*)-dione as precursors, and an amination/reductive cyclization sequence for imidazole ring construction.

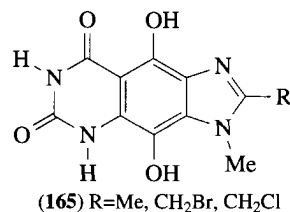
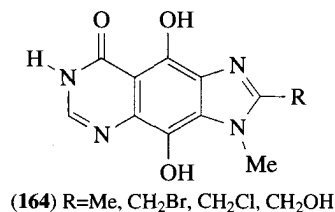
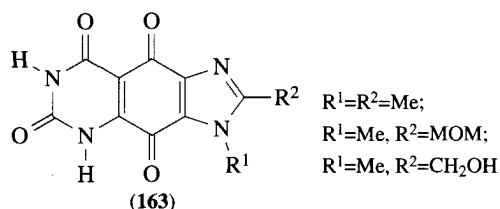
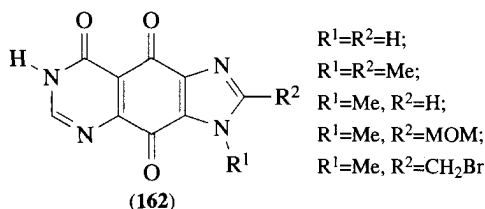


The first synthesis of *prox*-benzoguanine (160; R = NH₂) was accomplished by using a similar sequence on 2-amino-5-chloro-6-nitroquinazolin-4(3*H*)-one <86JOC4067>. This same report described a simplified preparation of *prox*-benzohypoxanthine (160; R = H) involving the catalytic hydrogenation of 3-amino-2,6-dinitrobenzonitrile in HCO₂H. Compound (161), the carbocyclic derivative of *lin*-benzo-separated 2',3'-dideoxyinosine (DDI, a potent anti-HIV antiviral drug) was prepared in two steps from 7-chloro-6-nitroquinazolin-4(3*H*)-one and the appropriate racemic amino-cyclopentane <89MI 722-01>.

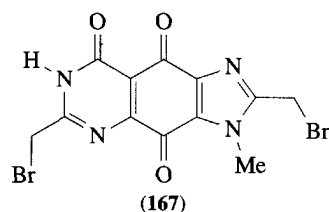
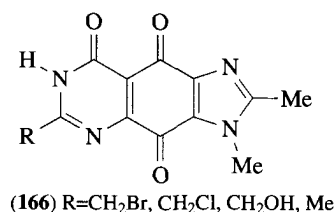
lin-Benzohypoxanthine derivatives in the form of the alkylated imidazo[4,5-*g*]quinazoline-



4,8,9(3*H*,7*H*)-triones (**162**) have been synthesized by Fremy radical oxidation of 4-amino-imidazo[4,5-*g*]quinazolines or by nitrogen dioxide oxidation of their 4,9-unsubstituted derivatives <86JOC4784, 87B7355>. As neither approach afforded the desired *lin*-benzoxanthine derivatives (**163**), these imidazo[4,5-*g*]quinazoline-4,6,8,9(3*H*,5*H*,7*H*)-tetrone were obtained instead by xanthine oxidase-mediated oxidation of the corresponding triones (**162**). A 48% HBr-mediated reduction was utilized to generate the 4,9-dihydroxylated forms (**164**) and (**165**) of *lin*-benzohypoxanthine and *lin*-benzoxanthine. These could be re-oxidized to their benzoquinone form by treatment with DDQ.

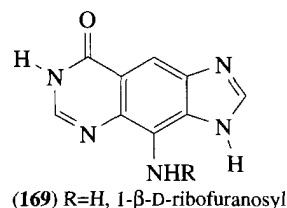
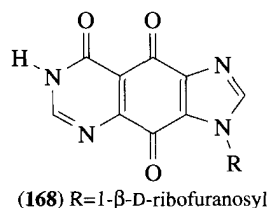


For all those *lin*-benzohypoxanthine and *lin*-benzoxanthine quinone derivatives possessing a leaving group at the 2α position described above, the requisite 3-methylimidazo[4,5-*g*]quinazoline precursors were synthesized by annelation of an imidazole ring onto 6-amino-7-(methyl-amino)quinazolin-4(3*H*)-one by acylative cyclization. By contrast, the precursors to those *lin*-benzohypoxanthine quinone derivatives (**166**) possessing a leaving group at the 6α position were synthesized by annelation of a pyrimidine ring onto ethyl 6-(α-methoxyacetamido)-2-(methoxymethyl)-1-methylbenzimidazole-5-carboxylate by aminative cyclization <89JOC3611>. Catalytic hydrogenation to the 7-amine then permitted the same Fremy's salt-mediated oxidation described above to be used in the generation of the imidazo[4,5-*g*]quinazoline-4,8,9(3*H*,7*H*)-trione. By this same synthetic route, the 2,6-bis(bromomethyl)-3-methyl-*lin*-benzohypoxanthine-4,9-quinone (**167**) was also prepared.

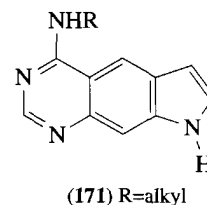
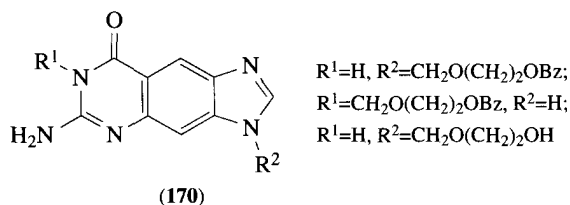


The preparation of *lin*-benzoinosine-4,9-quinone (**168**) was carried out by regioselective ribosylation of 4-nitroimidazo[4,5-*g*]quinazolin-8(3*H*,7*H*)-one followed by nitro group reduction, Fremy oxidation, and deacetylation <91JOC776>. 4-Amino-*lin*-benzohypoxanthine (**169**; R = H) was prepared (80%) by sodium dithionite reduction of 5-nitroimidazo[4,5-*g*]quinazolin-8(3*H*,7*H*)-one, but

the corresponding secondary amine riboside (**169**; R = 1- β -D-ribofuranosyl) deribosylated rapidly in water and could not be isolated.



As part of an investigation into modifications on the heterocyclic base of acyclovir (9-[(2-hydroxyethoxy)methyl]-9H-guanine (Zovirax) a potent anti-HSV antiviral drug, the *lin*-benzoguanine derivatives (**170**) have been prepared using a silylation/alkylation sequence conducted on *lin*-benzoguanine itself (85JMC982). Unfortunately, compound (**170**; R¹ = H, R² = CH₂O(CH₂)₂OH) did not show any inhibition of HSV-1, although it did exhibit some ability to compete with acyclovir for the binding site on the viral thymidine kinase. Finally, a 1995 communication describes the synthesis of certain *lin*-benzo-separated 7-deazaadenines (aminopyrrolo[3,2-*g*]quinazolines) (**171**) as ATP competitive inhibitors of the epidermal growth factor receptor (EGFR) (B-95MI 722-01).

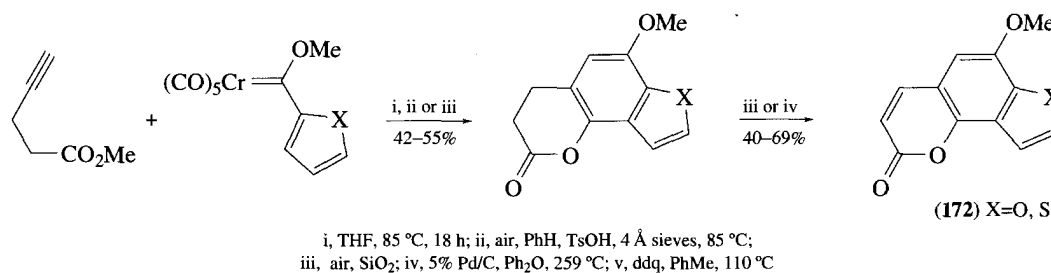


7.22.11.2 Furocoumarins and Furochromones

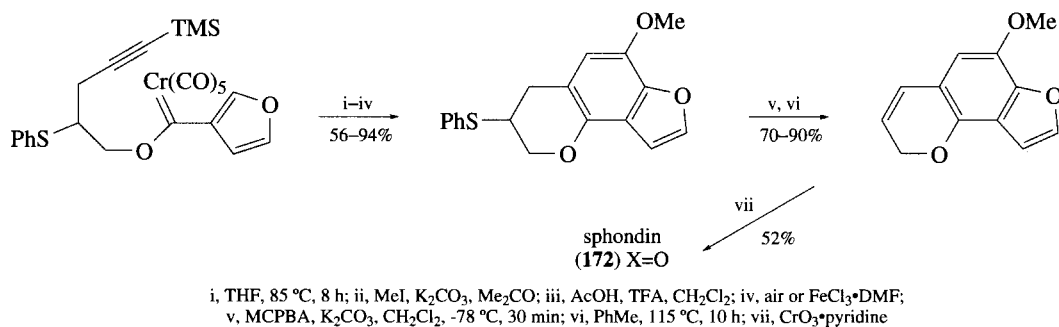
A general description of these compounds appears in Section 7.22.12.2.

7.22.11.2.1 Synthesis using chromium carbene complexes

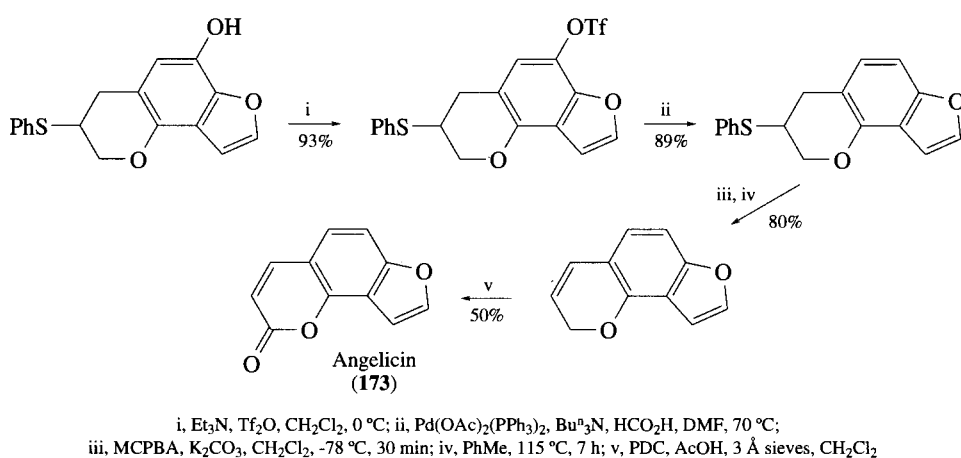
Wulff and co-workers have utilized chromium carbene complexes to synthesize nonlinear furocoumarins (87TL1381, 88JA7419, 88OM2346). The reactions of 2-furyl chromium carbene complexes with derivatives of pent-4-ynoic acid were utilized in the preparation of the naturally occurring compounds sphondin (**172**; X = O) and heratomin (Scheme 19). An analogous method using a 2-thienyl chromium carbene complex was employed to synthesize the unnatural thiosphondin (**172**; X = S). The use of a 3-furyl chromium carbene complex afforded another unnatural furocoumarin. Once the intermolecular approach to compounds (**172**; X = O, S) had been demonstrated to be general in nature, an alkyne was tethered to the 2-furyl complex to determine whether or not the reactions would occur in an intramolecular fashion. The reaction did take place, but in high yield only when a terminal trimethylsilyl group was resident on the alkyne moiety. This discovery enabled these investigators to develop convergent syntheses of sphondin (**172**; X = O) (Scheme 20) and angelicin (**173**) (Scheme 21).



Scheme 19



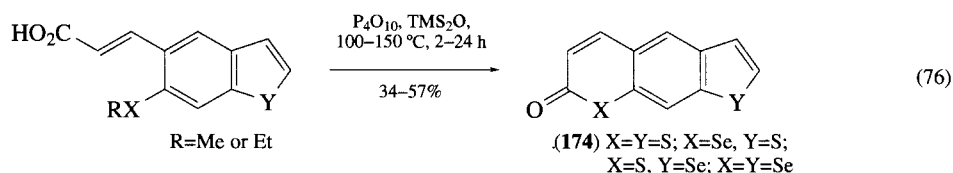
Scheme 20



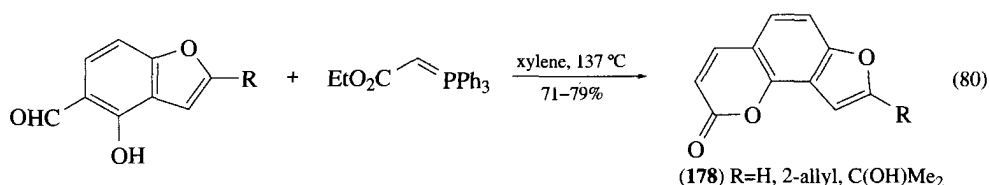
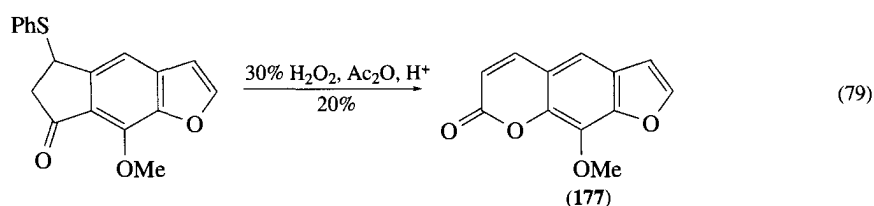
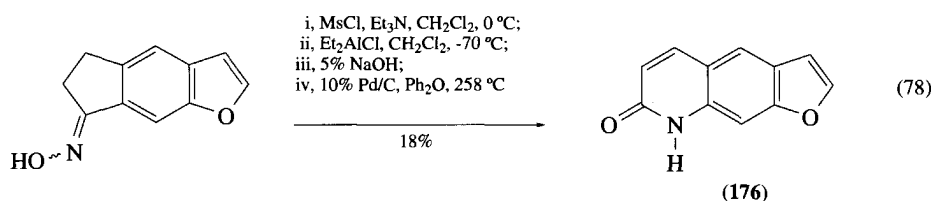
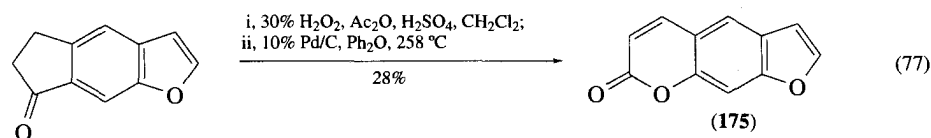
Scheme 21

7.22.11.2.2 Other methods

The last step in the synthesis of the sulfur- and selenium-containing psoralen analogues (**174**) (7*H*-thieno[3,2-*g*][1]benzothiopyran-7-one, 7*H*-seleno[3,2-*f*][1]benzothiophen-7-one, 2*H*-selenolo[3,2-*g*][1]benzothiopyran-2-one, and 7*H*-selenolo[3,2-*g*][1]benzoselenopyran-7-one) was the polyphosphoric acid silyl ether (PPSE)-mediated cyclization of benzo[*b*]-thiophenes or selenophenes shown in Equation (76) <92H(34)1119>.



Kanematsu and co-workers found that furo[2,3-*f*]indan-7-one could be converted to psoralen (**175**) using a Baeyer–Villiger oxidation followed by dehydrogenation (Equation (77)) <84JA6735>. Conversion of the indanone to its oxime followed by a Beckmann rearrangement and dehydrogenation was used to produce 8-azapsoralen (**176**) (Equation (78)). While a methoxylated furo[2,3-*f*]indan-7-one did not afford methoxsalen under the same conditions, 8-methoxy-3-(phenylthio)indan-7-one did produce the desired furocoumarin (**177**) (20%) under Baeyer–Villiger oxidation conditions (Equation (79)) <94TL9617>. Several furocoumarin natural products substituted at the 2-position (**178**; R = H, 2-allyl, C(OH)Me₂) have been prepared via a Wittig reaction using a 4-hydroxybenzofuran-5-carbaldehyde (Equation (80)) <95T3087>.

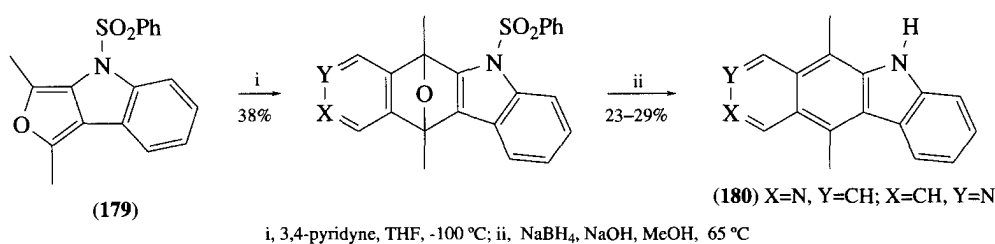


7.22.11.3 Ellipticines

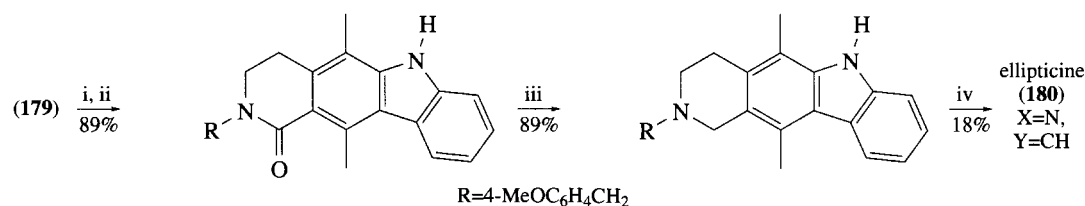
A general description of these compounds appears in Section 7.22.12.3.

7.22.11.3.1 Synthesis using cycloaddition reactions

Gribble and co-workers utilized the cycloaddition of the suitably substituted furo[3,4-*b*]indole (179) with 3,4-pyridyne (generated *in situ* from 3-chloro-4-iodopyridine and an alkyl lithium reagent) followed by a tandem oxygen-bridge extrusion/deprotection to afford a mixture of ellipticine and isoellipticine (Scheme 22) <84JOC4518>. MO calculations supporting a regioselective HOMO/LUMO interaction between (179) and an acrylate led these investigators to the route shown in Scheme 23 in which reaction of compound (179) and a suitably protected 5,6-dihydropyridone gave a single carbazole pyridone product which gave ellipticine after amide reduction and palladium-catalyzed dehydrogenation/debenzylation <90TL1081, 92JOC5878>.



Scheme 22

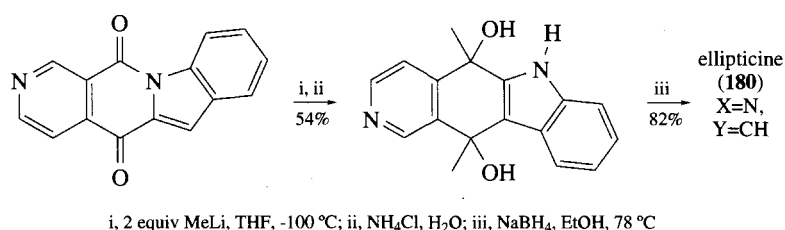


i, *N*-(4-methoxyphenyl)-5,6-dihydro-2-pyridone, TMS-OTf, CH_2Cl_2 ; ii, NaHCO_3 , H_2O ; iii, LAH, THF; iv, Pd/C

Scheme 23

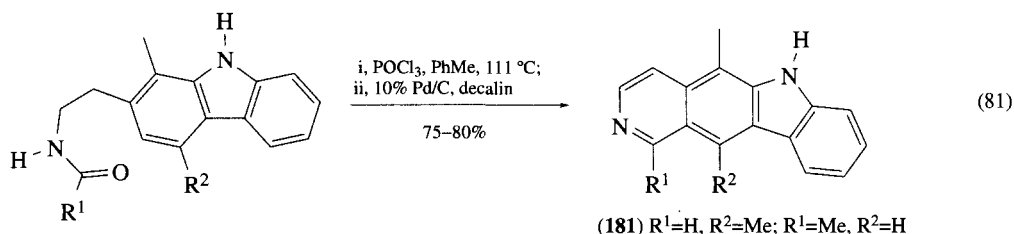
7.22.11.3.2 Other methods

Saulnier and Gribble used a tetracyclic keto lactam to prepare ellipticine by treatment with MeLi followed by NaBH_4 reduction of the resultant rearranged tetracyclic diol (Scheme 24) <82JOC2810>. Modifications of this method have been used to prepare several analogues of ellipticine <83JOC2690, 83TL3831, 85JOC5451, 86MI 722-01, 89JOC3264, 92JOC5891>.

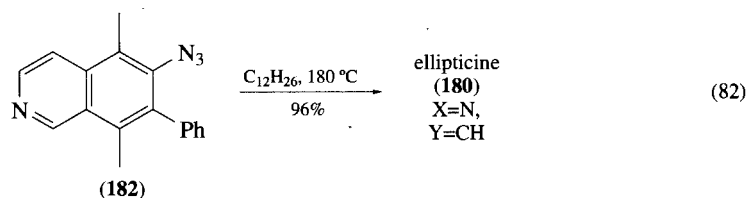


Scheme 24

Ellipticine and olivacine have both been synthesized via a Bischler–Napieralski cyclization and subsequent aromatization of alkylamidocarbazoles, as shown for the preparation of compounds (181) (Equation (81)) <90JOC4528>.



6-Azido-5,7-dimethyl-6-phenylisoquinoline (182) has been used to prepare ellipticine via a nitrene insertion reaction (Equation (82)) <89TL297>.

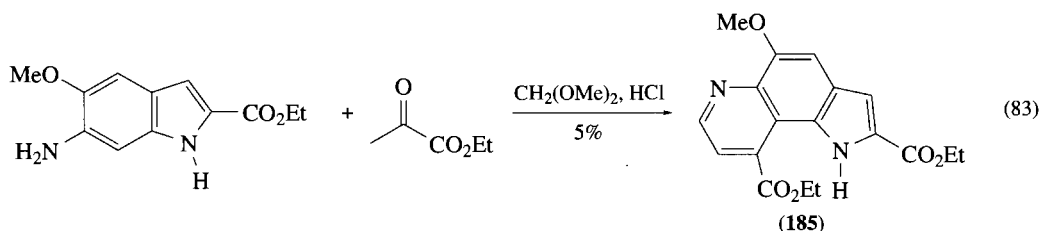
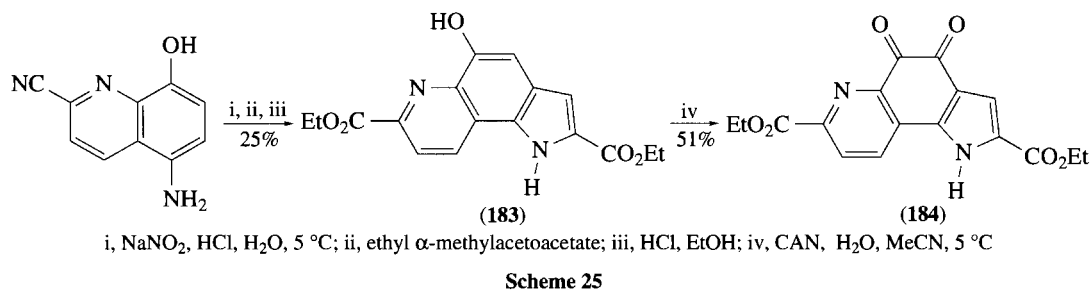


7.22.11.4 Pyrroloquinolinequinone and Related Compounds

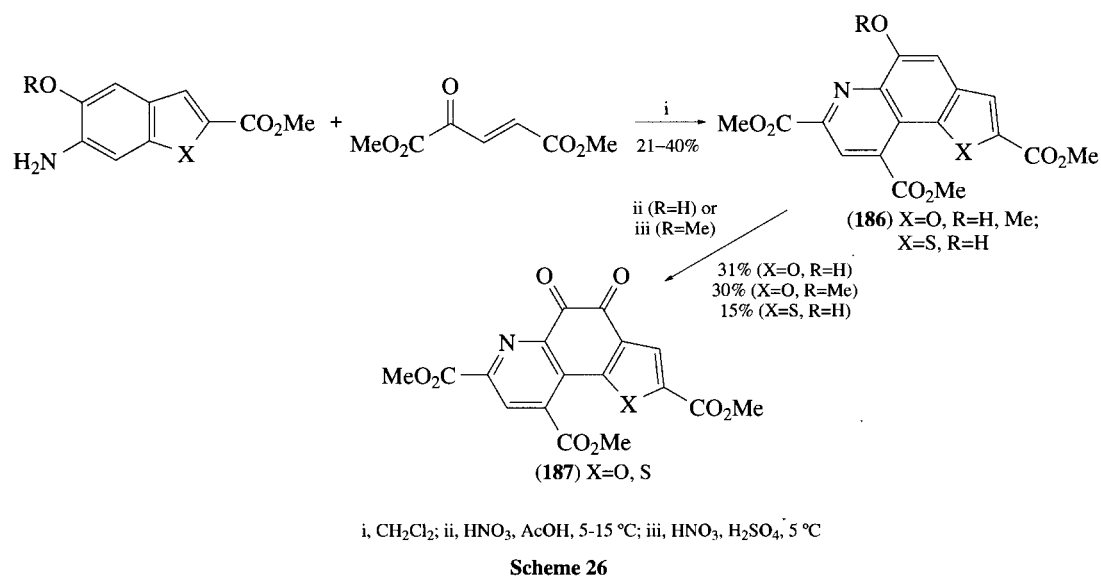
A general description of these compounds appears in Section 7.22.12.4. PQQ is also known as methoxatin.

Fischer indole cyclization and transformation of a nitrile to an ester (Pinner synthesis) to yield diethyl 5-hydroxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,7-dicarboxylate (183) was performed in one step by

treatment of either a 5-quinolylylhydrazone or an acetylated azo precursor with saturated ethanolic HCl (Scheme 25) <85JA7198, 87JOC1942>. Compound (**183**) was then oxidized with can to afford the decarboxymethoxatin (**184**), an analogue of PQQ. Although the yield of product was very low, a Doebner reaction was used as the key step in the preparation of diethyl 5-methoxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,9-dicarboxylate (**185**), which is the precursor to an isomeric decarboxymethoxatin (Equation (83)) <87JOC1942>. 7,9-Didecarboxymethoxatin has also been synthesized in order to compare its chemical (e.g., acid-base, electrochemical) properties to those of methoxatin <85JA3328>.



Furo- and thieno- analogues (**187**; X = O, S) of PQQ have been prepared via the cyclization of a 6-amino-5-hydroxybenzofuran or benzothiophene with the dimethyl ester of 4-ketoglutaconic acid, followed by oxidation (HNO₃) of the triesters (**186**) to the *ortho*-quinones (Scheme 26) <94HCA100>.



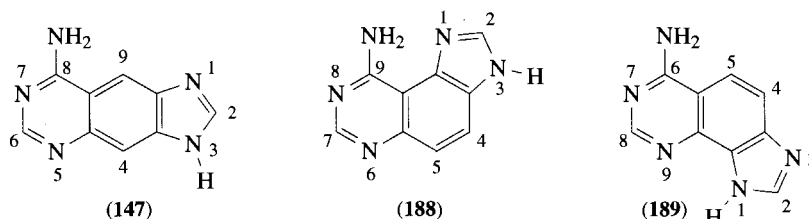
7.22.12 IMPORTANT COMPOUNDS AND APPLICATIONS

7.22.12.1 Benzo-separated Purines

Leonard and co-workers have synthesized *de novo* analogues of the purines, and especially of adenine, that differ from the natural bases, ribonucleosides, or ribonucleotides by defined dimen-

sional changes. With these dimensional probes, it is possible to assess the size of the space available or required for the purine (e.g., adenine) moiety in enzyme-coenzyme binding sites. In the best cases, the dimensional probes also serve as fluorescent probes. Several reviews on the subject covering the literature through the mid-1980s are available <82ACR128, B-84MI 722-01, 84PAC1025, 85MI 722-01, 86T1917>. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.1.

The initial synthetic target was 8-aminoimidazo[4,5-*g*]quinazoline (**147**), to which Leonard and co-workers gave the trivial name *lin*-benzoadenine. The prefix refers to the linear disposition of the three rings in compound (**147**), and the numbering is as shown. The formal insertion of a spacer into the center of the adenine ring system, in this case a benzene ring (actually four additional carbon atoms), stretches the natural adenine linearly by 2.4 Å, the width of the benzene ring known accurately from many x-ray structure determinations. The stretched-out analogue (**147**) has the advantage of retaining unobstructed the normal binding sites, e.g., N-1, N⁶, and N-7 of adenine. Similar to *lin*-benzoadenine (**147**) in containing the binding sites analogous to the 1,N⁶ binding sites found in adenine and related nucleosides and nucleotides are *prox*-benzoadenine (**188**) and *dist*-benzoadenine (**189**). In the abbreviated nomenclature, *prox* for proximal and *dist* for distal refer to the spatial relationship of the amino groups to the imidazole ring in the respective compounds. The rings are angulated within a common plane. The term benzo presents no ambiguity since only when the ring is central is it devoid of nitrogen and accordingly 'benzo'. The structural differences between (**147**), (**188**), and (**189**) reside in the spatial relationships of the pyrimidine and imidazole rings with respect to the central benzene ring and in the nature of the internal hydrogen bonding likely to occur in isomers (**188**) and (**189**). They are not actually *dimensional probes* since they also involve orientational changes.

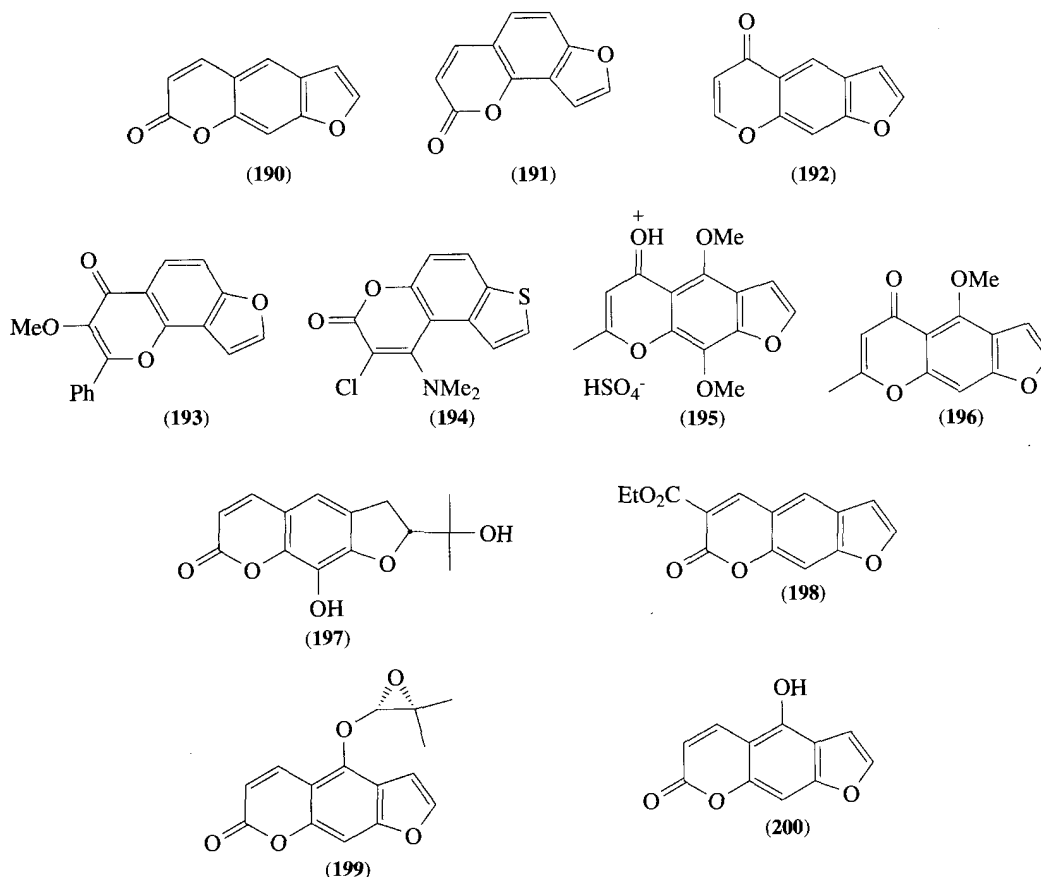


The concept of dimensional probes of binding and activity has stimulated the synthesis of analogues of (**147**), (**188**), and (**189**) that differ from natural bicyclic bases, ribonucleosides, and ribonucleotides by defined dimensional changes. These have found application in numerous biochemical investigations, including ones of the enzymes pyruvate kinase and *Escherichia coli* DNA polymerase I <84B3868>, adenosine deaminase (calf intestinal mucosa) and xanthine oxidase (butter-milk) <88JOC3873>, the cGMP-dependent protein kinase <85B1122, 88B1988>, and the catalytic subunit of cAMP-dependent protein kinase <83B2347, 83B6310, 84B4350, 88B1988>. Benzo-separated purines have been developed as potential PDE inhibitors <86JMC972>, potential A₁ or A₂ adenosine receptor antagonists <89JMC2247>, as reductive alkylators <86JOC4784, 87B7355, 89JOC3611, 91JOC776>, as potential antiviral agents <85JMC982, 89MI 722-01>, and as ATP competitive inhibitors of the epidermal growth factor receptor (EGFR) <B-95MI 722-01>.

7.22.12.2 Furocoumarins and Furochromones

The furocoumarins, both linear (**190**) and bent (**191**), and furochromones (**192**) are photoactive compounds which are often utilized in conjunction with UV light in the treatment of skin disorders such as psoriasis and vitiligo <90MI 722-01, 91MI 722-01>. As a result of this interest, many x-ray crystal structure determinations of furocoumarin and furochromone analogues have been made. Compounds (**193**)–(**200**) are some of these <86AX(C)1849, 87AX(C)2369, 88AX(C)676, 88AX(C)1475, 89AX(C)1520, 90AX(C)437, 90AX(C)2146, 91AX(C)2144>. Many are naturally occurring substances. Some of the linear furocoumarins, or psoralens as they are often called, have been found to be highly mutagenic and/or carcinogenic, perhaps often as a consequence of their ability to intercalate between base pairs in DNA and form double-stranded crosslinks by undergoing two [2 + 2] cyclo-photoadditions per molecule. As a result, research on the family of compounds known as the bent

furocoumarins has taken on new importance, since these derivatives are not as able to crosslink DNA. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.2.

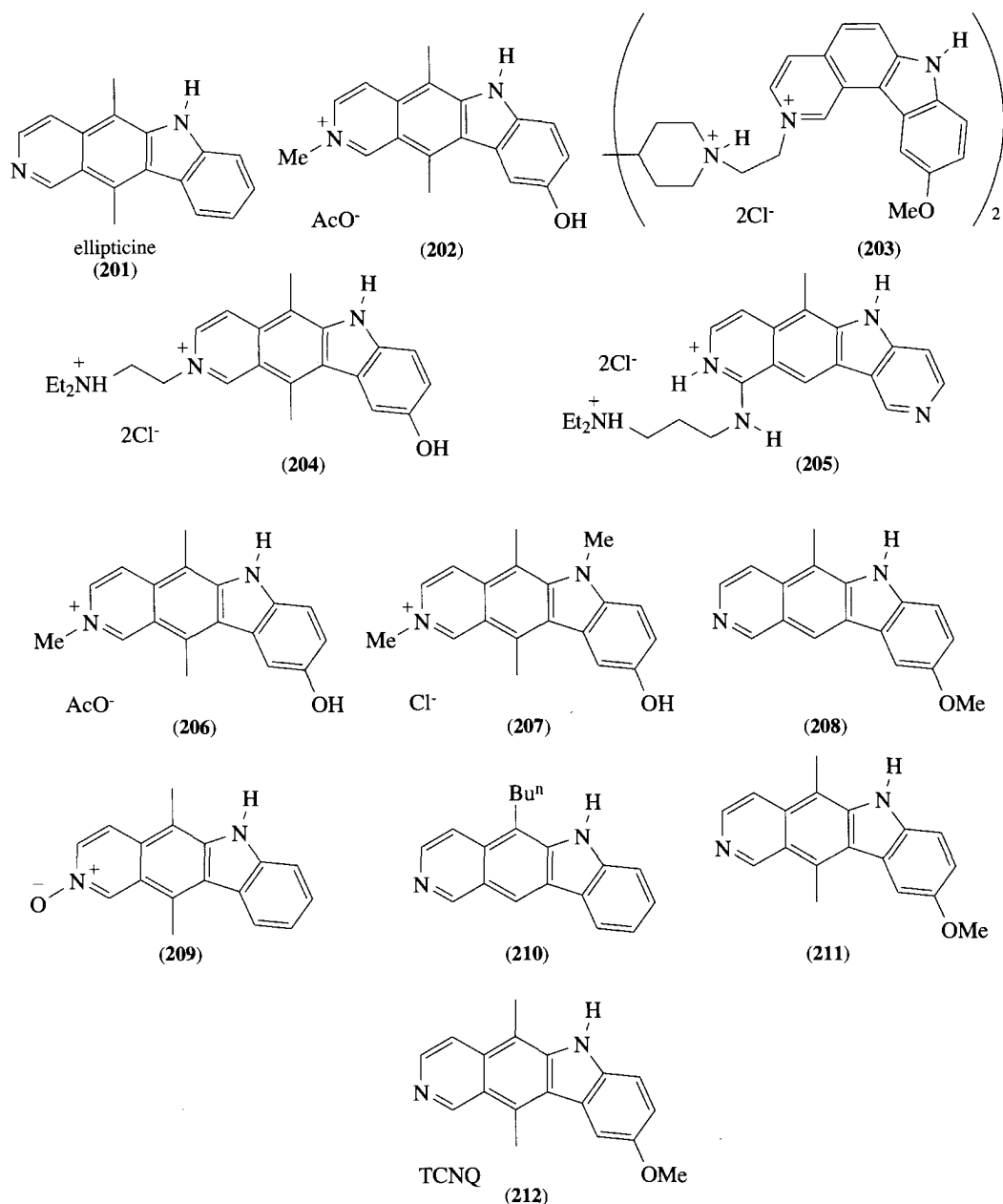


7.22.12.3 Ellipticines

Ellipticine (201) and its analogues have been a strong focus of investigation ever since the discovery that the parent compound showed good antitumor activity (for reviews, see <85H(23)1277, B-90MI 722-02, 91SL289>). Since that initial discovery, some of the ellipticine derivatives that have been used in chemotherapeutic clinical trials include elliptinium (202), ditercalinium (203), datelliptium (204), and pazellipticine (205). Because of the mixed results seen up to 1990, though, it is evident that additional structural modification will be required before any ellipticine derivative finds wide use as a chemotherapeutic agent. To support some of the ongoing efforts to improve upon the activity of these compounds, x-ray crystal structures of several ellipticine analogues and related compounds have been determined. Compounds (206)–(212) are some of these <83AX(C)631, 84AX(C)1871, 88AX(C)386, 88AX(C)1797, 88AX(C)2123, 88AX(C)2126>. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.3.

7.22.12.4 Pyrroloquinolinequinones and Related Compounds

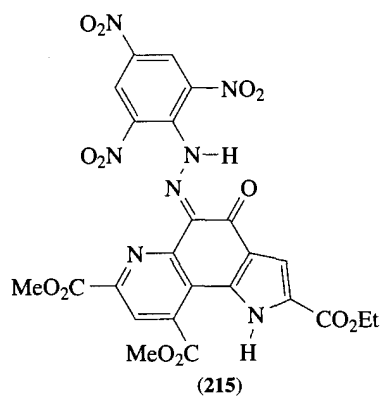
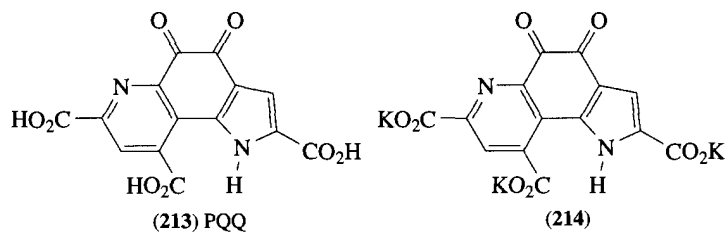
Pyrroloquinolinequinone (213) (2,7,9-tricarboxy-1*H*-pyrrolo[2,3-*f*]quinoline-4,5-dione, PQQ) (trivial name: methoxatin) has been identified as a co-factor in many enzymes, including those that oxidize MeOH to HCHO in methylotrophic and autotrophic bacteria. Quinoproteins appear in mammalian systems as well, and methoxatin itself (213) has even been identified as an inhibitor of HIV-1 reverse transcriptase (for PQQ reviews, see <91MI 722-02, 95MI 722-02>). Interest in under-



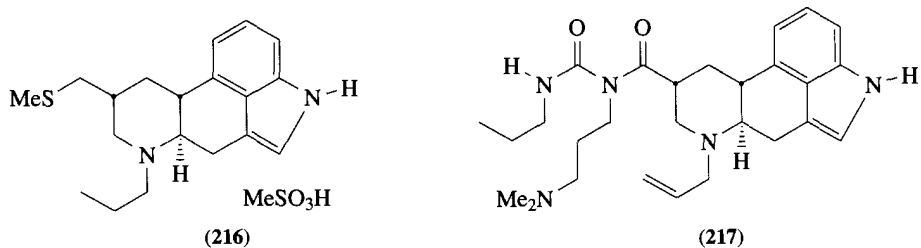
standing the co-enzymic behavior of PQQ has led investigators to determine the x-ray crystal structure of its tribasic salt (**214**) <93AX(C)2093> and the 1,3,5-trinitrophenylhydrazine (**215**) of a triester derivative <85AX(C)89>. The chemistry of PQQ (**213**) is noteworthy in that nucleophilic attack at the quinone ring occurs most often at C-5 instead of at C-4 <89MI 722-02, 93HCA1674, 95JA3278>. ¹³C NMR and IR spectroscopic data support the contention that the electrophilicity at C-4 is diminished relative to that at C-5 by conjugative interaction with the pyrrole ring nitrogen <94HCA100>. A theoretical study in 1995 employing semiempirical (AM1, PM3) and *ab initio* (3-21G, 6-31G, and 6-31G**) procedures has been conducted to examine three possible molecular mechanisms for the oxidation of MeOH by PQQ (**213**) <95JA8807>. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.4.

7.22.12.5 Ergolides

Pergolide mesylate (**216**) (Permax) <89MI 722-03> and cabergoline (**217**) (Dostinex) <94MI 722-01> are an antiparkinsonian and antiprolactin agent, respectively, with pyrrolo[3,4-*g*]quinoline-based



tetracyclic structural ergolide frameworks. They are both potent, long-acting dopamine agonists, and the latter is in clinical trials for Parkinson's disease and other maladies.



7.23

Tricyclic Systems: Central Carbocyclic Ring with Fused Six-membered Rings

KENNETH J. NICHOL

Formerly of Boots Pharmaceuticals, Nottingham, UK

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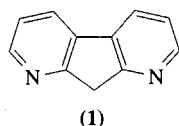
7.23.1 INTRODUCTION

The group of compounds represented by this chapter title embraces a very wide range of possible ring systems. Even the list of 160 compounds in the *Ring Systems Handbook* (B-93MI 723-01) is not

exhaustive. In reality, many of the possible structures are unknown in the chemical literature, some quite surprisingly so. This review provides examples of compounds with central four-, five-, six-, seven-, and eight-membered rings; no larger central rings have been found. Much of the knowledge of compounds in these categories has arisen from studies on the synthesis and metal-chelating properties of cyclic analogues of 2,2'-bipyridyl and from the search for improved medicinals and agrochemicals. This is also a factor in determining the high proportion of nitrogen-containing rings; in compounds with four- and five-membered central rings the only heteroatoms are nitrogen. The synthesis, reactions, and properties of compounds with six-membered central rings are mainly extensions of those of the corresponding bicyclic benzo-hetero systems.

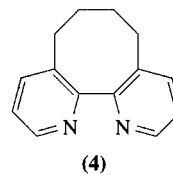
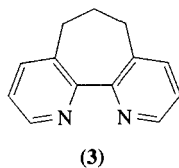
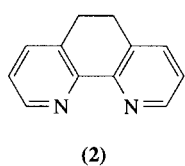
Although this category of compounds has not been previously reviewed as a group, comprehensive reviews exist for phenanthrolines <78AHC(22)1>, 1,10-phenanthroline <94CRV327>, and pyrido[2,3-*g*]quinoline and pyrido[3,2-*g*]quinoline <79WCH235>. The volume on six-membered nitrogen heterocycles with three condensed rings <58CHE14, 58CHE386, 58CHE457> includes examples of pyrido-, pyrazino-, and pyridazo-fused rings. The chemistry and properties of pyranochromenes are extensively covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-1) and are not reviewed further here.

Systematic IUPAC nomenclature is set aside in this chapter in the cases of compounds with four- and five-membered central rings in favour of the "aza" convention. For the sake of clarity compound (1), for example, is described as 1,8-diazafluorene instead of 9*H*-cyclopenta[1,2-*b*:4,3-*b'*]dipyridine.



7.23.2 THEORETICAL METHODS

Conformational analysis of the 3,3'-bridged 2,2'-bipyridyls (2), (3), and (4) has been performed using the MM-V4 force field method with comparisons to the corresponding carbocyclic compounds <90JOC2637>. Results showed that the bridged bipyridyls are more flexible than their carbocyclic counterparts; the cyclo-octadiene (4), surprisingly, proved to have a higher interconversion energy barrier, that is more rigidity, than compounds (2) or (3).



The ionization potentials, singlet and triplet excited states, and frontier molecular orbitals of 1,4-, 1,8-, and 4,5-diazafluorenones were investigated by the all-valence-electrons INDO/S-CI method. Calculated molecular properties were found to be in accordance with experimental results <81JST(86)1>.

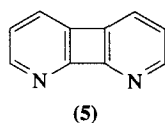
A modification of Dewar and Harget's method has been employed to predict the electronic spectra of a range of heterocyclic compounds, including pyrido[2,3-*g*]quinoline and all known phenanthrolines, and give satisfactory agreement with experimental values <82IJC(B)334>.

7.23.3 EXPERIMENTAL STRUCTURAL METHODS

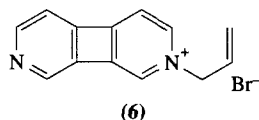
7.23.3.1 X-ray Methods

The x-ray analysis of 1,8-diazabiphenylene (5) indicates a planar structure with two molecules per unit cell. The heterocyclic ring angles are distorted in comparison with pyridine

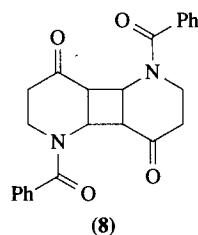
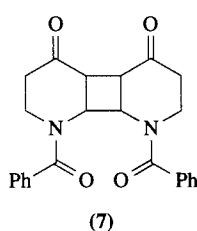
(C—N—C = 112.9°) with consequent reduction in basicity. Compound (5) has a pK_a of 1.92, whereas 2,2'-bipyridyl has pK_a 4.33 <84CJC2235>.



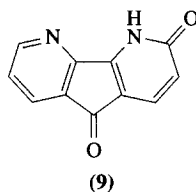
In the case of 2,7-diazabiphenylene the molecules are arranged in a random manner in the cell making structure confirmation uncertain. However, the mono *N*-allyl quaternary salt (6), gave results confirming the structure as the 2,7-compound. Bond lengths in both hetero-rings differ from those in pyridine and pyridinium rings. The 4a–4b and 8a–8b bonds in the four-membered ring are essentially single (1.502 and 1.499 Å) <80JCR(M)2911>.



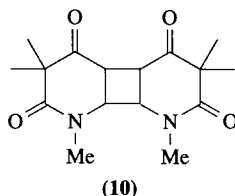
The “head-to-head” and “head-to-tail” configuration of the isomeric ketones (7) and (8) were discernable. A slight distortion of the cyclobutane ring in compound (7) suggests an imbalance in steric strain <81CJC3136>.



The colored by-product arising during the oxidation of 1,10-phenanthroline was found to have the structure (9) by examination of its sodium salt. Both oxygen groups were found to be directed out of the same side of the best plane through the molecule <92JCS(P1)1601>.



The photodimer (10) was shown to have the *trans-syn* configuration <88LA979>.

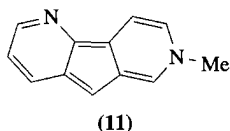


7.23.3.2 IR Spectroscopy

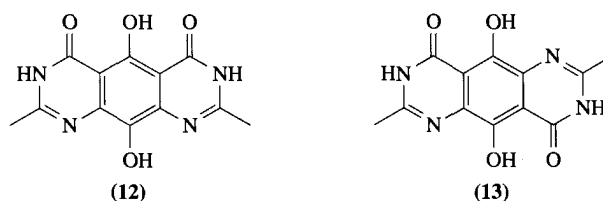
References to definitive studies on phenanthrolines are given in Summers' review <78AHC(22)1>. In many of the publications cited in this chapter, IR spectral observations are given as supporting evidence for structures by comparison with standard reference data.

7.23.3.3 UV and Visible Spectroscopy

1,5-, 1,8-, and 4,5-diazafluorenones all display $\lambda_{\max}$ at about 250 nm. <76CJC1870>. UV data for the pseudoazulenes derived from the methiodides of diazafluorenones shows that the $\lambda_{\max}$ displays a significant bathochromic shift in those compounds with an *o*-quinonoid structure in the nonmethylated ring, for example, as in compound (11) <79ZC374>.



The spectra of the hydroquinones (12) and (13) at various pH values provide evidence for their unusual stability to hydrolytic conditions <88JOC4209>.



7.23.3.4 Mass Spectrometry

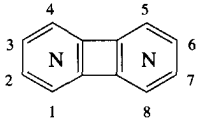
No specific study or data compilation of the mass spectra of diazabiphenylenes is available. Experimental figures for individual isomers are given in the references quoted in Table 1. The main peaks in the spectra correspond to loss of HCN and CH:CH. The EI spectrum of 4,5-diazafluoren-9-one <75JHC1023> and 9-methyl-4,5-diazafluoren-9-ol <78ZN(B)80> have been discussed in detail.

A comprehensive study and critical review of the MS of both diazabiphenylenes and diazafluorenes would be a valuable contribution in this area of chemistry. References to MS data on phenanthridines has been collected by Summers <78AHC(22)1>. MS data is given for many of the compounds in this chapter but largely as a property for reference and without critical analysis.

7.23.3.5 NMR Spectroscopy

The chemical shifts in ppm in the ^1H spectra of 1,6-, 1,8-, and 2,7-diazabiphenylenes are given in Table 1. Noticeable agreement exists for individual pyridine rings with the same fusion points. Overlap of the H-4 and H-8 signals was resolved by use of $\text{Eu}(\text{fod})_3$, which was shown to complex preferentially at N-6 <81TL4545>. Carbon-13 chemical shifts and coupling constants for 2,7-, 1,8-,

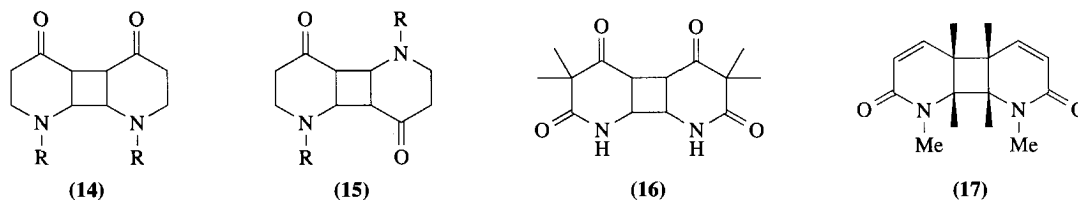
Table 1 Chemical shifts (ppm) in the proton spectra of unsubstituted diazabiphenylenes.



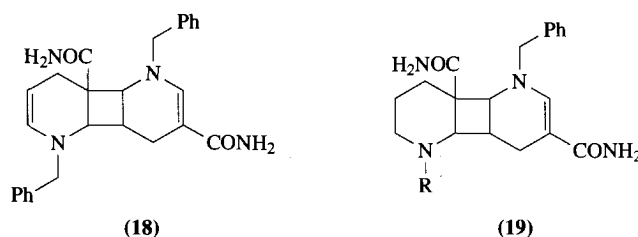
	1	2	3	Ring location					Ref.
				4	5	6	7	8	
N		7.91	6.68	6.99	6.99	6.68	7.91	N	75TL569
N		7.85	6.69	6.95	8.00	N	8.28	6.88	81TL4545
7.90		N	8.25	6.75	6.75	8.25	N	7.90	74CC359
8.0		N	8.3	6.8	8.0	N	8.3	6.8	72JA8336

and 1,6-diazabiphenylenes are reported <87MRC771>. The upfield shift relative to pyridine is attributed to a paramagnetic ring current in the four-membered ring.

Proton and carbon-13 data has been published for the pyridinone photodimerization products (14) and (15; R = CO₂Me) <91HCA163>, (14) and (15; R = CO·Ph) <81CJC3136>, (16) <88LA979>, and (17) <82JCS(P1)1187> and confirm the *trans* structure revealed by x-ray analysis.

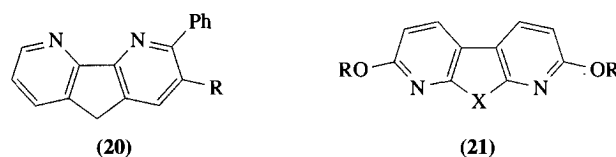


Nonequivalence of the benzyl groups in compound (18) (4.34 and 4.19 ppm) and its dihydro derivative (19; R = CH₂Ph) (4.53 and 3.83 ppm) provided evidence of the unusual structure. The mono-debenzylated product (19; R = H) lacked the signal at 3.83 ppm indicating loss of a benzyl group from the fully reduced ring <83TL5399>.

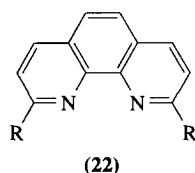


The ¹H spectra of 1,5-, 1,6-, 1,8-, 2,5-, 3,5-, and 4,5-diazafluoren-9-ones have been compiled by Mlochowski and co-workers <77JPR959>. The site of quaternization of unsymmetrical diazafluorenes and -fluoren-9-ones was resolved by comparison of ¹H signals to those of quaternized mono-azafluorenes <79CJC1506>. Proton NMR signals for 1,5-, 1,8-, 2,5-, and 4,5-diaza analogues are recorded. The position of bromination of 1,5-diazafluorenone was deduced from the ¹H signals (*J* = 2 Hz) in the monobrominated ring <80JPR971>.

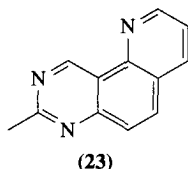
Detailed ¹H spectra are published of the 2,3-disubstituted 4,5-diazafluorenes (20; R = Me or Ph) <91CB571>, 2-aminoalkoxyl derivatives of 1,8-diaza compounds (21; X = CH₂, C=O) <84H(22)73>, and 3-hydroxy- and 3-methoxy-4,5-diazafluoren-9-one <92JCS(P1)1601>.



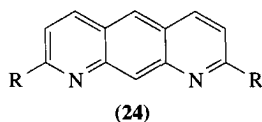
Much of the NMR spectroscopy of compounds with a central six-membered ring is routine and structure-confirmatory, employing comparisons to standard reference works. The relationship between spectral characteristics and structure in the benz-fused six-membered heterocycles is well covered in CHEC-I, Volumes 2 and 3. Leading references to the spectroscopy of phenanthrolines up to 1977 are collected in Summers' review <78AHC(22)1>. Comprehensive ¹³C data for 1,7-, 1,8-, 1,9-, 1,10-, 2,7-, and 4,7-phenanthrolines together with a correlation of chemical shifts with HMO electron densities <79OMR(12)696> and for chloro-derivatives of 1,7-, 1,10-, and 4,7-phenanthrolines <82OMR(20)16> and ¹H and ¹³C data for 2,9-disubstituted-1,10-phenanthrolines (22) is also reported <81JHC599>.



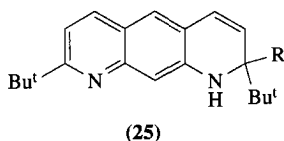
In common with many quinazolines, compound **(23)** crystallizes as a monohydrate. Its ^1H spectrum in CDCl_3 , however, reveals H-4 as a singlet (10.44 ppm) precluding 3,4 addition typical of covalent hydration of quinazolines. The ^1H spectrum in D_2SO_4 gives an H-4 signal 3.32 ppm upfield consistent with 3,4-hydration in aqueous solution <83JHC447>.



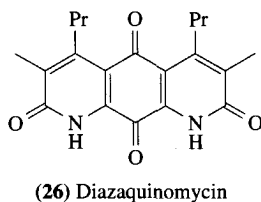
Full ^1H and ^{13}C data are given for the 2,8-disubstituted pyrido[3,2-*g*]quinolines (**(24)**). Assignment of ^{13}C signals in compound (**(24)**; $\text{R} = \text{Bu}^t$) to C-5 (125.3 ppm) and C-10 (128.1 ppm) was made by reference to the C-5/H-4 and C-4/H-5 coupling constants.



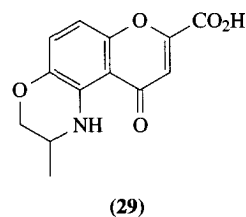
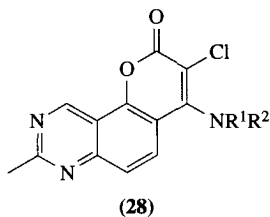
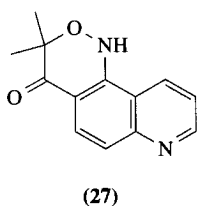
In the MeLi addition product (expected to be the 5-Me derivative) the C-5 signal was essentially unchanged whereas the H-2 signal (59.9 ppm) indicated a quaternary carbon confirming that attack had unexpectedly occurred at the sterically more hindered 2-position to yield compound (**(25)**; $\text{R} = \text{Me}$) <84LA133>.



Detailed ^1H and ^{13}C data for quinones and hydroquinones related to diazaquinomycin (**(26)**) are set out in two papers <83TL3643, 91TL1307>.



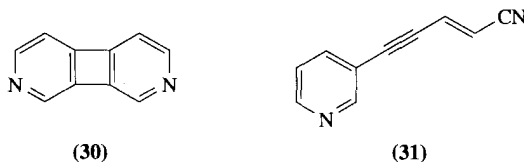
Data for the unusual pyrido[2,1-*h*]benz-2,1-oxazine (**(27)**) <86LA69>, various pyrano[2,3-*f*]quinazolines (**(28)**) <87JHC603>, pyrano[1,4]benzoxazines (**(29)**) <71JCS(C)2079>, and Reissert-type phosphonates of 1,7-phenanthroline <86BCJ2362> have been reported.



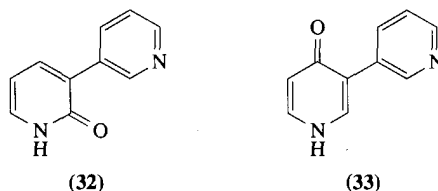
7.23.4 REACTIVITIES OF FULLY CONJUGATED RINGS

7.23.4.1 General Chemical Reactivities

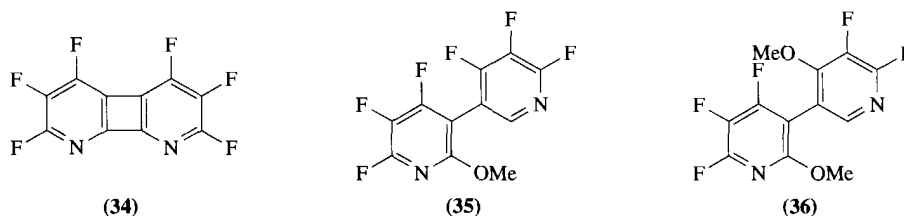
In the diazabiphenylene series many of the reactions involve fission of one of the rings. Although formed under high temperature conditions, 2,7-diazabiphenylene (**30**) is partially converted to 3-pyridylethynylacrylonitrile (**31**) at 800°C <86JCR(S)236>.



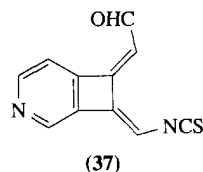
Nucleophilic attack by hydroxide ion breaks one of the cyclobutane ring bonds <82TL1109>. The 1,6- and 1,8-diazabiphenylenes both yield the same product (**32**) when treated with 2.5 M sodium hydroxide at 150°C. (Pyridine yields 2-pyridone under more forcing conditions.) 2,7-Diazabiphenylene, by contrast, yields 1*H*-3-(3-pyridyl)-4-pyridinone (**33**).



Analogously, hexafluoro-1,8-diazabiphenylene (**34**) with methanolic sodium methoxide yields the 3,3'-bipyridyls (**35**) and (**36**) <90JCR(M)1301>.



2,7-Diazabiphenylene reacts with thiophosgene in a two-phase system ($\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$) to yield the unusual product (**37**), presumably by first quaternization of the nitrogen atom followed by nucleophilic attack at C-3 <84JCR(M)3001>. In similar reactions isoquinoline is usually attacked at C-1.

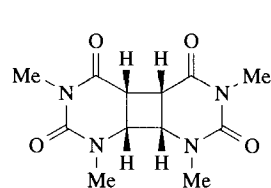


2,7-Diazabiphenylene (**29**) is unaffected by $\text{H}_2\text{SO}_4/\text{HNO}_3$ but readily forms an *N*-oxide and mono- and diquaternary salts <80JCR(M)2911>.

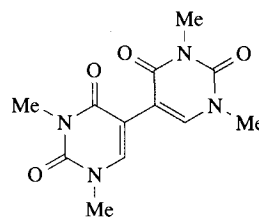
The photodimer (**38**) of 1,3-dimethyluracil, on UV irradiation (250 nm) in the presence of a sensitizer (quinone) yields the product (**39**) <71JCS(C)2053>.

The natural DNA repair process (enzymatic) is mimicked by unsensitized irradiation of pyrimidinedione dimers as, for example, compound (**40**; R = 2,5-dimethoxybenzyl) yielding the uracil derivatives (**41**; R = H and 2,5-dimethoxybenzyl) <93JA850>.

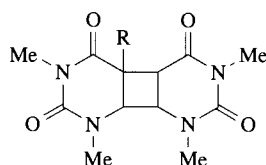
NaBH_4 reduction of compound (**42**) opens both heterocyclic rings giving the 1,2,3,4-tetra-substituted cyclobutane (**43**), whose stereochemistry assigns the configuration of the precursor (**42**) <71JA3493>.



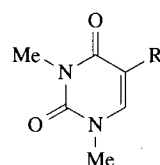
(38)



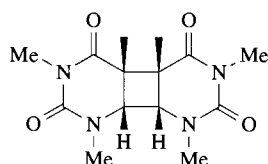
(39)



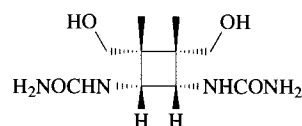
(40)



(41)



(42)



(43)

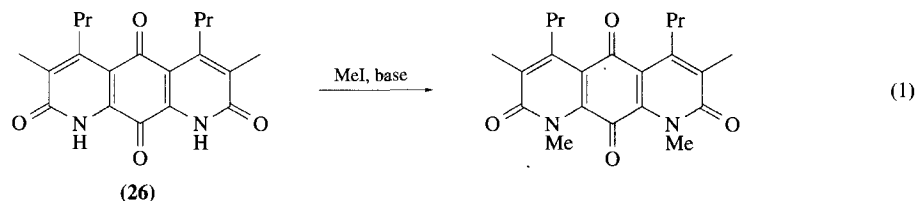
The *N*-oxidation of diazafluorenes and -fluorenones has been studied by Mlochowski and co-workers <79CJC1506>. The 1,8- and 2,5-diazafluorenones yielded bis *N*-oxides with H_2O_2 /acetic acid whereas the 1,5- and 4,5 isomers gave tars. $\text{H}_2\text{O}_2/\text{Na}_2\text{WO}_5$ proved to be a milder reagent and yielded oxides of all isomers. Because of the readily oxidized 9-position, diazafluorenes yielded only the *N*-oxides of the corresponding fluorenones.

The sites of bromination of 1,4-, 1,8-, and 4,5-diazafluorenones have been determined <80JPR971>.

Oxidation of 4,5-diazafluorenone with KMnO_4 yielded the cyclic amide (9) <92JCS(P1)1601>. None of the 2,8-dicarbonyl compound was formed, probably due to deprotonation of the intermediate (9) inhibiting further nucleophilic attack by MnO_4^- .

The 1,5-, 1,8-, 2,5-, and 4,5-diazafluorenes and -fluorenones readily form monomethiodides with methylation occurring in the 1,5- and 1,8-compounds at the 1-position, in the 2,5-isomer at the 2-position, and in the 4,5-isomer at the 4-position. The rate of quaternization of the diazafluorenes is 10–30 times faster than that of the diazafluorenones <79CJC1506>. The diazafluorene quaternary salts on treatment with alkali in sodium acetate buffer yield pseudoazulenes (e.g. (11)) <79ZC374>.

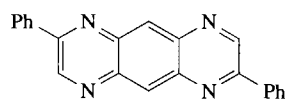
In the group of compounds with a central six-membered ring, many of the reactions of the ring systems are exact parallels of those of bicyclic analogues. For example, the pyridone antibiotic (26) methylates on nitrogen in the same manner as 2-pyridone (Equation (1)) <83TL3643>.



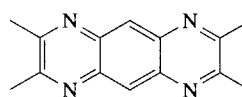
(26)

Space does not allow the listing of all examples of these and other straightforward reactions and therefore only unusual, unexpected, or illustrative examples will be given.

The redox chemistry of pyrazines has long been of interest to organic chemists. The chemical and electrochemical reduction of compounds (44) and (45) are reported in a comparative study.



(44)

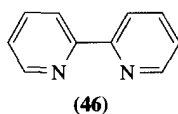


(45)

Catalytic hydrogenation of compound (**44**) and LAH reduction of compound (**45**) both yielded the 1,2,3,4-tetrahydro-derivative whereas Zn/acetic acid or electrochemical reduction gave the air-sensitive 1,4-dihydro-compounds $\langle 87CJC1619 \rangle$. Instead of the formation of the expected 5-methyl compound, MeLi attacked the highly hindered 2-position of compound (**24**; $R = Bu^t$) to yield compound (**25**; $R = Me$) $\langle 84LA133 \rangle$.

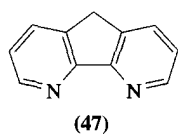
7.23.4.2 Complexes with Metal Ions

2,2'-Bipyridyl (**46**) has long been recognized as an important ligand, particularly for transition metal ions and its complexing properties are due to the proximity of the pyridine nitrogen atoms.

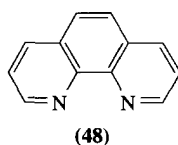


The possibility of modifying these properties by bridging the 3 and 3' positions has driven much of the chemistry in this area, as exemplified by the large number of compounds whose structures contain the 2,2'-bipyridyl moiety. (The structures in this section have been drawn to show their relationship to 2,2'-bipyridyl and may appear in other parts of this review in different orientations.)

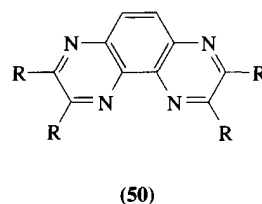
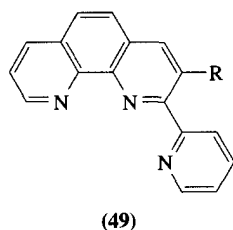
The photophysical properties of the Ni^{II} complex of compound (**47**) show that it is a weaker ligand than 2,2'-bipyridyl (**46**) due to the methylene bridge distorting the bipyridyl portion of the molecule $\langle 84JA5876 \rangle$. Comparison of the Ru^{II} complexes of compound (**47**) and of the corresponding 4,5-diazafluoren-9-one reveals the latter to be the weaker ligand $\langle 85MI 723-01 \rangle$.



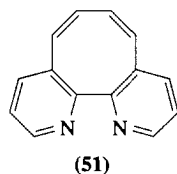
Undoubtedly the most investigated tricyclic ligand is 1,10-phenanthroline (**48**). Leading references to early work are given by Summers $\langle 78AHC(22)1 \rangle$; later chemistry and properties are comprehensively reviewed by Sammes and Yahioğlu $\langle 94CRV327 \rangle$.



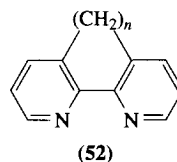
The ready applicability of synthetic routes to analogues of phenanthroline (**48**) bearing substituents and/or additional ring nitrogen atoms has led to a range of such structures as possible ligands including compounds (**49**; $R = H$ or 2-pyridyl) (Fe^{II} complexes) $\langle 66JOC3384 \rangle$, (**50**; $R = H$) (Pt complexes) $\langle 92JOM(436)367 \rangle$, and (**50**; $R = CH_3$) (Ag and Cu complexes) $\langle 88BSB983 \rangle$. In the last two references spectroscopy and x-ray analysis were used to prove the structure of the complexes.



The Mo and W complexes of compound (**51**) demonstrate a considerable flattening of the eight-membered ring as evidenced by the higher field of the alkenic protons in the complexes $\langle 90\text{PAC}565 \rangle$.

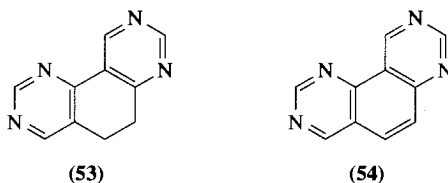


Ligands in which the 3,3'-bipyridyl bridge is saturated have been investigated by Thummel *et al.* $\langle 87\text{IC}2370 \rangle$. Ru^{II} complexes of compounds (**52**; $n = 1, 2, 3$, and 4) were prepared and their NMR and electronic spectra and redox potentials recorded. The ligand (**52**; $n = 1$) is planar whereas compounds (**52**; $n = 2$ and 3) have mobile conformations. The cyclooctadiene (**52**; $n = 4$) by contrast has a rigid structure and therefore is capable of enantiomerism.



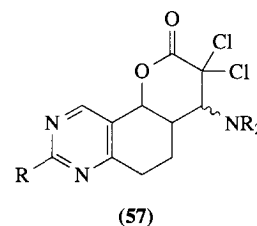
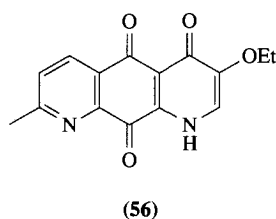
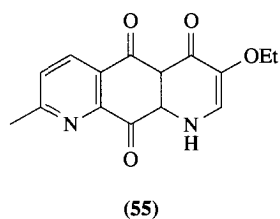
7.23.5 REACTIVITIES OF NONCONJUGATED RINGS

Several examples of the conversion of nonconjugated rings to conjugated rings are reported. Sulfur dehydrogenation remains a classic method of aromatization, although its use is limited by the sensitivity of substituents. Dehydrogenation of the cyclohexadiene derivative (**53**) at 230°C provided the fully aromatic compound (**54**) $\langle 76\text{CBP}591 \rangle$.

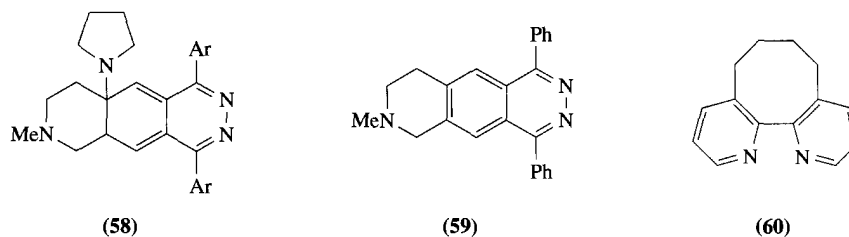


Compounds with potentially sensitive groupings are dehydrogenated using MnO₂, for example, the reduced quinolone (**55**) yields the fully aromatic quinone (**56**) $\langle 91\text{TL}1307 \rangle$. Successive treatments with DBN and DDQ convert the lactone (**57**; R = Me) to the product (**28**; R¹ = R² = Me) $\langle 87\text{JHC}603 \rangle$.

Thermal elimination of pyrrolidine from compound (**58**; Ar = Ph) effectively aromatizes the

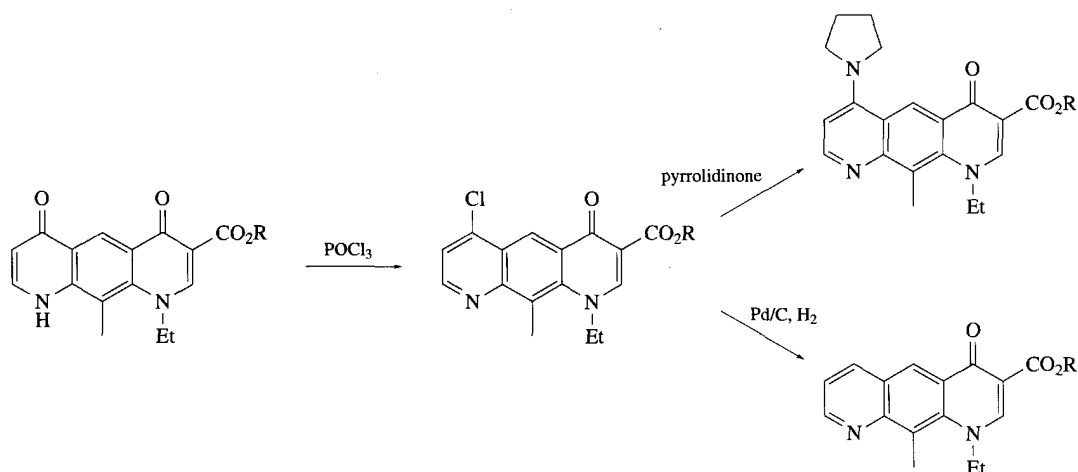


central ring yielding the pyridophthalazine (**59**) <91T3959>. Bromination/dehydrobromination of the 2,2'-bipyridyl analogue (**60**) provided an uncomplicated route to the cyclooctadipyridine (**51**) <90PAC565>.



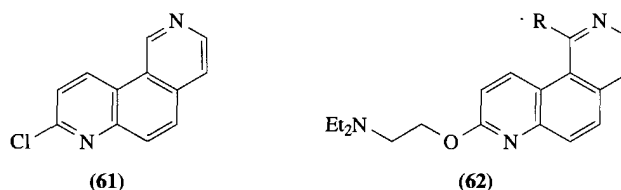
7.23.6 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

In the great majority of examples, the reactions of substituents on carbon are those to be expected from a basic knowledge of organic chemistry. For example, cyclic amides (adjacent or vinylogous) are readily converted into the ring chloro derivative from which the chlorine atom may be displaced by a number of standard reactions (Scheme 1) <93H(36)2753>. Similar examples are cited elsewhere <85CPB3336, 94TL397>.

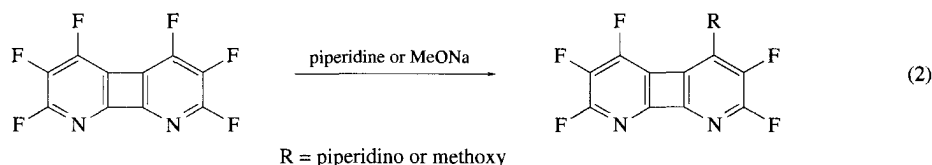


Scheme 1

Replacement of a chloro substituent by alkoxy can have unusual results. The chloro-phenanthridine (**61**) on reaction with 2-diethylaminoethanol in DMSO/NaOEt yielded, in addition to the expected product (**62**; R = H), substantial amounts of the bis-ether (**62**; R = O·CH₂·CH₂·NEt₂). The mechanism of this unusual reaction has not been fully explained; 1,8-diaza-phenanthrene does not react under these conditions <88M263>.



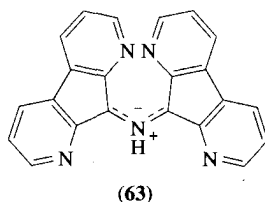
In the series of compounds with central four- and five-membered rings, *N*-oxide formation and conversion into ring chloro is commonplace <84H(22)73, 84JCR(M)3001>. Polyfluorodiazabiphenylene undergoes nucleophilic displacement of halogen by piperidine or methoxide ion (Equation (2)) <90JCR(S)172>.



The 9-carbonyl group of diazafluorenones behaves in an analogous manner to that in fluorenone: reduction to the 9-ol and to the fluorene <70AJC1023>, reaction with dialkyl phosphites to yield 9-hydroxy-9-phosphonic esters <84JPR349>, and with acetone to give the 9-hydroxy-9-(2-oxopropyl) analogue <62CB2137>.

9-Diazo-1,8-, 3,6-, and 4,5-diazafluorenes are obtained by alkaline decomposition of the respective 9-tosylhydrazones. Photolysis of these diazo compounds yields reactive carbenes whose properties and reactions were investigated by Schuster and Li <86JOC3806, 87JOC3975> and by Durr and co-workers <89TL1935>.

1,8-Diazafluorenone reacts with amino acids to produce the red, highly fluorescent compound (63) <90TL7215>.



7.23.7 REACTIONS OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The only examples of reactions in this category relates to *N*-oxides of ring heteroatoms (see Section 7.23.4.1) which on reaction with POCl₃ or POBr₃ form the α -halo compound; typical examples are given in Table 2.

Table 2 Conversion of *N*-oxides to ring halo compounds.

No.	Reactant(s)	Product(s)	Ref.
1	2,7-Diazabiphenylene-2-oxide	3-chloro-2,7-diazabiphenylene	84JCR(M)3001
2	1,8-Diazafluorenone-1,8-dioxide	2,7-dichloro-1,8-diazafluorenone	84H(22)73
3	1,7-Phenanthroline-7-oxide	8-bromo-1,7-phenanthroline	83JHC447
4	Phenanthroline <i>N</i> -oxides (various)	mono- and dichlorophenanthrolines	88M263

7.23.8 RING SYNTHESSES

7.23.8.1 Compounds with a Central Four-membered Ring

An example of the systematic nomenclature for compounds in this group is cyclobuta[1,2-*b*:3,4-*b'*]dipyridine: in this review this compound will be named as an "aza" analogue of biphenylene, that is, 1,8-diazabiphenylene. The only structural types found in the literature are those described below although there seems no reason why other variants are unknown. No record of unsuccessful attempts at synthesis were revealed.

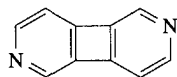
7.23.8.1.1 Compounds with one heteroatom in each heterocyclic ring

(i) Synthesis of the heterocyclic ring

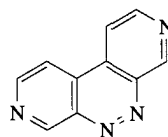
No examples of this approach have been found.

(ii) Synthesis of the carbocyclic ring

(a) *By formation of one bond.* The earliest synthesis of a diazabiphenylene involved the dimerization of 3,4-pyridyne formed *in situ* by photolysis of 3-diazopyridine 4-carboxylate <72JA8336>. Physical methods were unable to decide between the two possible structures (30) and (64) for the product and the question was only resolved when MacBride <74CC359> prepared 2,7-diazabiphenylene (30) by vacuum pyrolysis of compound (65), and showed that it differed from the pyridyne derived product which therefore had the structure (64).



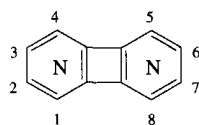
(64)



(65)

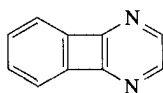
Nitrogen extrusion from tetraazaphenanthridines provides a useful route to diazabiphenylenes (Table 3) but although the synthesis of the pyridazine analogue (66) is reported <80JCR(M)2941> the method does not seem to have been applied to the synthesis of tri- or tetraaza analogues with heteroatoms in both rings. The 1,5- and 1,7-diazabiphenylenes are not known. C-Halogenated tetraazaphenanthridines yield, on pyrolysis, the expected diazabiphenylenes (Equation (3)) <90JCR(M)215, 90JCR(M)1301>. The mechanism was not unreasonably believed to involve a diradical, for example, (67), formed by extrusion of nitrogen. This view is now in some doubt on two counts: (i) both 3,6,9,10- and 2,7,9,10-tetraazaphenanthridines give, on pyrolysis, 2,7-diazabiphenylene in 60% yield and the by-product (31) in 12% yield; (ii) a consideration of the Arrhenius activation energy for the process <86JCR(M)2049>.

Table 3 Synthesis of unsubstituted diazabiphenylenes.

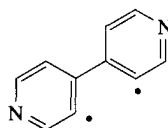


N location	Precursor	Yield (%)	Ref.
1,6	2,5,9,10-tetraazaphenanthrene	35	81TL4545
1,8	4,5,9,10-tetraazaphenanthrene	24	75TL569
2,7	2,7,9,10-tetraazaphenanthrene	60	74CC359
2,7	3,6,9,10-tetraazaphenanthrene	60	86JCR(M)2049
2,6	3-diazopyridine 4-carboxylate	^a	72JA8336

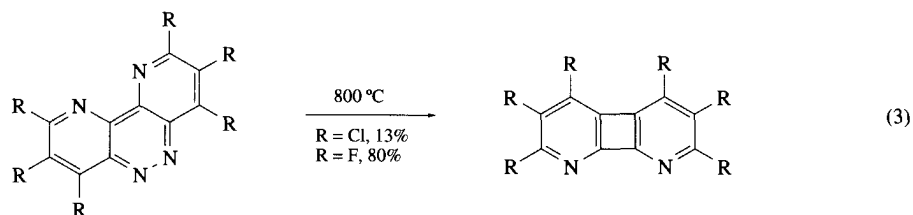
^aYield not stated.



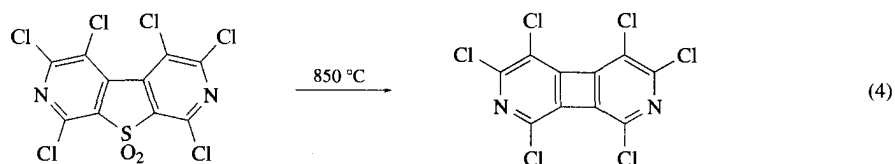
(66)



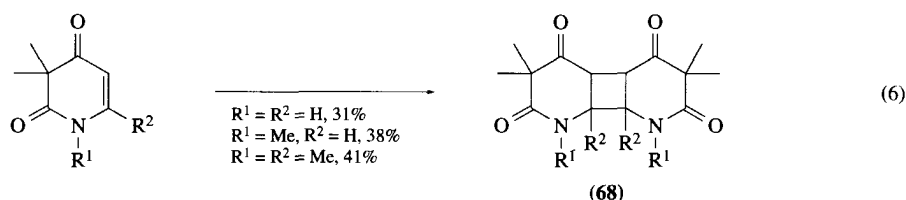
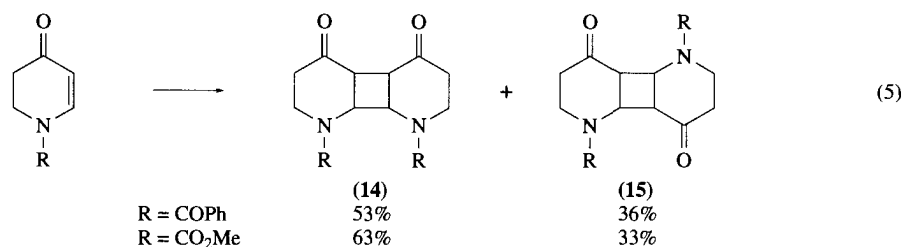
(67)



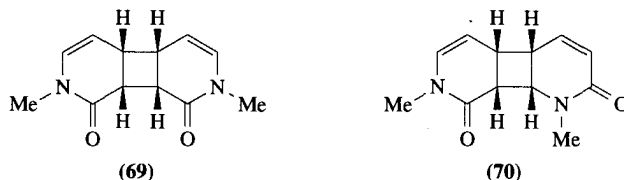
Extrusion of SO_2 from dipyridothiophene dioxides (vacuum pyrolysis at 800°C) gives diazabiphenylenes in very low yield (Equation (4)) <77JCR(M)1567>.



(b) *By formation of two bonds.* Photochemical dimerization of compounds bearing $\text{C}=\text{C}$ bonds is a well-established and useful method for the synthesis of derivatives of cyclobutane. 1-Acyl-2,3-dihydro-4-pyridones on irradiation by Pyrex-filtered mercury arc yielded the “head-to-head” and “head-to-tail” dimers (Equation (5)) which are separable by chromatography <81CJC3136, 91HCA163>. Pyridine 2,4-diones, by contrast, yield only the “head-to-head” products (**68**) (Equation (6)) <88LA979>.



The photochemistry of *N*-methyl-2-pyridones is more complex, the initial products of irradiation are [4 + 4] dimers, two of which further rearrange to the products (**17**), (**69**), and (**70**). The *cis-cis* configuration at the ring junction follows from the structure of the initial dimer and from an NMR analysis of the products <82JCS(P1)1187>.



The unusual variant (**18**) is formed by the photodimerization of 1-benzyl-1,4-dihydronicotinamide <83TL5399>, neither the “head-to-head” isomer of compound (**18**) nor the 5,5'-linked dimer was observed. Further investigation appears desirable to examine the mechanism and scope of this reaction.

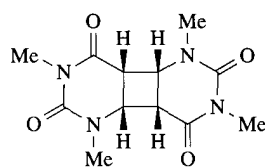
7.23.8.1.2 Compounds with two heteroatoms in each heterocyclic ring

(i) Synthesis of the heterocyclic ring

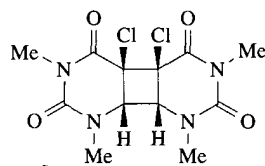
No examples of this approach have been found.

(ii) Synthesis of the carbocyclic ring

Since the seminal work of Beukers *et al.* <58RTC729> on the photodimerization of thymine and the realization that dimers formed between bases on adjacent strands of DNA were implicated in UV promoted lesions, this area of chemistry has received much attention. Reviews by Brown <94CHE476> and Wamhoff *et al.* <92AHC(55)140> provide many leading references. Experimentally, dimers are obtained by short wave (> 290 nm) irradiation of the substrate initially in a frozen matrix to represent immobilization in biosystems but subsequently solution experiments have been equally successful. 1,3-Dimethyluracil, for example, in a range of solvents, yields four dimers in yields ranging from 24% in acetone to 94% in acetonitrile <71JCS(C)2053>. The *cis* isomers (38) and (71) generally predominate in the product mixture from which all four components are isolated by chromatography.



Irradiation in water usually produces 5,6-hydrated compounds whereas in D₂O dimers are the main products. 6-Chloro-1,3-dimethyluracil yields the *cis-syn* dimer (72) <69TL2211>.



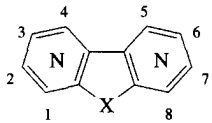
7.23.8.2 Compounds with a Central Five-membered Ring

Compounds in this group are heterocyclic analogues of the hydrocarbon fluorene which have heteroatoms in both six-membered rings. Surprisingly, only compounds with one nitrogen atom in each ring are widely known. The widely used and readily understood “aza” nomenclature will be used in this section. Table 4 lists the references to the known unsubstituted diazafluorene and diazafluoren-9-ones.

7.23.8.2.1 Compounds with one heteroatom in each heterocyclic ring

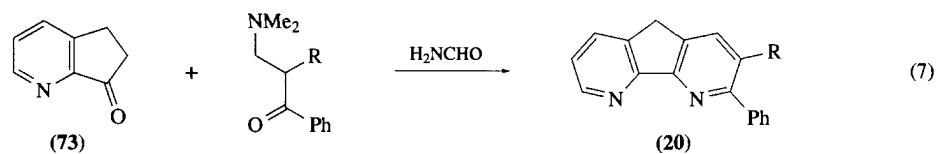
(i) Synthesis of the heterocyclic ring

The reaction of amino-ketones with the ketone (73) in the presence of ammonia or an ammonia source yields the substituted 4,5-diazafluorenes (20; R = Me) (15%) and (20; R = Ph) (24%) (Equa-

Table 4 References to unsubstituted diazafluorenes and diazafluoren-9-ones.


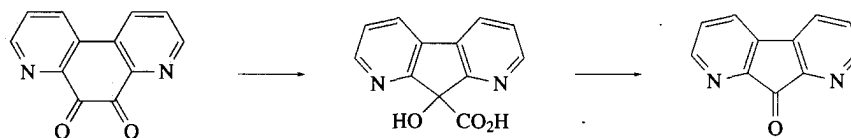
Aza locants	$X=CH_2$	Ref.	$X=C:O$
1,5	50HCA1080		50HCA1080
1,6			77JPR959
1,7			
1,8	50HCA1080		50HCA1080
2,5	78H(9)849		77JPR959
2,6			
2,7			
3,5			77JPR959
3,6			87JOC3975
4,5	70AJC1023		50HCA1080

tion (7)) <91CB571>. This variant of the Hantzsch pyridine synthesis appears to be of general application to cyclic ketones. This is the only example of construction of the heterocyclic ring of diazafluorenes.



(ii) Synthesis of the carbocyclic ring

The principal synthetic route to diazafluorenes involves the alkaline oxidation of phenanthrolines, presumed to give initially the rarely isolated 5,6-dione which (i) further oxidizes to a bipyridyl dicarboxylic acid (the main product) or (ii) undergoes a benzilic acid type rearrangement followed by oxidative decarboxylation to give diazafluorenones in moderate yields (Scheme 2) <77JPR959>. The process has been reviewed by Summers <78AHC(22)1>. The yields of 4,5-diazafluorenone have been optimized <73AJC2727>.

**Scheme 2**

It is noticeable that, although all isomers of phenanthroline are known, not all have been used as precursors to diazafluorenones.

7.23.8.3 Compounds with a Central Six-membered Ring

The methodologies by which a six-membered heterocycle is fused on to a six-membered carbocyclic ring form one of the most basic and extensively researched areas of organic chemistry. It can

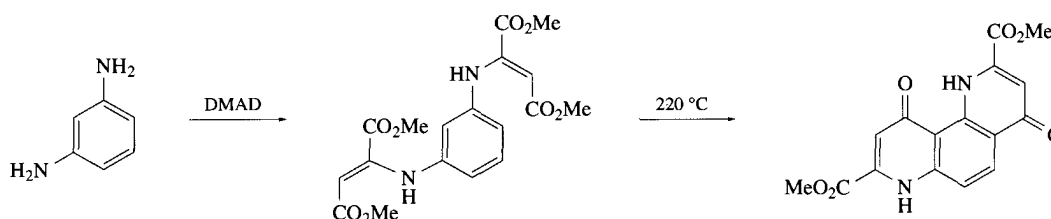
be of little surprise therefore, that the great majority of compounds within this group have been synthesized by such well-established methods, and that there are very few examples of the construction of the carbocyclic ring. Key review publications are to be found throughout CHEC-I, Volumes 2 and 3 (e.g. <84CHEC-I(2)395, 84CHEC-I(3)599>).

7.23.8.3.1 Compounds with one heteroatom in each heterocyclic ring

The chemistry of pyrido[2,3-*g*]quinolines and pyrido[3,2-*g*]quinolines up to 1952 is reviewed by Wilson <58CHE457> and from 1952 to 1979 by Czuba and co-workers <79WCH235>. In the latter publication, the ring systems are referred to as 1,5- and 1,8-diazaanthracenes, respectively.

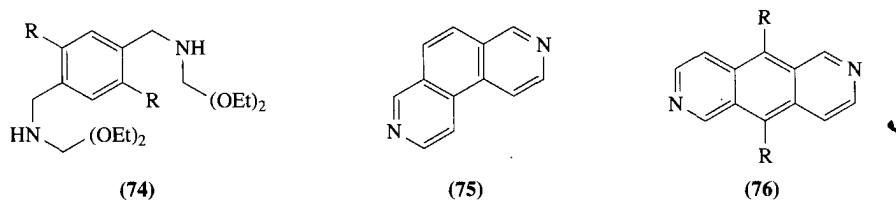
(i) Synthesis of the heterocyclic ring

(a) *By formation of one bond.* Syntheses of hetero-rings by single bond formation frequently involve the cyclization of a side-chain linked via a heteroatom to a carbocyclic ring. Typical precursors are the products of the reaction of amines with diethyl ethoxymethylenemalonate <93H(12)2753> and with diethyl alkenedicarboxylate (Scheme 3) <83JHC681>.

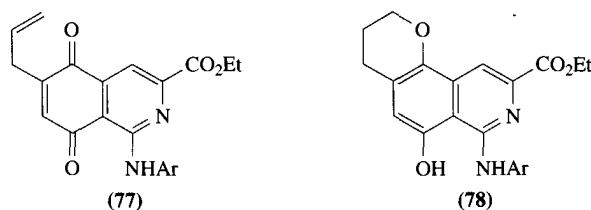


Scheme 3

Cyclization of compound (74; R = H) in fuming sulfuric acid yielded the angular (75) and linear (76; R = H) products. Identity was confirmed by reductive dechlorination of the single product (76; R = Cl) obtained from compound (74; R = Cl) <82JHC1351>.



In an unusual example of electrophilic cyclization in neutral aprotic medium, the 2-allyl quinones (77), on heating in benzene, yield the 2*H*-pyrano[2,3-*f*]isoquinolines (78) <90JOC6140>.

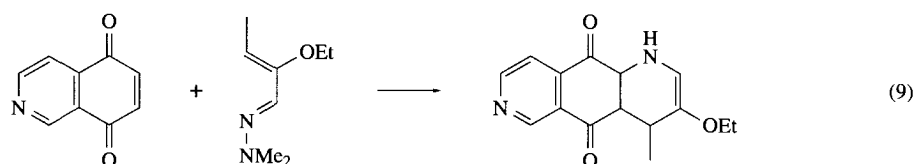
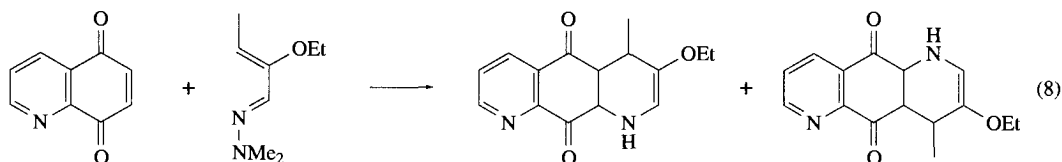


(b) *By formation of two bonds.* The 1,7-, 1,8-, 1,9-, 1,10-, 2,7-, 3,7-, and 4,7-phenanthrolines all possess at least one nitrogen atom linked directly to the central ring and thus contain the quinoline nucleus. All may be prepared by the Skraup reaction or a variant thereof. In the 2,8- and 3,8-

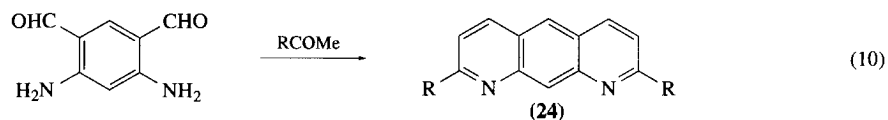
isomers neither nitrogen atom is linked directly to the central ring and these compounds are essentially isoquinolines. Neither appears to be accessible by classical isoquinoline synthesis methods.

There have been no significant advances in the synthesis of phenanthrolines since the review by Summers (78AHC(22)1). All ten isomers are known and some are commercially available.

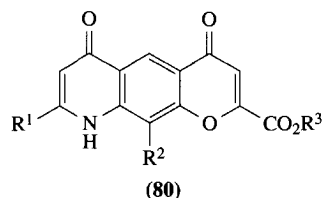
Diels–Alder addition of azadienes to quinones has been used to prepare analogues of the antibiotic diazaquinomycin (26). Quinoline-5,6-quinone yields both regioisomers (Equation (8)) while the isoquinoline quinone gives only the pyrido[3,4-*g*]quinoline (79) (Equation (9)) (91TL1307).



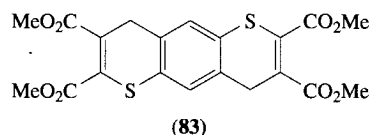
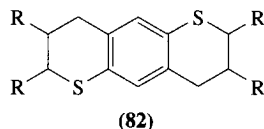
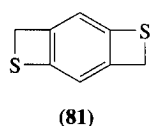
A series of 2,7-disubstituted pyrido[3,2-*g*]quinolines (24) were obtained by a double Friedlander reaction on 4,6-diamino-isophthalaldehyde (Equation (10)) (84LA133).



A large number of pyrano[3,2-*g*]quinolines (80) have been prepared as analogues of the anti-asthmatic drug sodium chromoglycate. Interesting variants of standard methods were developed to fuse pyridine rings to chromones and pyran rings to quinolines (88JMC1445).

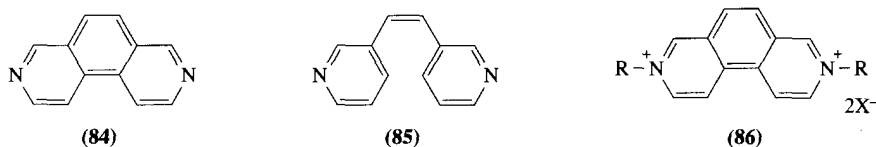


The reactive 2*H*,5*H*-benzo[1,2-*b*:4,5-*b'*]bisthiete (81) reacts readily in toluene at 90°C with (*E*)-1,2-bis(4-hexyloxyphenyl)ethene, dimethyl fumarate, or diethyl maleate to furnish the compounds (82; R = 4-hexyloxyphenyl, CO₂Me, and CO₂Et). Reaction with DMAD yields the tetraester derivative (83) (94AG(E)465).



(ii) Synthesis of the carbocyclic ring

Phenanthrolines (84) are obtained by photochemical cyclization of 1,2-dipyridyl ethylenes (85). Their bisquaternary salts (86) are obtained by polarography of the corresponding pyridinium salts (73LA339).

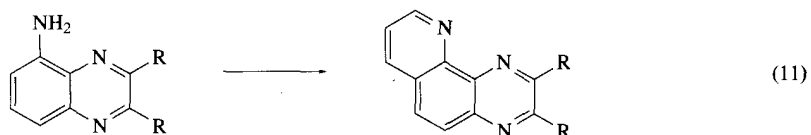


7.23.8.3.2 Compounds with two heteroatoms in one ring and one in another

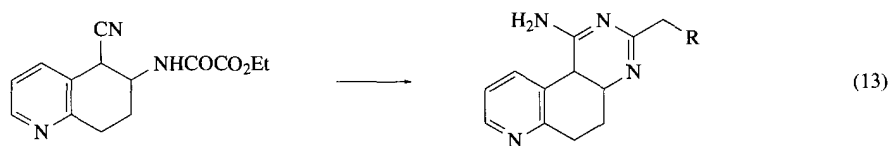
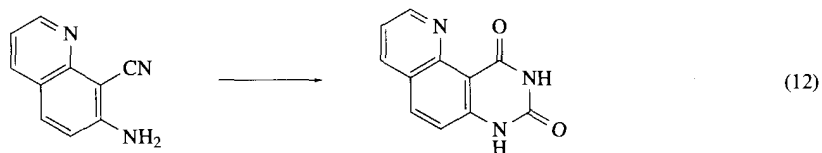
(i) Synthesis of the heterocyclic ring

The great majority of examples in this group involve the application of established, reliable methods for the fusion of a six-membered heterocycle on to a carbocyclic ring. Such is the versatility of these methods that, by the combination of a judicious choice of starting materials and route options, a very large number of the possible structural variants have been obtained. Those given below are illustrative of the range of variations reported.

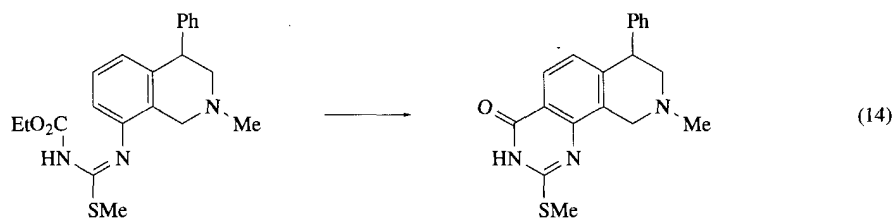
(a) *By formation of one bond.* The Skraup quinoline synthesis and its variants are widely used (Equation (11)) <66JOC3384, 90USP4965265>. The use of ethoxymethylenemalononic ester (EMME) provides 4-quinolone analogues with quinoxaline, benz[1,4]thiazole, and benz[1,4]oxazole fused rings.



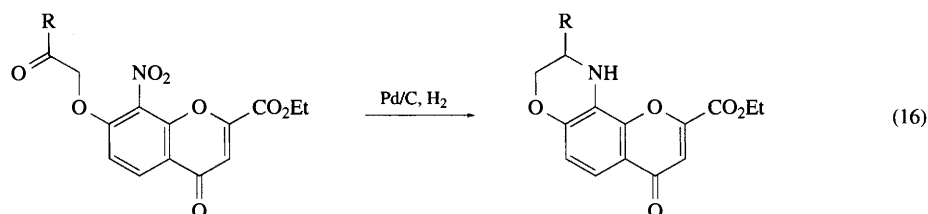
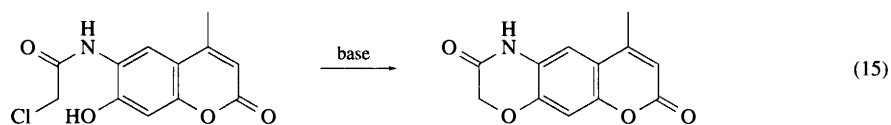
2-Aminonitriles are versatile starting points for a range of structures (Equations (12) and (13)) <81H(16)2115, 85CPB3336>.



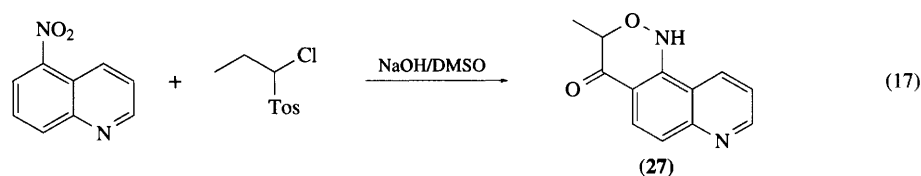
Thermal cyclization of *N*-ethoxycarbonyl-isothioureas leads to fused pyrimidine rings (Equation (14)) <81JHC1417>.



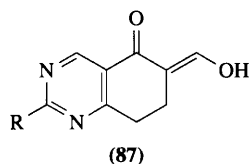
[1,4]Oxazine rings are readily attached by the base-induced cyclization of 2-chloroacetamides (Equation (15)) <86MI 723-01> and by reductive cyclization of *o*-nitroketoethers (Equation (16)) <71JCS(C)2079>. Interestingly, when $R = Bu^t$ the imine bond is not reduced and the 2*H* oxazine results.



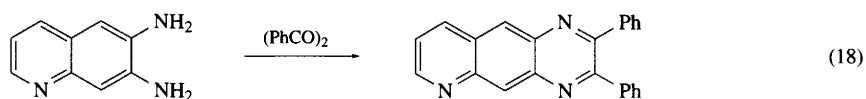
The unusual [2,1]oxazine (**27**) is formed by an interesting variation of vicarious nucleophilic substitution in the reaction of 1-chloropropyl-*p*-tolyl sulfone carbanion with 5-nitroquinoline (Equation (17)) <86LA69>.



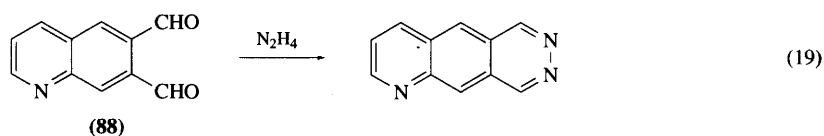
Condensation of 1,1-dichloroketene and secondary amines with the pyrimidine derivative (**87**; R = Ph) yielded the tricyclic products (**57**; R = Ph) but when the derivative (**87**; R = Me) was used the reaction was only successful when a secondary amine of the type HNPhR₂ was employed. This limitation is ascribed to the increased basicity of the 2-methylquinazoline system <87JHC603>.



(b) *By formation of two bonds.* Typical syntheses involve the reaction of 1,2-dicarbonyl compounds with 1,2-diamines (Equation (18)) <73KGS525>.

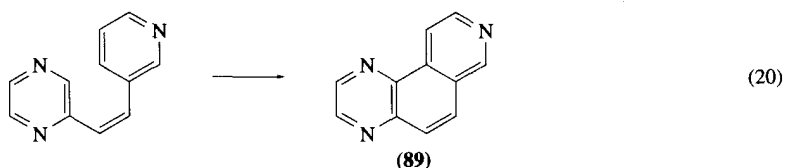


Pyrido[2,3-*f*]phthalazines are obtained from the dialdehyde (**88**) (Equation (19)) <73JHC1079>.

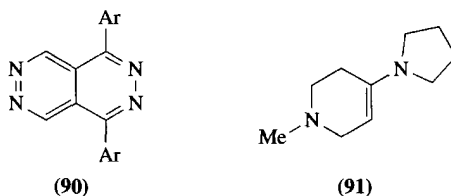


(ii) Synthesis of the carbocyclic ring

(a) *By formation of one bond.* Irradiation of 2-, 3-, and 4-pyridylvinylpyrazines with a 400 W high-pressure mercury lamp gave moderate yields of pyrido[*f*]quinoxalines. The 3-pyridyl compound gave only compound (**89**) and none of the pyrido[2,3-*f*] isomer (Equation (20)) <79CPB2596>.

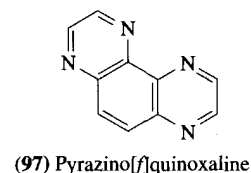
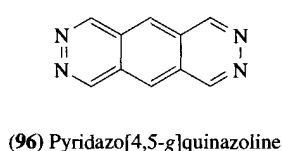
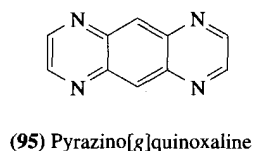
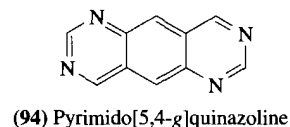
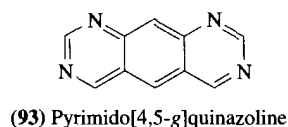
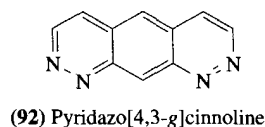


(b) *By formation of two bonds.* In an interesting exploitation of the inverse electron-demand variant of the Diels–Alder reaction the π -deficient 1,4-diarylpyridazo[4,5-*d*]pyridazines (90) add to the enamine (91) with concomitant extrusion of nitrogen to yield the products (58; Ar = phenyl) (91%) and (58; Ar = 4-methoxyphenyl) (75%) <91T3959>.



7.23.8.3.3 Compounds with two heteroatoms in each heterocyclic ring

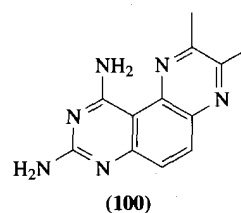
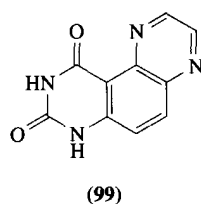
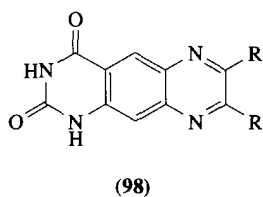
The literature up to 1953 on the six structural types (92) to (97) has been reviewed by Wilson <58CHE14>.



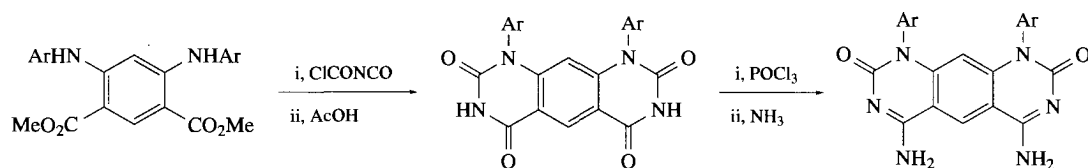
(i) Synthesis of the heterocyclic ring

(a) *By formation of one bond.* No examples of synthesis by formation of one bond have been found.

(b) *By formation of two bonds.* Several examples of tricyclic compounds containing the pyrimidine ring have been investigated for potential biological activity. One approach attracting attention is the interposition of a benzene ring between the two hetero rings of a biologically active bicyclic heterocycle. The “stretched” lumazines (98; R = H or Me) <81JHC539> and (99) <81JHC653> and the potential antimalarials (100) <79JHC1101> were obtained by typical quinoxaline syntheses.

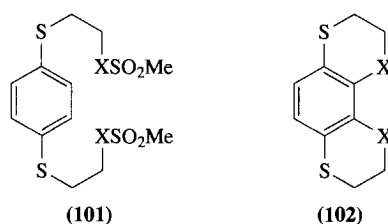


The so-called *Janus* molecules, which have the H-bonding sites of one face mirrored on the other face, were synthesized by the route shown in Scheme 4 <94TL397>.



Scheme 4

The dithiane (**102**; X = S) and thioxane (**102**; X = O) were obtained by Friedel–Craft type cyclizations of the precursors (**101**) <87CC223>.



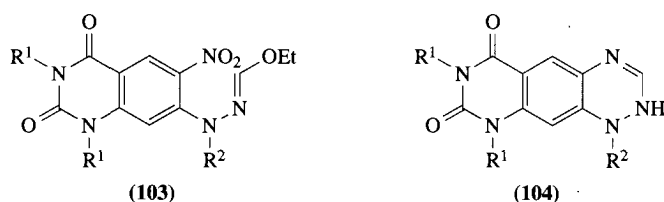
(ii) *Synthesis of the carbocyclic ring*

No examples of this approach were found

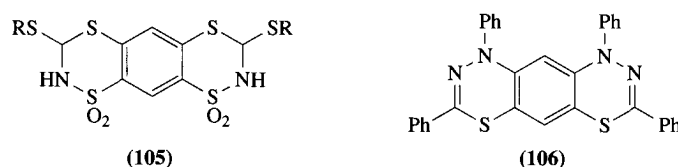
7.23.8.3.4 Compounds with more than two heteroatoms in either ring

(i) *Synthesis of the heterocyclic ring*

In studies on “stretched” pteridines and their aza analogues, pyrimido[5,4-*g*]-1,2,4-benzotriazines (**103**; R¹ = H, Me) have been prepared by catalytic hydrogenation of the *o*-nitrohydrazones (**104**). The products (**103**; R¹ = H) were readily oxidized to the *linear*-benzo separated analogues of the naturally occurring 7-azapteridines but for the derivative (**103**; R¹ = Me) the toxoflavin analogues could not be prepared <81JOC1699, 84JHC791>.

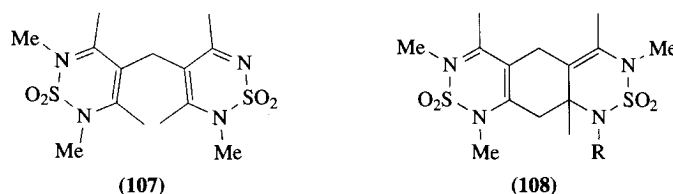


The reaction between 4,6-dichlorobenzene-1,3-disulfonamide and CS₂ yielded the unusual benzene bis[dithiazine] (**105**; R = H), which is readily methylated to the derivative (**105**; R = Me) <84MI 723-01>. Displacement of the fluorine atoms and nitro groups from 1,3-difluoro-4,6-dinitrobenzene by 1,3-diphenylthiohydrazide (PhCS, NHNHPh) yielded compound (**106**) <80JOC3677>.



(ii) *Synthesis of the carbocyclic ring*

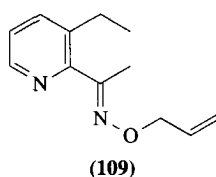
Under alkaline conditions compound (107) underwent an unusual cyclization to give the benzene bisthiadiazine (108; R = H) and in the presence of MeI the *N*-methyl derivative (108; R = Me) was obtained. No radical signals were detected by EPR during the course of the reaction and the authors postulate an ionic mechanism involving deprotonation of a *C*-methyl group followed by attack at the electron-deficient 3'-position. The apparent transfer of the *N*-methyl group to the other nitrogen atom in the same ring was not explained <85T3105>.



7.23.8.4 Compounds with a Central Seven-membered or Larger Ring

(i) *Synthesis of the heterocyclic ring*

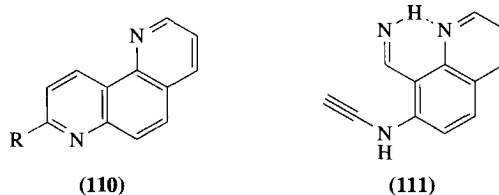
Compounds with central seven- and eight-membered rings (52; $n = 3$ or 4) are formed by the thermal cyclization of the *O*-allyl oximes (109) <87IC2370>.

(ii) *Synthesis of the carbocyclic ring*

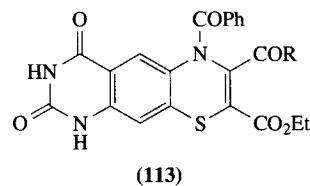
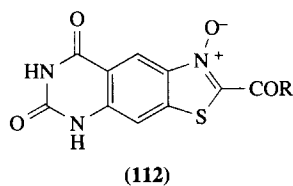
No examples of synthesis of the carbocyclic ring have been found.

7.23.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Attempted displacement of the bromo substituent from compound (110; R = Br) by KNH_2 in liquid ammonia gave compound (23) (55%) together with only a low yield of the expected product (110; R = NH_2) (19%) <83JHC447>. The reaction mechanism is assumed to involve initial attack by the amide ion at C-10 of reactant (110; R = Br) followed by ring-opening to give the intermediate (111), which is stable in liquid ammonia. The ^{13}C spectrum of the reaction mixture clearly shows the ethynyl carbons of the intermediate (111) at 110.4 and 118.3 ppm. This intermediate (111) spontaneously cyclizes to the product (23) on work-up.



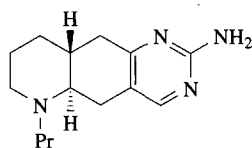
Compounds (**112**; R = OMe and 1-pyrrolidinyl) undergo an initial 1,3-dipolar cycloaddition with ethylphenylpropiolate, followed by ring-opening and recyclization to yield the corresponding 1,4-benzthiazine derivatives (**113**). A mechanism has been proposed <86CPB1384>.



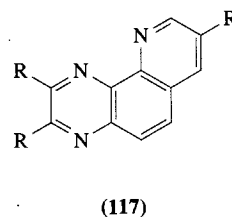
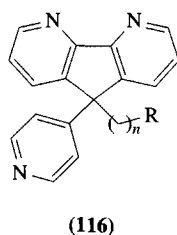
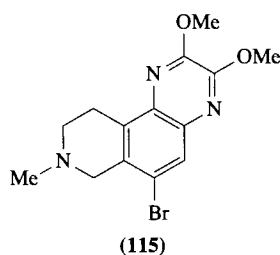
Several important examples of ring transformation are referred to elsewhere in this chapter. These include the extrusion of nitrogen from tetraazaphenanthridines and SO₂ from dipyridothiophene dioxides to yield diazabiphenylenes (Section 7.23.8.1.1), the benzylic-type ring contraction of phenanthridine diones to give diazafluorenones (Section 7.23.8.2.1), and the extrusion of nitrogen from the Diels–Alder adducts formed from enamines and pyridazo[4,5-*d*]pyridazines (Section 7.23.8.3.2).

7.23.10 IMPORTANT COMPOUNDS AND APPLICATIONS

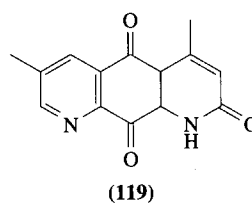
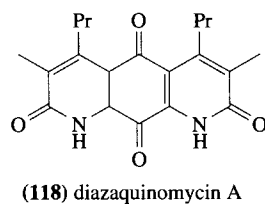
Several of the compound types in this chapter have useful biological activities. This is not unexpected since many of those compounds which are effective in the modification of responses to bioamines are themselves organic bases. Quinelorane (**114**) which is a potent dopamine (D2) agonist has been patented as an antihypertensive and antiparkinsonism agent <85USP4501890>.



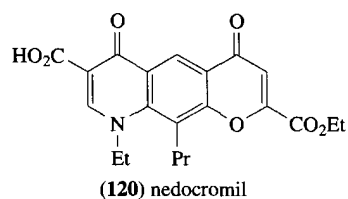
The pyrido[4,3-*f*]quinoline (**115**) is one of a group of substitution variants which are antagonists of excitatory amino acids and of use in the treatment of parkinsonism and cerebrovascular disorders <94MIP0900>. Three 4,5-diazafluorenones (**116**; *n* = 1 or 3, R = CO₂Et) and (**116**; *n* = 4, R = CN) are claimed as cognition enhancers <93MIP14092>. A large number of pyrido[2,3-*f*]quinoxalines (**117**; R = H or alkyl) are effective as agricultural fungicides for crop protection <90USP4965265>.



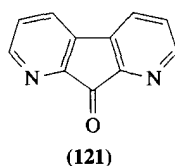
Heterocyclic analogues of anthraquinone are a family of potent antibiotics, many with antitumor and cytostatic properties. Diazaquinomycin A (**118**) is a thymidine synthetase inhibitor <88TL3545>. Low solubility of compound (**118**) has led to the development of more soluble active analogues, for example, (**119**) <92JPS815, 94EUP574195>.



The sodium salt of nedocromil (**120**) is a prophylactic antiallergy treatment <88JMC1445>.



1,8-Diazafluorenone (**121**) which has found wide use in forensic science for the detection of latent fingerprints on paper reacts with amino acids to give the red, highly fluorescent compound (**63**) and is several times more sensitive than ninhydrin <90TL7215>. 1,10-Phenanthroline (**48**) is a powerful chelating agent and has found widespread use in analytical chemistry and biology. Its properties have been reviewed by Summers <78AHC(22)1> and by Sammes and Yahiolu <94CRV327>.



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	Acad. Naz. Lncei
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	Forschr. 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. Energy 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. Priir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendelev 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	Nat.
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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